

Second Edition

Farm Animal Anesthesia

Cattle, Small Ruminants,
Camelids, and Pigs

Edited by
HuiChu Lin
Thomas Passler
Stuart Clark-Price



WILEY Blackwell

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Camelids, and Pigs

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Edited by

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I dedicate this book to my colleagues in the Food Animal Section of Auburn University for your team spirit and for making my job as an anesthesiologist easy and fun. I appreciate all the more your unreserved friendship and support. This book would not be a reality without you all.

HuiChu Lin,
DVM, MS, DACVAA

To the most important people in my life: my parents Barbara Fechner and the late Hans Passler, my wife Nicole, my son William, and my American family, the Borgmeyers. Thank you for your unwavering love and support! And to my colleagues – the Auburn family – for their collegiality, friendship, and words of wisdom.

Thomas Passler,
DVM, PhD, ACVIM

I would first like to start by thanking Dr. Hui-Chu Lin for inviting me to participate in the second edition of this textbook. It is exciting to see anesthesia and pain management for farm animals advance and to know that practitioners are utilizing this information to improve the lives of the animals and clients they serve. I therefore dedicate this book to those practitioners, some of whom have been students of mine, who tirelessly endeavor to provide care to the best of their abilities.

Stuart Clark-Price,
DVM, MS, DACVIM, DACVAA

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Preface

The first edition of *Farm Animal Anesthesia: Cattle, Small Ruminants, Camelids, and Pigs* was published in 2014. Since then we have received encouraging comments from veterinarians on the usefulness and practicality of the information provided in the book. Many veterinarians complimented the ease of searching for the information needed for their daily practice: anesthetic patient care, drug dosages, and drug combinations for different circumstances and surgical procedures (Chapters 1–6 and Chapters 8 and 10). Information on the local and regional anesthetic techniques and pain management chapters provided many options to minimize perioperative and postoperative pain, and reduce patient suffering (Chapters 7 and 10). The chapter on regulatory and legal considerations of anesthetics and analgesics ensured avoidance of human consumption of drug residues in meat and milk from food-producing animals (Chapter 11). The euthanasia chapter offered clear information on different methods that a veterinarian can use to effectively and humanely end an animal's suffering when there are no available treatments that can improve an animal's deteriorating condition (Chapter 12). The contributing authors and editors are extremely proud and honored that the first edition of the book was well received by our professional colleagues, who continue to provide best patient care.

Great advances have been made in farm animal medicine and surgery in the recent years. Many farm animal species are now also kept as companion animals, particularly small ruminants and potbellied pigs. Advanced treatment options and complex surgeries have become available. The second edition of the book includes new information published since the first edition, including newer anesthetics and analgesics, surgical procedures, fluid therapy, and updates on regulations pertaining to anesthetic drugs used in farm animals. We believe farm animal veterinarians will continue to find the second edition to be a useful and practical guide for anesthetics and pain management in their daily practice. Included in this edition are videos of different local and regional anesthetic techniques to guide veterinarians to perform nerve blocks for intended surgeries safely and effectively. Also included is information on the application of neuromuscular blocking agents and the clinical use of ventilators when complicated and long duration surgery is necessary. As surgical techniques progress, the increased complexity will require that some patients are administered neuromuscular blocking agents and the knowledge of the use of these drugs and mechanical ventilators will become an essential part of anesthetic management.

The editors greatly appreciate the contributing authors, Drs. Benjamin Newcomer, Manuel Chamorro, Jessica Rush, and Jenna Workman Stockler, for their work and efforts in making this book a complete book on farm animal anesthesia. We thank the illustrators, Kim Crosslin and Katlyn King, for their picture-perfect artwork and Dr. Ray Wilhite for excellent anatomical images. We also want to thank Merryl Le Roux, Managing Editor, and her staff at John Wiley & Sons for their patience and much needed assistance throughout this process.

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About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/lin/farm



The website includes:

- Video clips

1

Preanesthetic Considerations

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General anesthesia in farm animals, like cattle, sheep, goats, llamas, alpacas, and pigs, requires special attention due to the uniqueness of the anatomical and physiological characteristics as compared to dogs, cats, and horses. Camelids (llamas and alpacas) only have two forestomachs but are otherwise similar in many ways to cattle and small ruminants. Although some farm animals may cost as much as purebred companion animals, farm animal veterinarians are often faced with economic constraints and a limited number of approved drugs for use in surgical procedures requiring anesthesia. Physical restraint and local anesthetic techniques are most commonly employed to produce immobility and analgesia for these species. Ruminants generally tolerate physical restraint and recumbency well. This, along with local and/or regional anesthetic techniques, allows many minor surgical procedures to be performed in the standing position and under field conditions. General anesthesia is more frequently performed in camelids and swine for even minor surgical procedures due to their intolerance of physical restraint. It is important to remember that farm animals perceive pain no differently than other species, therefore analgesia for prevention and easing of pain is just as important as it is for companion animals. With surgical procedures requiring general anesthesia, balanced anesthetic technique should be employed to provide narcosis, analgesia, and muscle relaxation, thereby minimizing the stress response induced by surgery and anesthesia. Most of the anesthetics and anesthetic adjuncts commonly used in farm animal practice do not have Food and Drug Administration (FDA) approval for use in ruminants, camelids, and swine [1, 2]. However, per the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994, extralabel use of drugs is permitted when animal health is threatened or death may result if not treated [3]. While prevention of violative residues should always be considered, anesthetics are usually used for a short duration, and anesthetized animals are unlikely to be marketed immediately after surgery. Furthermore, anesthetics used today tend to have very short half-lives ($t_{1/2}$), and they are potent enough that only low doses are required to produce general anesthesia. The possibility of an animal carrying anesthetic residues within its edible tissues after the surgical incision has healed, which normally occurs within an average of 14 days, is extremely low. Thus, problems with anesthetic drug residues appear to be rare [4]. Nevertheless, veterinarians should consult the Food Animal Residue Avoidance Databank (FARAD) for meat and milk withdrawal intervals for extralabel use of analgesics, sedatives, and injectable anesthetics as well as for updates of drugs prohibited from extralabel use [1, 2].

Farm Animal Anesthesia: Cattle, Small Ruminants, Camelids, and Pigs, Second Edition.

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Prior to anesthesia, an appropriate patient history, including breed, age, sex, condition, and temperament of the patient, and a complete physical examination are indicated. Due to economic reasons, blood work including complete blood count and chemistry profile is performed only in farm animals with significant systemic diseases and those considered to have a higher anesthetic risk. For example, animals with severe gastrointestinal (GI) abnormalities often suffer extreme dehydration with or without electrolyte alteration, which may require intervention to optimize the patient's condition with fluid therapy prior to the induction of anesthesia [5]. In healthy animals, total plasma protein and packed cell volume are sufficient indicators of a patient's hydration status.

Most sedatives and general anesthetics cause some degree of cardiovascular depression, which may not be a great concern for healthy patients. However, normal cardiovascular protective mechanisms or reflexes in response to the depressing effects of anesthetics may be obtunded in animals with compromised cardiac function or severe electrolyte imbalances as a consequence of disease conditions. Maintaining a balance of concentrations of electrolytes like calcium, sodium, and potassium across the cell membranes is essential in establishing normal cell membrane potential and contractility. Disturbance of these electrolyte balances across cell membranes changes cellular resting membrane potentials and subsequent initiation and propagation of cellular depolarization and repolarization. Acidosis has been shown to cause electrolyte imbalances resulting in decreased myocardial contractility and increased response of the myocardial cells to circulating catecholamines. Therefore, anesthetic-induced cardiovascular depression combined with severe preexisting acidosis and electrolyte imbalances can lead to detrimental side effects like severe cardiac arrhythmias, bradycardia, decreased myocardial and vascular cellular contractility, reduced cardiac output, and hypotension. As a result, anesthetized animals may not be able to maintain adequate cardiac output or arterial blood pressure leading to significantly decreased peripheral tissue and muscle perfusion with subsequent development of severe adverse effects such as irreversible postanesthetic neuromyopathy [6].

1.1 Positioning

Ruminants, camelids, and swine are susceptible to complications associated with anesthesia and recumbency. Positioning of these animals, particularly adult cattle, in dorsal or lateral recumbency for surgery allows for the weight of abdominal viscera to shift ventrally and cranially, causing the diaphragm to be pushed further into the thoracic cavity, thereby reducing the functional residual capacity of the lungs (Figure 1.1). As a result, an increased ventilation/perfusion

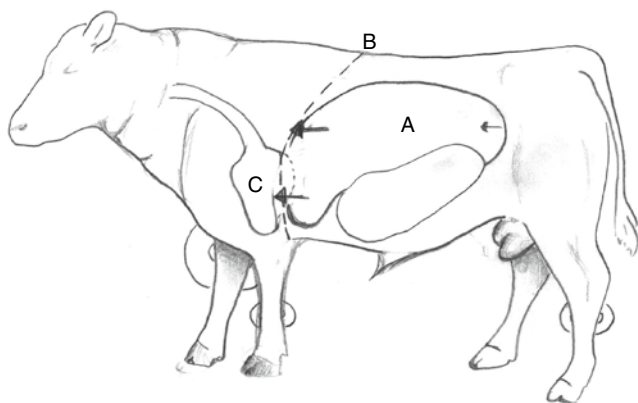


Figure 1.1 The effect of lateral recumbency on the position of the diaphragm in ruminants: A, rumen; B, diaphragm; C, lungs. *Source:* Illustration by Kim Crosslin.

mismatch may lead to significant hypoventilation and hypoxemia during anesthesia. Furthermore, the weight of the abdominal viscera may compress great vessels such as the vena cava leading to decreased venous return, cardiac output, and arterial blood pressures [7]. Therefore, close monitoring of cardiovascular and pulmonary functions and institution of appropriate treatments to ensure normal arterial blood pressure and adequate ventilation are important parts of perioperative anesthetic management.

1.2 Ruminal Tympany

Ruminal tympany, bloat, regurgitation, and aspiration pneumonia are common problems associated with general anesthesia in farm animal species that should be anticipated and addressed with proper precautions. Ruminal fermentation continues even in anesthetized animals. Postprandial gas production at an average of 30 l per hour has been reported in cattle [8]. Normal, awake animals are able to relieve the gas produced by fermentation through the eructation. Sedatives and anesthetics tend to inhibit GI motility and prohibit eructation, thus allowing gas to accumulate in the rumen. The rumen of an adult large ruminant has a capacity of 115–150 l [9]. An average capacity of 15–18 l has been reported in small ruminants [10]. Bloating, especially in nonfasted animals, can occur during anesthesia and compromise the cardiopulmonary systems by increasing intra-abdominal pressure resulting in compression of the diaphragm and great vessels such as the vena cava in the abdominal cavity, thus further complicating the already compromised cardiopulmonary function resulting from abnormal positioning required by the surgery. Fasting of these animals prior to anesthesia reduces the amount of gas produced by fermentation and minimizes its detrimental effect on the cardiopulmonary systems.

1.3 Regurgitation

Regurgitation and aspiration of stomach content can occur in farm animal species during anesthesia, especially in nonfasted animals. The risk of regurgitation decreases significantly when water is withheld for 6–12 hours and feed is withheld for 12–24 hours prior to anesthesia in small ruminants. Pigs are monogastrics. It has been indicated that alfalfa or any type of hay delays gastric emptying time, and vomiting with possible aspiration may occur during induction of anesthesia after a recommended fasting period of 12 hours. Thus, removal of alfalfa or other types of hay from their routine diet should be instituted 2–3 days prior to anesthesia [11].

Domestic ruminants have a large rumen that is usually full of liquid materials, and it does not empty completely even after 24–48 hours of fasting. Regurgitation can occur either during light (active regurgitation) or deep (passive regurgitation) anesthesia in ruminants and camelids in spite of preoperative fasting and withholding of water. Active regurgitation usually occurs during light anesthesia and is characterized by explosive discharge of large quantities of ruminal materials. Passive regurgitation occurs during deeper planes of anesthesia when the esophageal muscles and transluminal pressure gradients relax as a result of anesthetic-induced muscle relaxation. If the airway is not protected, a large amount of ruminal materials can be aspirated into the trachea and reach the small airways. Aspiration of acidic stomach fluid causes immediate reflex airway closure and destruction of type II alveolar cells and pulmonary capillary lining cells. Consequently, pulmonary edema and hemorrhage, hypoxemia, and arterial hypotension develop due to loss of alveolar and capillary integrity leading to reflex airway closure,

bronchospasm, dyspnea, hypoxemia, and cyanosis. Recovery from aspiration pneumonia depends on the pH and amount of ruminal materials aspirated [10]. Pigs tend to have very acidic stomach fluid with a pH as low as 1.5–2.5 [12], whereas the rumen pH remains within 5.5–6.5 in cattle, sheep, and goats [13] and 6.4–7.0 for C1 of camelids [14]. Thus, the greater impact of aspirating rumen contents lies in the amount of bacterial microflora and solid food materials aspirated. In pigs, the level of acidity of stomach fluid is the primary factor affecting the severity of damage to the pulmonary tissues upon aspiration. Severe consequences like reflex airway constriction, mechanical airway obstruction, and aspiration of bacteriologically active materials can still occur in the presence of a neutral pH in ruminants [10]. Animals may die before an endotracheal tube can be placed to protect the airway in extreme cases. Please refer to Chapter 7 for prevention and treatment of aspiration pneumonia. Preoperative withholding of feed and endotracheal intubation with an adequately inflated cuff immediately following induction of anesthesia are recommended in all anesthetized farm animals.

1.4 Salivation

Ruminants normally salivate profusely during anesthesia. Total amounts of saliva secretion in conscious adult cattle and sheep have been reported to be 50l and 6–16l per 24 hours, respectively [15, 16]. In the past, anticholinergics like atropine were used routinely as part of the anesthetic induction regimen in an effort to prevent salivation. However, atropine only reduces the water content of the saliva [17], thus causing the saliva to become more viscous and increasing the potential of airway obstruction, particularly in neonates. If the trachea is left unprotected during anesthesia, large amounts of saliva may be aspirated. Thus, tracheal intubation with appropriate inflation of the cuff immediately following induction should be instituted to protect the airway. For large ruminants, setting up the surgery table in a way that the head is lower and the throatlatch area is elevated relative to the mouth and thoracic inlet will help drainage and prevent pooling of the saliva and ruminal contents in the oral cavity (Figure 1.2). Placing a sandbag or rolled-up towel under the neck of a small ruminant or camelid patient to elevate the throatlatch so that the mouth opening is lower than the occiput allows saliva to escape, avoiding the potential for aspiration (Figure 1.3). This technique also helps to minimize the flow of passive regurgitation during deep anesthesia [18].



Figure 1.2 Lateral recumbency of an adult bovid; note the elevation of the throatlatch.
Source: Illustration by Kim Crosslin.

Figure 1.3 Lateral recumbency of a small ruminant; note the elevation of the throatlatch.



1.5 Malignant Hyperthermia

Malignant hyperthermia, also referred to as *porcine stress syndrome*, is a genetic disorder that occurs due to mutation of the ryanodine receptors (ryr-1 locus) of the calcium channels in the skeletal muscles [19–21]. The presence of abnormal ryanodine receptors allows a massive amount of calcium to be released from the cells into the sarcoplasmic reticulum, resulting in generalized extensive skeletal muscle contraction. Though malignant hyperthermia has been reported in other animal species, pigs and humans seem to be the most susceptible. Certain breeds of pigs, like Pietrain, Poland China, or Landrace, are very susceptible to this syndrome, while Large White, Yorkshire, and Hampshire, on the other hand, are much less so [22, 23]. The clinical signs of malignant hyperthermia syndrome in susceptible pigs are manifested in a sudden and dramatic rise in body temperature and end-tidal CO₂ followed by muscle fasciculation, muscle rigidity, tachypnea, tachycardia, arrhythmias, myoglobinuria, metabolic acidosis, renal failure, and often death. The prognosis is usually poor once the episode is initiated. The triggering agents of malignant hyperthermia include stress (e.g. excitement, transportation, or preanesthetic handling), halogenated inhalation anesthetics (e.g. halothane, isoflurane, sevoflurane, and desflurane), and depolarizing neuromuscular blocking drugs (e.g. succinylcholine). Stress associated with transportation or preslaughter conditions can trigger malignant hyperthermia/porcine stress syndrome. Pigs affected by this mutation tend to develop pale, soft, and exudative meat, which can lead to significant economic loss for the procedures [24]. Lidocaine and ketamine have been indicated as triggering agents, but there is no evidence to support this theory [25].

Halogenated inhalation anesthetics are known triggers for malignant hyperthermia, and halothane has been indicated to be the most potent trigger [26]. However, a report in humans demonstrated that in a total of 75 malignant hyperthermia cases, 42 were isoflurane related, 12 were sevoflurane related, 11 were halothane related, eight were enflurane related, and only two were desflurane related [27]. Further study showed that the augmentation of caffeine-induced contractions of frog sartorius muscle by isoflurane is three times and by enflurane is four times, whereas by halothane is 11 times [28]. Similarly, halothane appears to be the most potent and most frequently reported trigger of malignant hyperthermia in pigs. Isoflurane has been reported to trigger

malignant hyperthermia in susceptible pigs like Pietrain or Pietrain-mixed pigs [29]. Only one incidence of isoflurane-induced malignant hyperthermia has been reported in a potbellied pig [30]. Sevoflurane-induced malignant hyperthermia also has been reported in purebred Poland China pigs [31]. Episodes of malignant hyperthermia induced by desflurane have been reported in Large White, Pietrain, and Pietrain-mixed pigs [29, 32].

A case of malignant hyperthermia in cattle was reported in an isoflurane-anesthetized Angus bull [33]. At 75 minutes after induction, progressive increase of heart rate from 55 to 70 beats/minute and end-tidal CO_2 from 38 to 60 mmHg occurred and the result of arterial blood gas taken at this time showed a respiratory acidosis (pHa 7.268) with moderate increase of PaCO_2 (from 29.7 to 66.4 mmHg) and a decrease in PaO_2 (from 449 to 267 mmHg). Isoflurane was discontinued at this time, but heart rate (from 70 to 155 beats/minute) and end-tidal CO_2 (from 60 to 218 mmHg) continue to increase at 140 minutes post-induction. Body temperatures recorded from nasopharyngeal probe increased from 39.5 °C (103.1 °F) at 75 minutes and 43.5 °C (110.3 °F) at 140 minutes. Unlike malignant hyperthermia in pigs [34, 35], muscle rigidity, one of the typical clinical signs of malignant hyperthermia, was not observed in this bull. In addition, clinical signs of malignant hyperthermia in pigs developed within minutes of exposure to triggering agent, whereas progression of the clinical signs in this case did not occur until 75 minutes after initiation of isoflurane. The delay onset of clinical signs has also been observed in horses [36], dogs [37], and cats [38]. Unfortunately, the bull developed ventricular fibrillation which progressed to asystole and cardiopulmonary resuscitation was unsuccessful [33].

In 1981, McGrath et al. [39] reported that intramuscular (IM) acepromazine at 1.1 and 1.65 mg/kg reduced the incidence of malignant hyperthermia by 40% and 73%, respectively. A lower dose of 0.55 mg/kg IM was only able to delay but not prevent the onset of the episode [39]. Because of limited availability of effective drugs for treatment, minimizing the stress prior to anesthesia and avoiding using anesthetics that are known triggers are imperative in susceptible animals to prevent a malignant hyperthermia episode. In recent years, the development of a DNA test for malignant hyperthermia has enabled the accurate identification of the malignant hyperthermia mutation genotypes from carriers to noncarriers, resulting in the elimination of the malignant hyperthermia mutation from breeding stock, which is a significant economic gain for the pork industry [40–42].

1.6 Differences in Sensitivity to Anesthetics

Xylazine is a potent sedative, analgesic, and muscle relaxant that is frequently used as a preanesthetic or anesthetic adjunct in farm animal species. Cattle are more sensitive to xylazine than horses, and they require only one-tenth of the dose needed in horses to produce equipotent sedation [43]. Apparently, there are differences in the level of sensitivity to xylazine among breeds and species of these animals. It appears that Brahman are the most sensitive, Herefords intermediate, and Holsteins are the least sensitive [44, 45]. Small ruminants are more sensitive to xylazine than camelids, whereas goats tend to be more sensitive than sheep and llamas are more sensitive than alpacas. Administration of xylazine to pregnant ruminants in the final trimester may cause premature parturition and retention of fetal membranes [46, 47]. In pregnant dairy cows during late gestation, intravenous (IV) administration of xylazine (0.04 mg/kg) resulted in a significant increase in uterine vascular resistance (118–156%) and a decrease in uterine blood flow (25–59%), which were accompanied by a drastic decrease in O_2 delivery to the fetus (59%) [48]. Therefore, the use of xylazine during late gestation in pregnant ruminants is not recommended to avoid detrimental effects to the fetus. Fayed et al. [49] observed pronounced and prolonged response when xylazine was

administered to cattle under high ambient temperature. Interestingly, camelids are less sensitive to xylazine than ruminants, thus higher doses are required to produce a similar degree of sedation as in ruminants. In addition, the dose requirement is higher for alpacas than llamas. Compared to other farm animal species, pigs are the least sensitive to xylazine and other α_2 agonists. These drugs when used alone in pigs are not effective in producing adequate sedation. Vomiting has been observed following the administration of xylazine to pigs with digestive disturbances [11]. In addition to α_2 agonists, pigs are also less sensitive to the pharmacologic effects of opioids [50, 51]. Benzodiazepines, for example diazepam and midazolam, seem to produce reliable sedation in pigs even at doses that do not produce effective sedation in other species [52].

In regard to α_2 antagonists, ruminants and camelids are more sensitive to tolazoline than other species [53, 54]. When administered intravenously alone at 1.5 mg/kg to nonsedated Holstein calves, tolazoline caused coughing, increased frequency of defecation, and a mild increase in breathing effort. At higher IV doses from 2 to 10 mg/kg, adverse effects including bright red conjunctival mucous membrane, coughing, nasal discharge, profuse salivation, labored breathing, central nervous system depression, signs of abdominal pain, straining, head pressing, restlessness, and severe diarrhea were observed. However, there were no long-lasting adverse effects observed in those calves [54]. Currently, lower doses of tolazoline at 0.5–1.5 mg/kg IV are recommended for use in all ruminants, including camelids. Others have suggested that IV administration of tolazoline should be avoided, except in emergency situations, to prevent adverse effects such as cardiac asystole [55].

There are concerns from potbellied pig owners and breeders regarding the statement that “injectable anesthetics should not be used in young pigs” and that “ketamine in particular should not be used in potbellied pigs of any age” [56]. These statements have never been proven or supported by controlled, scientific studies. Furthermore, the clinical experiences of this author and of most practicing veterinarians indicate otherwise.

Ruminants recover gradually but smoothly from Telazol anesthesia as a result of the slower metabolism and longer-lasting effect of zolazepam [57, 58]. Pigs, on the other hand, often experience prolonged and stormy recovery characterized by swimming and paddling with repeated attempts to right themselves when recovering from Telazol anesthesia, similar to that observed when ketamine was used alone [52, 59]. Studies have shown that tiletamine and zolazepam are both eliminated more slowly in pigs than in other species [59] and tiletamine apparently outlasted zolazepam in pigs [57].

1.7 Preanesthetic Preparation

When possible, adult cattle should be fasted for 24–48 hours and water withheld for 24 hours before induction of anesthesia. Small ruminants, camelids, and swine should be fasted for 12–24 hours and water withheld for 8–12 hours before induction of anesthesia. Preanesthetic fasting may not completely prevent regurgitation, but it will decrease the amount of solid matter in the rumen content. Fasting also does not prevent bloating during anesthesia, but it reduces the rate of fermentation, thus reducing the amount of gas formation, the severity of bloating, and its effect on ventilation. In pigs, removal of alfalfa or other types of hay from their routine diet should be instituted 2–3 days prior to anesthesia to avoid prolonged gastric emptying time caused by this type of diet [11]. A shorter fasting period of 6–8 hours is sufficient for pigs undergoing most elective surgeries due to rapid intestinal transport times in the upper GI tract and less time required to empty the stomach [60]. Ruminants are born without a developed forestomach system and thus can be treated as monogastrics until 3 weeks of age [61]. Fasting of young ruminants less than 4 months

old is not recommended because of the potential for hypoglycemia and prolonged recovery. Fasting may not be possible under emergency situations, and precautions should be taken to avoid aspiration of gastric fluid and ingesta. Prevention of regurgitation and aspiration of ruminal content can be achieved effectively by placing the animal in sternal recumbency and endotracheal intubation instituted immediately following induction. However, some practices may induce anesthesia with adult cattle already strapped to the table and in lateral recumbency. In this case, it is even more important to ensure animals are under an adequate plane of anesthesia to prevent stimulation of active regurgitation and allow immediate intubation. Regurgitation does not occur in pigs as commonly as in ruminants. However, vomiting can result from nonfasting prior to induction of anesthesia and following administration of xylazine. In general, removal of hay or alfalfa and withholding food for 12 hours and water for 6–8 hours the night before anesthesia should be sufficient for most elective surgeries [23].

In adult cattle, a 14-gauge and 2- to 3-in. needle is placed in the jugular vein for administration of IV anesthetics for induction of anesthesia and for maintenance of fluid therapy. A 14-gauge, 5¼-in. indwelling catheter can be used if postoperative IV medication or fluid therapy is needed. Cutdown of the skin at the catheterization site may be helpful to facilitate insertion of the catheter. A 16- or 18-gauge catheter is appropriate for younger animals. The technique for IV catheterization in sheep and goats is similar to that used in calves. Venipuncture can be difficult in camelids because they have thick fiber coats and neck skin, and a less-apparent jugular groove. The jugular vein lies deep to the sternomandibularis and brachiocephalicus muscles, ventral to the cervical vertebral transverse processes, and superficial to the carotid artery and vagosympathetic trunk within the carotid sheath for most of its length [62–66]. The jugular vein of camelids is not always visible even after occlusion of the vessels, particularly in adult males. The right internal jugular vein is the best choice for catheterization in these animals. A 14- or 16-gauge indwelling catheter is appropriate for adult camelids, and an 18-gauge catheter is suitable for younger animals. Catheters should be secured with suture or bandage. Skin cut down with a #15-scalpel blade or a sharp 14-gauge needle is helpful in passing the catheter into the vein [67]. An ear vein can be an alternative site for IV injection using a 25-gauge needle or butterfly catheter to deliver a small volume of chemical restraint drugs in camelids. Also, camelids have four or five jugular valves that prevent flow of venous blood into the head when they lower the head during grazing. These valves may occlude the IV catheter and prevent backflow of the blood into the catheter, giving a false impression that the catheter may not be correctly placed in the vessel.

In swine, IV injection poses a greater challenge than in other species because pigs resist restraint and they have very few superficial veins accessible for IV injection or catheterization for administration of drugs or fluid therapy. In Vietnamese potbellied pigs, IV catheterization has been even more difficult because they have small ears with small vessels and their skin is usually dark colored. In large adult pigs with proper restraint, a central dorsal ear vein can be used for IV injection and/or catheterization. An 18- or 20-gauge, 1- to 1½-in. hypodermic needle or butterfly catheter can be used for large adult pigs. A 21- or 23-gauge butterfly catheter will be suitable for smaller-sized pigs with small ears. This author prefers a butterfly catheter because it has a shorter needle and tends to stay in the vessel better than hypodermic needles, especially when the animal struggles during injection. Shorter needles are easier to hold in place and decrease the chance of perivascular injection. IM injection of anesthetics or anesthetic combinations to pigs has been shown to produce short-term anesthesia effectively. Always keep in mind that pigs have a thick subcutaneous layer of fat, and thus, to ensure the drug is deposited into the muscle, a longer needle ($\geq 1\frac{1}{2}$ in. for large, mature pigs; 1 in. for piglets) should be used [23].

Tracheal intubation is somewhat difficult in ruminants, camelids, and pigs. Blind intubation as in horses is less likely to be successful. For large ruminants, this author's preference is to use digital palpation to guide the endotracheal tube into the trachea immediately following induction of anesthesia with the animal in either sternal or lateral recumbency (Figure 1.4a). Another technique involves use of a stomach tube as a stylet with the aid of digital palpation to place the stomach tube in the trachea; the stomach tube then serves as a guide tube (Figure 1.4b). The endotracheal tube is threaded into the trachea and the stomach tube removed once the endotracheal tube is in place. Intubation should be performed immediately after induction. In calves, intubation is easier when placing the animal in sternal recumbency and an assistant pulls the mouth open by placing a loop of gauze around the upper jaw and a second loop around the lower jaw and tongue. An assistant should lift the head and keep the head and neck in a straight line to allow visualization of the epiglottis and the larynx. If the larynx cannot be visualized, the neck should be extended further. A long laryngoscope blade (250–350 mm) can be used to suppress the tongue base and epiglottis to enable visualization of the larynx. A guide tube or stylet (preferably a 10-French, 22-in.-long polyethylene canine urethral catheter that is three times the length of the endotracheal tube) can be used (Figure 1.5). A cuffed endotracheal tube will prevent regurgitation and aspiration of ruminal contents, and the calf should be maintained in sternal recumbency until the cuff is inflated.

Figure 1.4 (a) Intubation in an adult bovid using digital palpation technique: A, trachea; B, epiglottis; C, endotracheal tube/guide tube; D, wedge. (b) Intubation in an adult bovid using a guide tube technique: A, trachea; B, epiglottis; C, guide tube; D, wedge. *Source:* Illustration by Kim Crosslin.

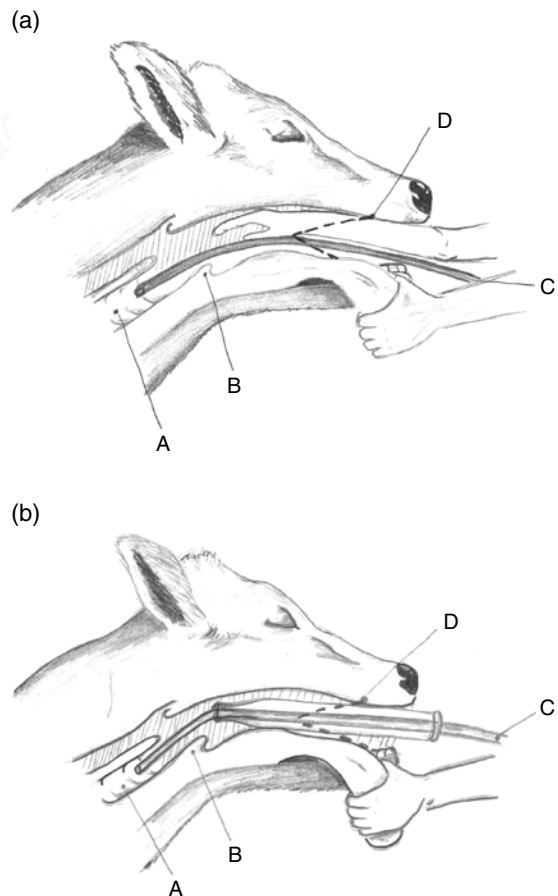




Figure 1.5 Guide tube/stylet and laryngoscope used for endotracheal intubation for small ruminants, camelids, and pigs.

Intubation is more difficult in small ruminants and camelids as compared to large ruminants and other animal species because their mouths do not open widely, the intermandibular space is narrow, and the laryngeal opening is distant to the thick base of the tongue (Figure 1.6). In camelids, the presence of glottal folds adds to the difficulty in visualizing the epiglottis. The technique used for tracheal intubation of small ruminants and camelids is similar to the technique used in calves. It is easier when the animal is placed in sternal recumbency immediately after induction of anesthesia. Intubation is best accomplished with the help of a guide tube/stylet and long-bladed laryngoscope (250–350 mm) as described for intubation in calves. Hyperextending the animal's neck helps visualization of the larynx (Figure 1.7). The method makes endotracheal intubation in small ruminants and camelids much easier to achieve than with other methods. A cuffed endotracheal tube should be used to provide an adequate seal between the tube and the tracheal mucous membrane to prevent aspiration of saliva and regurgitated ruminal contents. The animal should be maintained in sternal recumbency until the cuff is inflated. Blind intubation, similar to that used in horses, has been used for intubation in sheep and goats; however, it may require multiple attempts to successfully place the endotracheal tube in the trachea. Another technique, described as *stick intubation*, has been used effectively at Auburn University. With the animal in lateral recumbency, a small-diameter rod made of wood or stainless steel can be used as a stylet to stiffen the endotracheal tube. One hand occludes the esophagus, and the other hand manipulates the endotracheal tube into the trachea (Figure 1.8). Care and gentle maneuvering should be used to prevent initiating laryngeal spasm and to minimize trauma to the oral mucous membrane.

Similar to small ruminants and camelids, pigs' mouths cannot be opened wide, the epiglottis is often entrapped behind the soft palate, and the small larynx slopes downward, creating a sharp angle to the tracheal opening (ventral floor fornix) (Figure 1.9). Laryngeal spasms are easily elicited by repeated attempts at tracheal intubation. Vomiting can also occur if attempting intubation while the pig is under a light plane of anesthesia, especially when the animal is not appropriately fasted prior to anesthesia. Spraying a small amount of local anesthetic to desensitize the larynx will reduce the potential for laryngeal spasm. In larger or adult pigs, tracheal intubation is easier to accomplish with the pigs placed in sternal recumbency. Using the same technique as in small ruminants and camelids, with the aid of laryngoscope and guide tube/stylet, the epiglottis and laryngeal aperture can be visualized. Be aware of the sharp angle between the larynx and tracheal opening; it is helpful to apply some pressure to the end of the endotracheal tube as it enters the

Figure 1.6 Anatomic structures for endotracheal intubation in camelids.
Source: Illustration by Kim Crosslin.

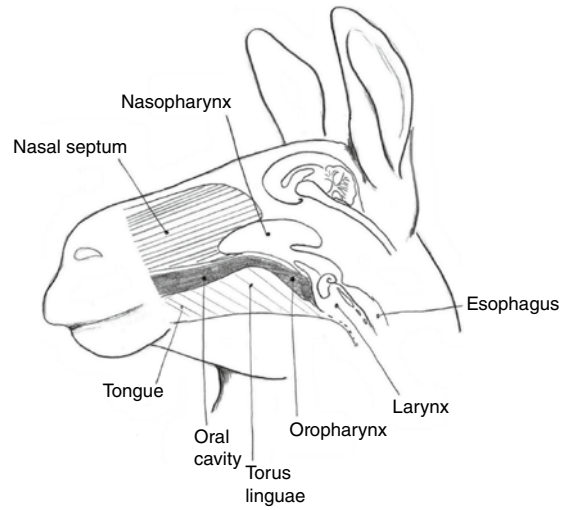


Figure 1.7 Endotracheal intubation in anesthetized goats.



Figure 1.8 “Stick intubation” (blind intubation) in anesthetized goats.



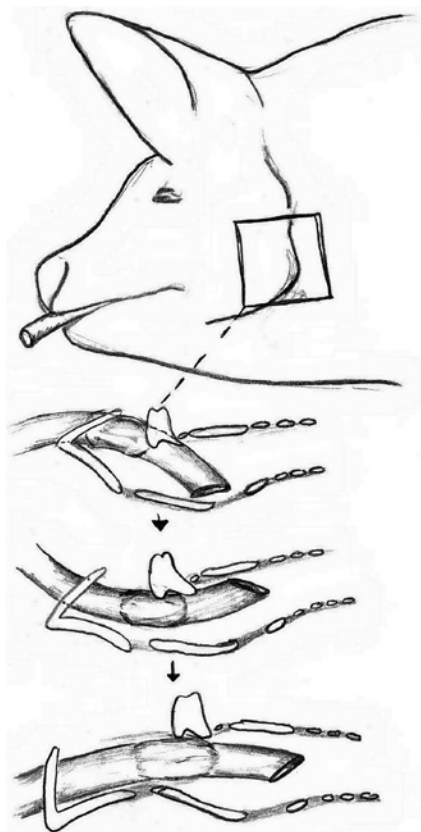


Figure 1.9 Technique for endotracheal intubation in swine. *Source:* Illustration by Kim Crosslin.

larynx. This technique keeps the tip of the tube slightly elevated and enables the endotracheal tube to pass into the trachea. Another helpful tip for successful endotracheal intubation in pigs is to spin the tube 180° or in a screwlike fashion, advancing it in a dorsal direction while the tube passes through the arytenoid cartilages into the trachea [68].

It is important to understand the anatomical and physiological differences of ruminants, camelids, and pigs as compared to other species. Veterinarians should incorporate this knowledge with proper preanesthetic preparations and appropriate perioperative management to ensure successful outcome of anesthesia in these animals.

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2

Commonly Used Preanesthetics

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Preanesthetic tranquilization or sedation is rarely necessary in ruminants, but on occasion its use may be required to calm intractable animals for the safety of the animals and also for the safety of the personnel handling the animals. The choice of whether a tranquilizer/sedative is needed for a particular animal is based on that animal's temperament and physical condition. However, a complete physical examination prior to anesthesia in large ruminants often is not feasible because some of these animals are not accustomed to being handled and restrained, particularly free-ranging animals. In addition to relocation to unfamiliar surroundings for the intended procedure, special equipment like a head catch or restraining chute that may be used for proper restraint of an intractable animal can add another level of stress to the patient. In large aggressive animals, the use of a tranquilizer/sedative will minimize the stress from forceful restraint, ease the anesthetic induction process, and decrease the dose of general anesthetic required, thus preventing the possibility of disastrous hypotension due to the use of large doses of an anesthetic. Camelids and swine are less tolerant of physical restraint; consequently, deep sedation or general anesthesia is often needed to perform even minor surgical procedures. Oral administration of a tranquilizer/sedative may be used to reduce stress associated with physical restraint in free-ranging animals under field conditions or for animals intolerant of physical restraint. Drugs used for tranquilization and sedation are also used to produce chemical restraint. In ruminants and camelids, oral medication has to pass through the rumen or rumen-like C1 compartment, respectively. Thus, the absorption and distribution of the drug will be affected by forestomach motility and the pH of the contained fluid [1]. Reticuloruminal motility is controlled by the medullary gastric center of the brain. Physical conditions affecting the patient, such as depression, pain, fear, excitement, and extreme distension of the ruminal wall (e.g. bloating), or administration of analgesics like opioids, α_2 agonists, or anesthetics (e.g. thiopental and propofol) have been reported to decrease gastric motility resulting in prolonged gastric emptying time and increased absorption of a drug [1].

The difference in pH between saliva (8.2), plasma (7.4), and ruminal content (5.5–6.5) also affects the absorption and distribution of the drug by its effect on the degree of ionization of the drug. Nonionized drugs have higher lipid solubility and easily diffuse across cell membranes, whereas ionized drugs have lower lipid solubility and are therefore less capable of diffusion across cell membranes. Weak acidic drugs ionize and accumulate in the alkalized saliva and thus allow the delivery of large quantities of the drug into the rumen with the flow of saliva. Once in the more

acidic environment of the rumen, ionized drugs become nonionized and diffuse across the rumen membrane into the local blood circulation. On the contrary, drugs that are weak bases become ionized and accumulate in the rumen. The degree of ionization and the diffusion of the drug between saliva, ruminal content, and plasma is constantly changing, which increases the difficulty in predicting the bioavailability, distribution, and calming effect of an orally administered tranquilizer/sedative [1]. Drugs administered intramuscularly or intravenously usually produce more predictable and reliable calming effects in ruminants and camelids, and are the preferred routes for administering a tranquilizer/sedative when possible. For monogastric animals like pigs, the pH in the stomach is acidic (1.5–2.5) [2], therefore orally administered acidic drugs will present with a greater percentage in nonionized form and thus better and faster absorption from the stomach and greater bioavailability of the drug. Basic drugs tend to have lower bioavailability due to a higher degree of ionization of the drugs in the stomach.

2.1 Acepromazine (Phenothiazine Derivatives)

2.1.1 Cattle

Acepromazine produces mild tranquilization without analgesia in animal species. It produces a calming effect by blocking dopaminergic receptors at the basal ganglia in the brain [3]. The drug has minimal effects on heart rate and respiratory function. Direct depression on myocardial contractility and a decrease in cardiac output with subsequent hypotension often observed with the administration of acepromazine are the result of its effect on blocking α_1 adrenoceptors located at the myocardium [4, 5]. In addition to a calming effect, acepromazine produces beneficial effects such as antiarrhythmic and antiemetic effects. Acepromazine may cause relaxation of the esophagus and cardia, which increases the risk of regurgitation in ruminants [6, 7]. Thus, special measures to protect the airway should be taken if the animal is to be placed in lateral or dorsal recumbency during the procedure. Use of the coccygeal vein for intravenous (IV) injection should be avoided when administering acepromazine because of its close proximity to the coccygeal artery [3]. Prolapse of the penis with potential subsequent trauma following the administration of acepromazine as reported in horses may occur in ruminants as well. The IV and intramuscular (IM) doses of acepromazine recommended for ruminants are 0.01–0.02 and 0.03–0.1 mg/kg, respectively [8]. The duration of tranquilization of acepromazine is usually 2–4 hours when administered at recommended dosages, but effects of 4–8 hours have been reported [9]. The use of acepromazine is contraindicated in debilitated or hypovolemic animals due to its hypotensive effect [3]. In addition, acepromazine depresses the thermoregulatory center, resulting in significant hypothermia and prolonged recovery in anesthetized newborns and neonatal animals. Acepromazine (0.03 mg/kg IM) has been administered occasionally to calm fractious bulls prior to induction of anesthesia with IV xylazine and ketamine.

2.1.2 Small Ruminants and Camelids

Acepromazine, though rarely used in small ruminants, can be administered at 0.05–0.1 mg/kg to produce mild tranquilization [10]. The drug has been used as an alternative for xylazine in goats with urethral obstruction where increased urine output associated with α_2 agonists is contraindicated. Doses from 0.05 to 0.2 mg/kg can be administered IM or IV to produce tranquilization in sheep and goats [11]. In camelids, 0.033 mg/kg has been used to produce some calming effect in a female guanaco for eye examination [12]. However, a dose of up to 0.15 mg/kg was needed to quiet an aggressive male llama prior to induction of anesthesia with halothane [13].

2.1.3 Swine

Acepromazine is not an effective tranquilizer in pigs, for though tranquilized, they can still resist and fight the imposing restraint viciously. The doses of acepromazine recommended for pigs are 0.11–0.44 mg/kg IV or IM with a maximum total dose of 15 mg [8]. Large doses of acepromazine have been administered in addition to local anesthesia to sows undergoing cesarean section surgery, resulting in severe hypotensive shock. Several sows did not recover following the surgery [14]. IM doses of 0.05–0.5 mg/kg have been given to Vietnamese potbellied pigs with an unreliable calming effect even with high doses [15]. Acepromazine is frequently used in combination with ketamine or Telazol (tiletamine/zolazepam) to produce excellent sedation and muscle relaxation [16]. In pigs susceptible to malignant hyperthermia, acepromazine at 1.1 and 1.65 mg/kg IM has been reported to reduce the incidence of malignant hyperthermia by 40% and 73%, respectively. A lower dose of 0.55 mg/kg IM only delayed but did not prevent the onset of the episode [17].

2.2 Droperidol and Azaperone (Butyrophenone Derivatives)

Butyrophenone derivatives like droperidol and azaperone have pharmacological effects very similar to acepromazine (phenothiazine derivatives). Droperidol alone has been administered to pigs at 0.3 mg/kg IM to produce sedation for 2 hours [18]. However, droperidol is seldom administered alone to animals; it is manufactured as a proprietary combination of droperidol (20 mg/ml) and fentanyl (0.4 mg/ml) and marketed as Innovar-Vet for veterinary use. Innovar-Vet is a neuroleptanalgesic combination which consists of a tranquilizer (droperidol) and an analgesic (fentanyl). The combination of two drugs not only potentiates the central nervous system (CNS)-depressing effect and the analgesic effect of each drug but also reduces the dose requirement for each drug, which decreases the side effects of each drug. Innovar-Vet is often used to calm intractable or vicious animals but is rarely used in ruminants. When given at 0.19, 0.25, or 0.3 ml/kg to sheep, Innovar-Vet was reported to produce adequate analgesia and smooth induction and recovery [19]. Innovar-Vet had been shown to produce satisfactory calming effect in pigs (1 ml/12–25 kg [26.4–55 lb] IM). However, pigs often sneezed and became more excited if stimulated while under the influence of Innovar-Vet [20]. Variable responses ranging from light sedation to pronounced relaxation and analgesia have been reported when 1 ml/10 kg (22 lb) of Innovar-Vet was administered to young pigs [21]. Better and more reliable sedation was observed when xylazine was administered with Innovar-Vet [14]. When administered to miniature pigs, Innovar-Vet induced CNS stimulation rather than sedation [22]. Contrary to the previous report, Piermattei and Swan [23] showed that 1 ml/14 kg (30.8 lb) of Innovar-Vet IM produced good sedation prior to halothane anesthesia.

Azaperone, another butyrophenone derivative, has pharmacologic effects similar to acepromazine and droperidol. Hughes et al. [24] compared the effects of azaperone and acepromazine in free-ranging sheep. At 1 mg/kg, azaperone produced a calming effect and reduced the stress response as evidenced by calmer behavior and a greater comfort level of the animals studied. In this study, azaperone appeared to be more effective in reducing the stress response than acepromazine [24]. Madsen et al. [25] observed greater disorientation for a longer duration with azaperone. Interestingly, sheep tended to disperse with acepromazine but they tended to congregate with azaperone.

In pigs, azaperone has been shown to be the most effective tranquilizer. Azaperone has been used for the prevention of aggressiveness and savaging of newborn pigs by sows, for the treatment of stress, and for the completion of minor surgical procedures. At 2.2 mg/kg IM, azaperone was effective in reducing fighting following intermingling [26]. Approximately 20 minutes of deep

sedation sufficient for minor surgeries was produced by 4–8 mg/kg of azaperone IM. Excessive salivation during deep sedation has been observed [26–31]. Practitioners should keep in mind that tranquilizers like acepromazine, droperidol, azaperone, diazepam, and midazolam do not possess analgesic effect. Therefore, a tranquilizer may render the animal unresponsive to painful manipulations, but the physiological stress response resulting from painful stimulations still exists. Similar to acepromazine, azaperone is effective in preventing malignant hyperthermia episodes due to halothane in susceptible pigs. Doses of 0.5–2.0 mg/kg IM azaperone offered 100% protection against malignant hyperthermia in susceptible Pietrain pigs [32].

2.3 Detomidine, Dexmedetomidine, Medetomidine, Romifidine, and Xylazine (α_2 Agonists)

The α_2 agonists (e.g. xylazine, detomidine, medetomidine, dexmedetomidine, and romifidine) are classified as sedatives/analgesics. In addition to effective sedation, these drugs produce profound analgesia and good central muscle relaxation. The α_2 agonists produce their pharmacologic effects by their actions on both the central and peripheral α_2 adrenoceptors. Stimulation of central (presynaptic) α_2 adrenoceptors inhibits the release of catecholamines, thus reducing the response to excitatory input, and as a result sedation occurs. Peripheral (postsynaptic) α_2 receptors are found in the vasculature, pancreatic islet cells, and uterine muscles. As a result, transient hypertension, hypoinsulinemia, hyperglycemia, and oxytocin-like effect are often associated with the administration of an α_2 agonist [33]. Other side effects associated with the administration of α_2 agonists include direct myocardial depression and augmentation of parasympathetic stimulation resulting in a decrease in cardiac output, bradycardia, and hypotension. Up to a sixfold increase in urine output subsequent to a decrease in secretion of antidiuretic hormone is a common side effect of α_2 agonists. The central muscle-relaxing effect produced by α_2 agonists is believed to be mediated through the inhibition of nerve impulse transmission at the internuncial neurons of the spinal cord, brain stem, and subcortical level of the brain [34]. Because of this, α_2 agonists are often given in combination with anesthetics that do not provide adequate muscle relaxation for surgical procedures. For example, when ketamine is administered alone, it is often associated with muscle tremors, jerking activity, and rigidity; xylazine is administered concurrently to improve the muscle relaxation during ketamine anesthesia. All α_2 agonists, though considered as pure α_2 agonists, also have affinity for α_1 receptors. The $\alpha_2 : \alpha_1$ selectivity ratios for xylazine, detomidine, romifidine, and medetomidine/dexmedetomidine are 160 : 1, 260 : 1, 340 : 1, and 1620 : 1, respectively [35, 36].

2.3.1 Cattle

2.3.1.1 Xylazine

Xylazine is the most popular sedative in large animal practice today. Cattle are much more sensitive to xylazine than horses and require only one-tenth of the dose needed for horses to produce the same degree of sedation [33]. The degree of sensitivity to xylazine varies within breeds, and Brahman appear to be the most sensitive, Herefords intermediate, and Holsteins are the least sensitive [37]. Xylazine produces potent sedation, profound analgesia, and good muscle relaxation. It is frequently used for chemical restraint or anesthetic adjunct in ruminants. Xylazine alone produces dose-dependent CNS depression from standing sedation (0.015–0.025 mg/kg IV or IM) [21, 38] to recumbency and immobilization (0.1 mg/kg IV or 0.2 mg/kg IM) [39]. Administration of xylazine to ruminants in the final trimester of pregnancy may cause premature parturition and

retention of fetal membranes [40, 41]. In pregnant dairy cows during late gestation, administration of xylazine (0.04 mg/kg IV) resulted in a significant increase in uterine vascular resistance (118–156%) and a decrease in uterine blood flow (25–59%) accompanied by a drastic decrease in fetal O₂ delivery (59%) [42]. Due to these detrimental effects on the fetus, the use of xylazine during late gestation in pregnant cows is not recommended. Fayed et al. [43] observed pronounced and prolonged drug effects when xylazine was administered to cattle under high ambient temperature. Xylazine should be used with extreme caution in animals with preexisting cardiopulmonary disease or urinary tract obstruction due to its adverse effects on the myocardium and urine output [33]. Higher dose of xylazine (single average dose, 0.55 ± 0.18 mg/kg) delivered by tranquilizer gun has been used to produce complete immobilization to capture free-ranging cattle [44]. Xylazine is often used with butorphanol to produce neuroleptanalgesia. Enhanced sedation and analgesia develop when these two drugs are administered concurrently. Administration of high doses of butorphanol alone to nonpainful cattle may induce slight CNS stimulation and behavioral changes. Thus, when used in combination with xylazine, it is recommended the dose of butorphanol be maintained below 0.05 mg/kg to avoid butorphanol-induced CNS excitation offsetting the sedative effect of xylazine [45]. Detailed discussion of chemical restraint techniques using xylazine combinations is described in Chapter 3.

Epidural administration of xylazine to standing cattle produced effective perineal analgesia for 2.5–4 hours. Compared to epidural lidocaine, xylazine produced less disruption of hind limb motor function and provides a longer duration of perineal analgesia [46, 47]. Systemic effects like mild to moderate sedation and slight ataxia sometimes occur following caudal epidural administration of xylazine, which is a result of absorption of the drug into blood circulation from the injection site and/or diffusion of the drug into cerebrospinal fluid (CSF) with subsequent cranial migration of the drug into the CNS. Similarly, studies in humans [48] and dogs [49] showed that diffusion of epidurally administered morphine into the CSF and the subsequent migration of the drug up the spinal cord, rather than the total injected drug volume, were the primary factors responsible for the widespread analgesia of epidural morphine. IV administration of an α_2 antagonist such as tolazoline reversed the systemic effects (sedation and ataxia) but did not affect the caudal epidural analgesia of xylazine [50]. It is believed that the epidural analgesia of xylazine is the result of the binding of xylazine to the α_2 adrenoceptors located in the dorsal horn of the spinal cord, not the effect of xylazine on the central α_2 adrenoceptors in the CNS [51, 52]. Therefore, IV or IM administration of an α_2 antagonist does not affect the binding of an α_2 agonist to the receptors in the epidural space due to low concentration of the α_2 antagonist in the epidural space.

2.3.1.2 Detomidine

Detomidine has pharmacologic effects that are very similar to those of xylazine. Interestingly, ruminants appear to be less sensitive to detomidine than they are to xylazine. The dose of detomidine required to produce standing sedation is similar to the dose required for horses. When administered at 0.05 mg/kg IV or IM to adult cattle, detomidine produced effective sedation, though the analgesic effect appeared to be more intense when the drug was administered intravenously [53]. Standing sedation of 30–60 minutes was evident with 0.025–0.01 mg/kg IV of detomidine [38, 54, 55]. Unlike xylazine, detomidine does not produce an oxytocin-like effect on the uterus in gravid cattle at IV doses less than 0.04 mg/kg. However, doses greater than 0.04 mg/kg were observed to cause increased electrical activity of the uterine muscle without inducing synchronizing burst potentials characteristics of parturition [56, 57]. This indicates that detomidine is less likely to induce premature parturition in pregnant ruminants at recommended doses and this may make it safer for use in pregnant ruminants. Slight sedation without analgesic effect was observed when

0.01 mg/kg of IM detomidine was given to Lanka buffaloes. Moderate sedation with analgesia was observed at 0.02 mg/kg, while deep sedation with excellent analgesia occurred with 0.04 mg/kg. However, 50% of the animals receiving 0.04 mg/kg became recumbent. When increasing the dose to 0.08 mg/kg, detomidine induced recumbency and complete immobilization in these buffaloes. The author of the study concluded that 0.02 and 0.04 mg/kg of detomidine induced adequate sedation and analgesia that suffices most clinical and practical purposes [58]. At higher doses (0.08–0.1 mg/kg IM), detomidine induced complete immobilization and excellent muscle relaxation, but regurgitation and subsequent aspiration pneumonia could be a risk if the animal's airway is not protected [58, 59]. In dairy cattle, IV detomidine alone (0.1 mg/kg) induced moderate sedation with significant decreased heart rate and respiratory rate for 39–55 minutes. Similar to xylazine and butorphanol administered to Holstein cows as mentioned previously, CNS excitation produced by butorphanol (0.05 mg/kg IV) seemed to offset the sedative effect of detomidine (0.1 mg/kg IV) when the two drugs were administered concurrently [45].

Caudal epidural administration of detomidine (0.04 mg/kg) induced perineal analgesia within 5 minutes following administration and lasted for 175 minutes [60]. In horses, caudal epidural detomidine has a slightly faster onset and shorter duration of perineal analgesia than xylazine, 12.5 ± 2.7 and 160 ± 8 minutes versus 13.1 ± 3.7 and greater than 165–180 minutes, respectively [61].

Recently, sublingual detomidine gel with a concentration of 7.6 mg/ml in a 3-ml syringe is available for horses to be used in the field or on the farm. When administered sublingually to horses, the oral bioavailability was 22% and the peak plasma concentration was approximately 40% that of the plasma concentration following IM administration. A mild to moderate degree of sedation occurred within 30–40 minutes and lasted 90–180 minutes [62, 63]. Minor procedures like grooming or examination can be accomplished with this application [64]. The pharmacokinetic results from blood and urine samples in horses suggested a 48-hour and 3-day withdrawal time of detomidine should be sufficient [63, 65]. In calves undergoing disbudding, the efficacy of sublingual administration of detomidine (0.08 mg/kg) was compared to IV detomidine (0.03 mg/kg). The bioavailability of detomidine was 34% with time to maximum plasma concentration at 66.0 ± 36.9 minutes. Maximal sedation occurred at 40 minutes following sublingual application as compared to 10 minutes following IV administration. Heart rate decreased in both groups. All calves were adequately sedated and offered little resistance for injection of local anesthetic prior to disbudding [66].

When administered at 0.08 mg/kg IV or IM to six cows, the concentration of detomidine measured in milk was below 0.4 ng/g at 11 hours, and no detectable concentration was measured at 23 hours post administration. Drug residue was detected in the liver of three cows (0.3–3.9 $\mu\text{g/kg}$ tissue weight) and in the lung (2.3 $\mu\text{g/kg}$), kidney (0.3 $\mu\text{g/kg}$), and muscle of the injection site (0.5 $\mu\text{g/kg}$) of one cow, respectively. Only minute concentrations of 0.4 and 2.5 ng/g in the lungs and 0.7 and 0.8 ng/g in the muscle sample from the injection site were detected in two cows at 48 hours post administration [67]. These residual concentrations of detomidine in different tissues would affect the withdrawal time in food-producing animals.

2.3.1.3 Medetomidine

IV administration of medetomidine (0.005 mg/kg) to domestic ruminants produced a short duration of standing sedation with minimal analgesia [54]. However, IM administration of 0.03 mg/kg in domestic calves resulted in lateral recumbency with analgesia lasting for 60–75 minutes [68]. Higher doses of medetomidine (0.04 mg/kg in heifers, 0.08 mg/kg in cows) delivered by tranquilizer gun have been used successfully to produce immobilization for the capture of free-ranging cattle. In both studies, atipamezole was used effectively to reverse medetomidine's effect [69, 70]. In one study, two cows were in the last month of pregnancy and both calved normally at full

term [70]. Caudal epidural injection of medetomidine (0.015 mg/kg) has been reported to induce rapid onset of perineal analgesia, similar to that of lidocaine, but with a significantly longer duration (4–9.5 hours). Moderate sedation and ataxia were observed in these cows. Two cows became recumbent at 20 and 40 minutes following drug administration, but both were easily coaxed to stand. It was believed that the recumbency in these two cows was caused by the nature of the ruminants during deep sedation and was not the result of motor nerve function disruption due to caudal epidural medetomidine [71].

2.3.1.4 Romifidine

When administered at 0.02 mg/kg IM to cattle, romifidine produced deep sedation with recumbency at 14.8 ± 3.4 minutes after injection. The duration of immobilization was 45.2 ± 3.4 minutes, and standing recovery occurred at 78.7 ± 17.7 minutes. The degree of analgesia produced by romifidine at this dose was similar to that produced by 0.2 mg/kg of IM xylazine. Similar to other α_2 agonists, romifidine caused bradycardia, and the heart rate was significantly lower with romifidine. Other side effects of romifidine observed included bradypnea, decreased hematocrit, and ruminal tympany [72]. Romifidine (0.05 mg/kg) and morphine (0.1 mg/kg) have been combined and diluted in saline to a total volume of 30 ml and administered through a caudal epidural to Holstein–Friesian cows. Significant perineal analgesia with moderate sedation lasted 6 hours, but on occasion analgesia lasted up to 12 hours. Cows in this study tended to sit down and assume a recumbent position. The authors were not clear whether the recumbency was due to the deep sedation and ataxia from systemic absorption of romifidine and morphine into the blood circulation or the natural instinct of the cattle to sit down during sedation. One cow developed hind limb paresis and became recumbent 24 hours after drug administration. The cow showed no improvement 72 hours later and was humanely euthanized. Postmortem examination did not reveal any pathological changes like necrosis, inflammation, or degenerative lesions in the spinal cord to explain the hind limb paresis. However, the cow did have severe muscle necrosis of the adductor muscles, mild hepatic lipidosis, and moderate acute abomasal ulceration [73].

2.3.2 Small Ruminants and Camelids

2.3.2.1 Xylazine

Similar to cattle, small ruminants (e.g. sheep and goats) are very sensitive to xylazine, and goats are more sensitive than sheep [6]. Camelids (e.g. alpacas, llamas), though more sensitive to xylazine than horses, are not as sensitive as cattle and small ruminants. Therefore, the dose of xylazine required to produce a similar degree of sedation in goats is equal to or slightly less than that of cattle, whereas a slightly higher dose is required in camelids than in cattle and small ruminants. Compared to llamas, alpacas require dosages 10–15% higher than the recommended dose for llamas. Xylazine alone produces dose-dependent CNS depression ranging from standing sedation to recumbency and immobilization in small ruminants and camelids. Extreme caution should be practiced when xylazine is used in animals with preexisting cardiopulmonary disease and urinary tract obstruction or in late pregnancy [33, 40, 74]. Severe hypoxemia and pulmonary edema have been implicated as the cause of death in sheep under xylazine sedation/anesthesia [75–78]. Lateral recumbency in conscious sheep has been reported to induce a significant decrease in PaO_2 [79]. Xylazine has been reported to cause hypoxemia in xylazine-sedated standing sheep [80, 81]. Apparently, all α_2 agonists cause similar and significant decrease in PaO_2 in sheep without affecting the PaCO_2 [82]. Nolan et al. (1986) [83] demonstrated that xylazine-induced increased airway pressure (from 13.7 to 35 mmHg) in sheep was a result of dose-dependent stimulation of peripheral (postsynaptic) α_2 adrenoceptors located in the

airway smooth muscles (0.002–0.02 mg/kg). The effect of xylazine on the airway smooth muscles occurred within 5 minutes following IV administration and lasted longer than 60 minutes, long after the measured cardiovascular variables had returned to baseline values [83]. Furthermore, severe pulmonary parenchymal damage was seen with substantial morphological changes, such as extensive damages to capillary endothelium and alveolar type I cells, intra-alveolar hemorrhage, and interstitial and alveolar edema. Such changes occurred almost immediately following IV administration of 0.15 mg/kg of xylazine [84]. Bronchospasm and venospasm due to direct action of α_2 adrenoceptors on the vascular and bronchial smooth muscles, transient α_2 -induced platelet aggregation with pulmonary microembolism, and release of cytokines and other inflammatory mediators subsequent to α_2 -induced pulmonary intravascular macrophage activation have been suggested as the contributing factors for the development of hypoxemia in sheep [85].

Caudal epidural administration of xylazine (0.07–0.1 mg/kg), with or without lidocaine, induced long-lasting somatic analgesia for open castration in rams (8 hours, without lidocaine) and correction of vaginal prolapse in ewes (24 hours, with 0.5 mg/kg of lidocaine) [86, 87]. However, visceral analgesia induced by epidural xylazine alone may not be sufficient for ligation of the spermatic cord [86].

2.3.2.2 Detomidine

At 0.02 mg/kg IV, detomidine produced sedation which is comparable to that of 0.04 mg/kg of xylazine [88]. Increasing the dose to 0.03 mg/kg, detomidine induced recumbency in sheep with sedation that was equivalent to 0.15 mg/kg of xylazine and 0.01 mg/kg of medetomidine [89]. Effective sedation and significant but transient hypotension and bradycardia followed by tachycardia and hypoxemia were reported during sedation with 0.091 ± 0.004 mg/kg of IV detomidine. Cardiac arrhythmias (e.g. atrioventricular block, ST elevation, and premature ventricular contraction) were also observed in this study [90]. Deep sedation with hypotension of 108 ± 9.1 minutes occurred when detomidine (0.092 ± 0.006 mg/kg IV) was combined with diazepam (0.7 ± 0.2 mg/kg IV). Cardiac arrhythmias, but not hypoxemia or hypercapnia, were observed when diazepam was administered with detomidine [91]. Obviously, hypoxemia and pulmonary edema can occur with any of the α_2 agonists, but the severity of hypoxemia was reported to be less with detomidine [85]. IV administration of α_2 agonists normally induces a characteristic biphasic blood pressure response characterized by transient hypertension followed by longer-lasting hypotension. The initial hypertension is the result of vasoconstriction from stimulation of peripheral (postsynaptic) α_2 adrenoceptors, and the subsequent hypotension is due to activation of central (presynaptic) α_2 adrenoceptors resulting in decreased sympathetic outflow and catecholamine release [33]. Celly et al. [82] reported a longer-lasting hypertension was observed following IV administration of detomidine (0.03 mg/kg). Interestingly, in that study, mean arterial blood pressure showed the characteristic biphasic patterns for all four α_2 agonists (xylazine, detomidine, medetomidine, and romifidine), but all the values were within or above normal values. In other words, hypotension, defined as below-normal arterial blood pressure values, was not observed with any of the α_2 agonists in this study [82]. Unlike xylazine, detomidine at IV doses less than 0.04 mg/kg did not produce an oxytocin-like effect on the uterus in gravid cattle. Doses higher than 0.04 mg/kg may increase the electrical activity of the uterine muscles, but it did not induce the synchronization of the bursts of potentials that is characteristic of parturition. Therefore, detomidine at the therapeutic dose is unlikely to induce premature parturition in pregnant ruminants [56, 57].

The sedative effects of detomidine gel applied intravaginally (0.2 mg/kg) has been studied in alpacas. The onset, the time to maximal sedation, and the duration of sedation were 13.0 ± 2.5 , 25 ± 4 , and 65 ± 12 minutes, respectively. Four of six alpacas assumed sternal recumbency position during sedation. The result of this study showed that intravaginal detomidine produced moderate sedation which was not as profound as that of IV detomidine [92].

2.3.2.3 Medetomidine

Medetomidine induced dose-dependent sedation and analgesia in sheep at doses of 0.001–0.007 mg/kg IV, with the level of analgesia produced by 0.005 mg/kg comparable to that of 0.015 mg/kg of fentanyl [93]. At 0.04 mg/kg IM, medetomidine induced 30–45 minutes of good analgesia and marked muscle relaxation and 58 minutes of recumbency. Full recovery usually occurred within 1½–2 hours after regaining the righting reflex [94]. When used as a preanesthetic administered 30 minutes prior to induction with propofol and maintenance with isoflurane, medetomidine (0.005 or 0.01 mg/kg IM) decreased heart rate and respiratory rate. Mean arterial blood pressure values were significantly higher following a high dose (0.01 mg/kg IM) as compared to those without preanesthetic medetomidine or those administered at a lower dose (0.005 mg/kg IM). In general, the administration of medetomidine reduced the dose requirement of propofol for induction and isoflurane for maintenance of anesthesia during surgery [95]. In sheep breathing room air that are anesthetized with medetomidine (0.02 mg/kg IV) and ketamine (2 mg/kg IV), PaO₂, arterial pH, and arterial O₂ saturation (SaO₂) decreased and PaCO₂ increased significantly. Supplementation of 100% O₂ improved PaO₂ and SaO₂ [96]. Similar to all other α_2 agonist drugs, medetomidine (0.01 mg/kg IV) caused characteristic hypoxemia in sheep breathing room air during sedation [82].

When given to produce lumbosacral analgesia in goats, medetomidine at doses of 0.01, 0.02, and 0.03 mg/kg diluted in sterile water to a total volume of 5 ml produced satisfactory analgesia in the perineum and flank regions, and the analgesia extended to the thorax, forelimbs, neck, and head for a period of at least 3 hours. Ten goats receiving 0.02 mg/kg underwent laparotomy surgery; adequate analgesia was apparent in all tissue layers (from skin to external and internal oblique muscles and transverse muscles). All 10 goats recovered uneventfully from surgery. Lateral recumbency and characteristic side effects of other α_2 agonists were observed during the study, particularly with higher doses (0.02 and 0.03 mg/kg). One goat receiving 0.01 mg/kg was paralyzed following lumbosacral injection and was humanely euthanized. Because of the caudal extension of the spinal cord into the cauda equina in goats, it was speculated that the trauma to the conus medullaris and/or cauda equina resulting from struggling of the animal at the time of spinal needle insertion was responsible for the paralysis observed in this goat [97].

IM administration of medetomidine (0.01–0.03 mg/kg IM) has also been used in llamas. Sternal recumbency (5.3 ± 4.7 minutes) and mild to moderate sedation (37.3 ± 9.5 minutes) without analgesia were observed in two of three llamas receiving 0.01 mg/kg of the drug. All llamas receiving 0.02 mg/kg assumed sternal recumbency but with only slightly more profound sedation (58 ± 12.1 minutes) and analgesia (30 minutes) than that of 0.01 mg/kg. When the dose was increased to 0.03 mg/kg, medetomidine induced immobilization (91.5 ± 24.7 minutes) with profound analgesia (61.7 ± 2.9 minutes) and muscle relaxation. The only side effect observed during the period of immobilization was a significant decrease in heart rate. Atipamezole (0.125 mg/kg IM) effectively reversed the effect of medetomidine (0.03 mg/kg IM), and standing recovery occurred within 5.8 ± 3.3 minutes [98].

2.3.2.4 Romifidine

In foals, romifidine was reported to produce sedation and analgesia with greater intensity and longer duration than xylazine [99]. Celly et al. [82] reported that romifidine at 0.05 mg/kg IV produced a similar degree of hypoxemia but a significantly longer duration of initial hypertension than other α_2 agonists. When xylazine (0.15 mg/kg IV), detomidine (0.03 mg/kg IV), romifidine (0.05 mg/kg IV), and medetomidine (0.01 mg/kg IV) were administered to sheep at quasiequipotent doses, similar decreases in PaO₂ and increases in respiratory rate and maximum changes in transpulmonary pressure (ΔP_{pl}) were observed with all four drugs except the duration of increase in respiratory rate, and ΔP_{pl} were longest with romifidine [82].

When romifidine (0.05 mg/kg) was administered by lumbosacral epidural injection, it produced moderate to complete analgesia of the perineum, flank, and abdominal regions. Increasing the dose to 0.075 mg/kg did not enhance the degree of analgesia but only prolonged the duration. Khattri et al. [100] indicated that higher doses of romifidine (0.075 mg/kg) produced a wider region of analgesia from the tail regions to the thorax. This may be the result of a higher concentration of the injected drug solution with 0.075 mg/kg than 0.05 mg/kg since the total volume of the injected solution was maintained at the same 4 ml for both dosages in this study. Side effects resulting from spinally administered romifidine included dose-dependent ataxia and decreased heart rate, respiratory rate, and mean arterial blood pressures [100].

In camels, the sedative and analgesic effects of romifidine were assessed at three different doses (0.04, 0.08, and 0.12 mg/kg IV). Both the sedative and analgesic effects were dose dependent with the duration of sedation (37, 51, and 65 minutes, respectively) lasting longer than the analgesic effect (21, 34, and 46 minutes, respectively). Bradycardia, ruminal tympany, increased urine output, and hyperglycemia are commonly observed side effects during romifidine sedation. Camels may not represent domestic camelids like llamas and alpacas, and they have been reported to require higher doses of xylazine to produce a similar degree of sedation. Thus, llamas and alpacas may require a lower dose of romifidine to produce desirable sedation and analgesia [101].

2.3.3 Swine

2.3.3.1 Xylazine

Compared to other domestic species, pigs are the least sensitive to xylazine. A higher dose (1.65 mg/kg IV, 2.2 mg/kg IM) is required to produce mild to moderate sedation, but still the pigs are easily aroused and able to flee when approached [8, 14]. Vomiting and bloating have been observed in pigs that were not fasted prior to anesthesia [16, 21]. When tested at doses of 1, 2, 4, 8, and 16 mg/kg IV in young pigs, xylazine alone did not produce effective sedation and analgesia. Xylazine induced a significant decrease in mean arterial blood pressure, but it gradually returned to baseline values 10 minutes after administration [102].

2.3.3.2 Detomidine

In pigs, doses of detomidine at 0.04 mg/kg IV or 0.08 mg/kg IM have been used in combination with ketamine to produce short-term anesthesia [103]. Analgesia following lumbosacral epidural administration of detomidine was not as profound as xylazine in pigs [104]. In addition, detomidine- or xylazine-induced epidural analgesia may be mediated through a different mechanism of action in that IV administration of an antagonist was capable of antagonizing epidural detomidine-induced sedation, analgesia, and immobilization but was only able to antagonize the sedation induced by epidural xylazine but not the analgesia and immobilization [104]. This observation is supported by reports in horses and cattle [105–107]. Perhaps the difference of response to the IV administration of an antagonist lies in the fact that xylazine itself has local anesthetic effect and detomidine does not [108].

2.3.3.3 Medetomidine

In pigs, medetomidine at IM doses of 0.03–0.08 mg/kg induced dose-dependent sedation and muscle relaxation. Increasing the dose to greater than 0.1 mg/kg did not increase the degree of sedation or muscle relaxation but did prolong the duration of activity. Compared to 2 mg/kg of xylazine, enhanced sedation, better muscle relaxation, and greater analgesia were observed with 0.03 mg/kg of medetomidine [109]. Medetomidine has been used in combination with butorphanol (0.2 mg/kg IM) and ketamine (10 mg/kg IM) (MBK) to produce anesthesia for 98.8 ± 22.5 minutes, which is significantly longer

than for a xylazine (2 mg/kg IM)–butorphanol (0.2 mg/kg IM)–ketamine (10 mg/kg IM) combination (47.5 ± 16.5 minutes). The muscle relaxation was adequate for tracheal intubation, but moderate cardiovascular depression was observed during MBK anesthesia [110]. Atipamezole effectively reversed the effects produced by 0.16–0.32 mg/kg IM of medetomidine [103].

2.4 Atipamezole, Tolazoline, Yohimbine, and Vatinoxan (α_2 Antagonists)

The pharmacologic effects induced by any one of the α_2 agonists can be antagonized effectively with an α_2 antagonist, such as yohimbine, tolazoline, or atipamezole. These antagonists can be used to shorten the time of recovery to standing, to treat severe α_2 agonist-induced bradycardia, and to minimize adverse effects associated with accidental overdose. The α_2 agonists are known to cause bloating and ruminal tympany by decreasing gastrointestinal (GI) motility. Administration of any of the α_2 antagonists effectively reversed the decrease in GI motility [88, 111]. However, administration of these antagonists is not without risk. Sudden awareness of pain, significant peripheral vasodilation, and CNS excitement have occurred following rapid IV administration of an antagonist. The death of a sheep after administration of a large dose of yohimbine (0.8 mg/kg IV) has been reported [75]. Rapid IV injection of tolazoline has also been reported to cause significant cardiac stimulation, tachycardia, increased cardiac output, vasodilation, and GI distress [112]. Ruminants and camelids are more sensitive to tolazoline than other species, and death has been reported after its use [113, 114]. When administered alone at 1.5 mg/kg IV to Holstein calves, tolazoline caused coughing, an increased frequency of defecation, and a mild increase in breathing effort. At higher doses (2–10 mg/kg IV), adverse effects including bright red conjunctival mucous membranes, coughing, nasal discharge, salivation, labored breathing, CNS depression, signs of abdominal pain, straining, head pressing, restlessness, and severe diarrhea were observed. All calves in the study recovered uneventfully [114]. Currently, lower doses of tolazoline (0.5–1.5 mg/kg IV) are recommended for use in all ruminants including camelids. Others have suggested that, except in emergency situations, IV administration of tolazoline should be avoided to prevent adverse effects such as cardiac asystole [115]. When atipamezole (0.1 mg/kg IV) was administered to six goats to antagonize medetomidine (0.02 mg/kg IV)-induced sedation and recumbency, all goats stood within 2 minutes. Four goats developed piloerection and all appeared to be agitated and vocalized [116]. When given to reverse IM xylazine- or medetomidine-induced sedation in free-ranging cattle, atipamezole (0.04–0.09 mg/kg) induced a brief period of excitement following IV administration. Relapse into medetomidine (0.04 mg/kg IV)-induced sedation 1–2 hours after the administration of atipamezole (0.2 mg/kg IV) as a result of the shorter half-life ($t_{1/2}$) of the drug has been observed in dairy calves. In free-ranging cattle, atipamezole (0.057 ± 0.017 mg/kg IV) has been administered to reverse xylazine-induced immobilization. Eight cows receiving xylazine in this report were in the last 2 months of pregnancy and all cows calved normally and no premature parturition occurred [70]. Administration of a reversal agent (atipamezole) may have shortened the duration of xylazine-induced increases in uterine contraction, thus preventing the adverse effect of xylazine on pregnant cows. Slow injection is recommended when administering an antagonist to avoid sudden awareness of pain and excitement. The undesirable effects of α_2 antagonists are extremely rare in healthy animals when the drugs are administered at appropriate dosages and by slow IV injection.

Vatinoxan, also known as MK-467, is a peripherally acting α_2 antagonist. The drug is incapable of entering the CNS to act on the central α_2 receptors due to its low lipophilicity and inability to penetrate the blood–brain barrier [117]. Studies in dogs [118–121], cats [122], horses [123, 124], and sheep [125] have shown that concurrent administration with an α_2 agonist, vatinoxan, was able to

attenuated the adverse cardiovascular effects that are often associated with the α_2 agonists. Studies in dogs and horses also showed that vatinoxan enhanced the absorption and volume of distribution of an α_2 agonist following IV or IM administration [123, 124, 126, 127]. In sheep, concurrent IM administration of vatinoxan (0.15, 0.3, or 0.6 mg/kg) with medetomidine (0.03 mg/kg IM) and ketamine (1 mg/kg IM) showed that the drug did not completely prevent early vasoconstriction-related cardiopulmonary effects of medetomidine, but it accelerated, in a dose-dependent manner, the return of certain physiologic variables to baseline values [128]. It appeared that the absorption of IM vatinoxan was slower than that of the IM medetomidine and hence the presence of the initial cardiopulmonary effects of medetomidine. When vatinoxan (0.25 mg/kg) was administered prior to medetomidine, it was able to attenuate medetomidine-induced reduction in heart rate and changes in mean arterial blood pressure in sheep [125]. α_2 agonist-induced hypoxemia was believed to be the result of activation of peripheral α_2 adrenoceptors in sheep [82] and the administration of vatinoxan was able to increase PaO₂ and SpO₂ and minimize the detrimental effect of hypoxemia by blocking the effects of the α_2 agonist on the peripheral α_2 receptors [128].

2.5 Diazepam and Midazolam (Benzodiazepine Derivatives)

Benzodiazepine derivatives like diazepam and midazolam are classified as minor tranquilizers. These drugs are used for their anxiolytic, anticonvulsant, and central muscle-relaxing effects. Benzodiazepines produce little or no analgesic effect, but they can reduce the dose requirement of the concurrently administered general anesthetics [22]. Benzodiazepines produce minimal cardiovascular depression. For this reason these drugs are favorable for use in animals with increased anesthetic risk. Benzodiazepines can be used as alternatives to α_2 agonists to produce tranquilization when adverse effects associated with α_2 agonists (e.g. hypoxemia, pulmonary edema, or increased airway pressure) become undesirable. Diazepam and midazolam are the two most commonly used benzodiazepines in clinical veterinary practice. Diazepam is insoluble in water; its injectable solution contains 40% propylene glycol as solvent. IV propylene glycol administered rapidly sometimes results in hypotension and vascular irritation. Dilution, mixture of the injectable solution of diazepam with water, or a water-soluble drug solution may cause cloudiness of the mixture which does not affect the potency of the drug. Midazolam is two to three times more potent than diazepam. Its injectable solution is water soluble. Thus, IM administration of midazolam will not cause tissue irritation [129]. In contrast to the general perception that benzodiazepines like diazepam and midazolam do not produce an analgesic effect, Kyle et al. [130] and Lizarraga and Chambers [131] reported that midazolam appeared to provide mediation of antinociception at the level of the spinal cord in sheep. Midazolam was rapidly absorbed with an elimination $t_{1/2}$ of midazolam of 0.79 and 0.94 hours following IV and IM administration, respectively. A transient decrease in respiratory rate has been observed during midazolam-induced tranquilization [132]. Diazepam and midazolam can be used as a preanesthetic for their anxiolytic and muscle-relaxing effect, or they can be used with ketamine to improve muscle relaxation during anesthesia [133]. Other benzodiazepines, including flurazepam (2 mg/kg IV) [134], lorazepam (0.1 mg/kg IV) [135], and brotizolam (1–10 mg/kg PO) [136], have been used in pigs.

2.5.1 Cattle, Small Ruminants, and Camelids

Diazepam can be administered alone to produce dose-dependent CNS depression from mild sedation to recumbency for 15–30 minutes. The tranquilizing effects of diazepam in healthy animals tend to be variable and somewhat unreliable [10]. Doses from 0.55 to 1.1 mg/kg IM have

been recommended for use in ruminants and swine [137]. Diazepam at 0.2 mg/kg IV has been used to produce mild tranquilization for performing a transdermal tracheal wash [10]. Diazepam (0.1 mg/kg IV) has been administered with xylazine (0.2 mg/kg IV) to a bull to produce immobilization for wire placement during mandibular fracture repair. No additional local anesthetic was needed during the wiring process. The duration of deep sedation was 30 minutes and the bull stood within an hour after administration of the drugs [138]. Diazepam (0.1 mg/kg IV) and butorphanol (0.1 mg/kg IV) induce recumbency for a short period of time in camelids [139].

Midazolam (0.2 mg/kg IV) was able to reduce the response of sheep to painful mechanical stimulation [130]. In goats, IM midazolam (0.6 mg/kg) induced 20 minutes of sedation. Hypnosis with recumbency occurred and lasted for 10–20 minutes when midazolam was administered intravenously at 0.6 and 1.2 mg/kg. Increasing the dose to 1.2 mg/kg enhanced the degree of reflex suppression, and the animals appeared to be in a light plane of anesthesia as indicated by the lack of response to mechanical stimulation applied using the tail base clamp [140]. In goats with urethral obstruction, when the effect of increasing the urine output of xylazine is contraindicated, diazepam or midazolam can be given alone or with other anesthetics to induce anesthesia. Flumazenil, a benzodiazepine antagonist, can be administered at 0.02 mg/kg IV or a 1 : 13 ratio (1 part of flumazenil to 13 parts of diazepam) to antagonize the CNS effects of diazepam and midazolam [10].

2.5.2 Swine

Diazepam has been given to miniature pigs at doses from 5.5 to 8.5 mg/kg IM with maximal sedation occurring within 30 minutes following administration [22]. Prolonged recovery has occurred when large doses of diazepam are given intramuscularly to older sows and boars. A continuous rate infusion (CRI) of diazepam (CRI: 1 mg/kg/hour IV, following 0.5–10 mg/kg IM and 0.44–2 mg/kg IV) has been used in pigs to maintain long-term hypnosis and sedation for up to 6 hours in a research setting [141, 142]. Satisfactory sedation with 0.1–0.5 mg/kg of midazolam IM has been reported [18], whereas a calming effect and sedation occur within 3–4 minutes following intranasal administration of 0.2–0.4 mg/kg of the drug [143]. In piglets and adult swine, midazolam administered either intramuscularly or intranasally at 0.1–0.2 mg/kg produced effective tranquilization [143, 144]. Midazolam (1 mg/kg IM) has been combined with azaperone (4 mg/kg IM) to produce preanesthetic tranquilization prior to induction with propofol [145]. Midazolam in general has minimal cardiopulmonary effects. However, it has been shown to cause a 20% decrease in heart rate and 50% decrease in respiratory rate in pigs receiving 0.1 mg/kg IM of midazolam [144].

2.6 Chloral Hydrate

Chloral hydrate was one of the first general anesthetics used in large animal practice. Chloral hydrate itself does not have a CNS-depressing effect; it depends on its metabolite, trichloroethanol, to produce sedative and anesthetic effects. This latency of action as well as the narrow margin of safety of the drug makes it an undesirable anesthetic for use in clinical practice. Nonetheless, chloral hydrate is a very reliable sedative. In horses, chloral hydrate is often administered as an alternative when other tranquilizers or sedatives fail to produce the desired calming effect. Chloral hydrate does not have an analgesic effect, thus an additional analgesic is required if the animal is in pain or the procedure being performed is painful. Chloral hydrate is very irritating to the tissue. Therefore, IV injection of the drug is better via an IV catheter to prevent accidental perivascular injection and the consequential severe tissue damage. Chloral hydrate has been used to sedate unapproachable but

confined cattle via oral administration. Water should be withheld for 24–36 hours prior to offering the animal diluted chloral hydrate drinking solution to ensure complete consumption of the drug. The dose recommended for oral administration is 100–150 g in 8–12 l of water per animal for sedation and 5–7 g per 100 kg (220 lb) for light to moderate narcosis [146].

In pigs, oral chloral hydrate (13 g/50 kg [110 lb]) produced sedation within 20–30 minutes following administration via a stomach tube [147]. Though intraperitoneal administration (4–6 ml of 5% solution/kg) has been reported in the pig, the technique is not recommended as peritonitis is a common complication [148]. However, Jennings reported intraperitoneal chloral hydrate administration (0.3 mg/kg in 5% solution) produced sedation within 30 minutes with a duration of 60 minutes. No tissue irritation or signs of peritonitis were observed [146]. Chloral hydrate (1–4 ml of 5% solution) has been used in combination with azaperone (4 mg/kg IM) in 500 pigs to produce general anesthesia for 2 hours with complete recovery to standing within 4–5 hours [149].

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3

Standing Sedation and Chemical Restraint

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Standing sedation and chemical restraint with or without local or regional anesthesia are common techniques used to perform diagnostic and/or surgical procedures in farm animal species. Compared to general anesthesia, the ease of drug administration, minimal equipment requirements, low cost, shorter recovery time, and reduced potential for complications are advantages that make these techniques attractive to practitioners, particularly those who often do their work in the field or on the farm. Many minor surgical and diagnostic procedures may only require an animal to remain calm and motionless under the influence of standing sedation or chemical restraint for a short period of time. This is particularly true in the case of large or vigorous animals, where sedation or chemical restraint greatly minimizes the stress caused by forceful restraint. Drugs used for chemical restraint are often similar to the ones used for preanesthetic tranquilization or sedation (refer to Chapter 2). Higher doses of a single tranquilizer/sedative are often needed in order to produce desirable central nervous system (CNS) depression, whereas combinations of different classes of drugs are more likely to achieve the degree of sedation and restraint required for the procedure but with lower doses of each drug and thus reduction of the side effects of each drug.

3.1 Cattle

Xylazine produces varying degrees of CNS depression depending on the dose administered. Xylazine is frequently used alone or in combination with other drugs to produce standing sedation and chemical restraint. Intravenous (IV) administration of xylazine at 0.02–0.03 mg/kg induces standing sedation, while recumbency occurs at 0.1–0.18 mg/kg [1]. In adult cattle, intramuscular (IM) or IV administration of xylazine at 0.015–0.025 mg/kg produces standing sedation without recumbency; increasing the dose to 0.1–0.2 mg/kg causes recumbency and light anesthesia to occur [2]. However, at standing sedation doses, the analgesic effect of xylazine appears to be minimal. Doses up to 0.025–0.05 mg/kg IV are required to produce standing sedation in extremely anxious or unruly cattle [3]. Similarly, detomidine alone has been administered to produce dose-dependent standing sedation and recumbency. Sedation produced with doses from 0.002 to 0.075 mg/kg IV is adequate to calm tractable and anxious cattle, while doses from 0.01 to 0.015 mg/kg IV are required for unruly

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cattle [3]. In Norwegian cattle, a higher dose of xylazine (0.55 mg/kg IM) was capable of inducing complete immobilization [4]. However, if adequate standing sedation cannot be achieved with what would be expected to be an appropriate dose of an α_2 agonist, a drug from a different class should be used to improve sedation instead of increasing the dose of the α_2 agonist to avoid profound ataxia and recumbency. Acepromazine (0.03 mg/kg IV) with or without xylazine (0.03 mg/kg IV) can be administered to facilitate penile extension for examination of preputial injury in bulls [1]. A combination of 10 mg of xylazine and 10 mg of acepromazine administered IV can produce sedation for standing procedures in manageable bulls and cows to facilitate placing the animal on a tilt table or to perform casting with ropes [5] (Figure 3.1).

Butorphanol is an opioid agonist/antagonist. It has agonistic effects on κ receptors but antagonist effects on μ receptors. The analgesic potency of butorphanol is approximately three to five times that of morphine. Butorphanol has a unique “ceiling effect”, that is, after the effective action has been attained, further increases of the dose do not increase or enhance the degree of desired pharmacologic effects [6]. Butorphanol is the most frequently used opioid in ruminants, and recommended doses are 0.02–0.05 mg/kg IV or subcutaneous (SC) every 4–6 hours [7]. Butorphanol alone was administered at 0.05–0.07 mg/kg IV to produce adequate standing sedation and analgesia for laparotomy [8]. However, butorphanol alone may cause slight CNS stimulation, especially when used in animals that are not in pain. Twitching of the facial muscles, lips, and head and nystagmus may be observed [9]. In adult dairy cows, IV butorphanol (10 mg) can be combined with acepromazine (7.5 mg) to produce sedation during standing cesarean section [10]. One study reported the effectiveness of xylazine (0.02 mg/kg IV) or detomidine (0.01 mg/kg IV) with or without butorphanol (0.05 mg/kg IV) for standing sedation in adult cattle. The result of the study showed that detomidine alone produced more profound sedation for 40–55 minutes than xylazine or xylazine–butorphanol. While butorphanol may enhance the analgesic effect of detomidine, its CNS-stimulating effect at 0.05 mg/kg, as evidenced by nystagmus, seemed to offset the sedative effect of detomidine in three cows [11]. Ataxia and dysphoria were also reported in sheep when butorphanol was administered intravenously at 0.1–0.2 mg/kg [9].

A combination of low doses of xylazine and ketamine can be used for chemical restraint. IV xylazine (0.05 mg/kg) and ketamine (0.2–0.4 mg/kg) or IM xylazine (0.025–0.05 mg/kg) and ketamine (2 mg/kg) produce chemical restraint with recumbency in combative or unruly ruminants.



Figure 3.1 Acepromazine-induced calming effect in a rodeo bull prior to induction of anesthesia.

Opioid analgesics like morphine (0.05 mg/kg) or butorphanol (0.025 mg/kg) can be used with xylazine (0.025–0.05 mg/kg) and ketamine (0.05 mg/kg) administered either intravenously or intramuscularly for standing procedures [3]. A brief period of slight ataxia may occur following IV injection of this combination during standing sedation. Cattle receiving morphine appear to be more alert than those receiving butorphanol [3]. Ketamine can be given 10 minutes after a bolus of xylazine and morphine or xylazine and butorphanol to avoid significant ataxia [3]. A longer duration of sedation is produced when ketamine is administered intramuscularly immediately after IV xylazine and morphine or xylazine and butorphanol [12]. This combination is sometimes referred to as *ketamine stun*. The low-dose combination of butorphanol, xylazine, and ketamine at 0.02–0.1, 0.02–0.0275, and 0.05–0.1 mg/kg, respectively, administered intramuscularly produces standing sedation. When increasing the doses of butorphanol, xylazine, and ketamine to 0.05–0.1, 0.025–0.05, and 0.3–0.5 mg/kg, respectively, chemical restraint with recumbency for 15 minutes is induced [1, 12]. Standing sedation produced by this low-dose combination has been used for laparotomy in range cattle and endoscopy and head examination in rodeo bulls [5]. Using the high-dose combination, chemical restraint with recumbency along with a casting rope and local or regional anesthetic techniques allows the performance of fracture stabilization, unilateral castration, and preputial resection/amputation in bulls [1]. Animals under the sedation of this combination normally appear to be alert but are not bothered by the surroundings and remain quiet for the duration of the procedures [3]. A similar combination of butorphanol, xylazine, and ketamine using a 5–10–20 ratio (5 mg of butorphanol, 10 mg of xylazine, and 20 mg of ketamine) can be administered intramuscularly or subcutaneously to produce effective standing sedation in tame cows and Brahman cows for cesarean section. If repeat dosing is required, half of the initial ketamine and a quarter of the initial xylazine doses can be given 30–40 minutes after the initial administration. Adequate sedation with a cooperative animal lasts 60 minutes with this 5–10–20 combination. In adult bulls, 10 mg of butorphanol, 20 mg of xylazine, and 40 mg of ketamine (10–20–40) IM or SC combined with local anesthetic nerve blocks can be used successfully to perform standing preputial surgeries [1, 3]. Increasing the dose of each drug to butorphanol 20 mg, xylazine 40 mg, and ketamine 80 mg (20–40–80) can be used to produce standing sedation in large, unruly bulls. If deep sedation with recumbency is needed for the procedure, 20 mg of butorphanol, 25 mg of xylazine, and 250–500 mg of ketamine can be administered IV in cattle weighing 500–600 kg (1100–1320 lb) [5].

Standing sedation can be achieved with 0.005 mg/kg IV medetomidine alone in domestic ruminants [13]. Increasing the dose to 0.03 mg/kg and using an IM route of administration, lateral recumbency was induced for 60–75 minutes in domestic calves [14]. When delivered via tranquilizing gun at a higher dose (0.04 mg/kg), medetomidine has been used successfully to produce complete immobilization in capturing free-ranging cattle [4, 15].

A combination of xylazine (0.3–0.5 mg/kg IM), ketamine (0.7–1.0 mg/kg IM), and Telazol (0.7–1 mg/kg IM) has been used to produce dose-dependent chemical restraint and immobilization in free-ranging cattle, for example Limousin, Scottish highland cattle, and American bison, for nonpainful procedures [16]. There are times when remote delivery of drugs to produce chemical restraint or immobilization is required for capture of wild or free-ranging cattle, but the drug volume that can be delivered via a dart gun, pistol, or blow pipe is limited. Saddighi and Doherty [5] suggested that using a drug combination based on Telazol may be ideal under this situation because Telazol is available as a powder and can be reconstituted using xylazine and/or ketamine solutions. For example, by adding 1 ml of xylazine and 3–4 ml of ketamine into 500 mg of Telazol a small volume of drug mixture (4–5 ml) is created, which is sufficient to immobilize a 600- to 800-kg (1320- to 1760-lb) bovid. Caulkett et al. [17] reported that a medetomidine (0.06 mg/kg IM) and Telazol (1.2 mg/kg IM) combination produced immobilization and analgesia adequate for minor

procedures for a period of 60 minutes [17]. Atipamezole (0.18 mg/kg) was administered to shorten the recovery time. A reversible combination of butorphanol, azaperone, and medetomidine (BAM) can be used to restrain and immobilize domestic and wildlife ruminants that are difficult to handle, such as rodeo stock or free-ranging ruminants, e.g. bison, caribou, elk, or white-tail deer [18–21]. BAM is commercially available as a premixed compound in two different mixtures: butorphanol 27.3 mg/ml, azaperone 9.1 mg/ml, and medetomidine 10.9 mg/ml or butorphanol 50 mg/ml, azaperone 50 mg/ml, and medetomidine 40 mg/ml (Wildlife Pharmaceuticals, Fort Collins, Colorado, USA; ZooPharm, Laramie, Wyoming, USA). Induction to recumbency is usually smooth with acceptable induction times, although repeated dosing with a partial or full dose of the combination may be required if the initial dose is not completely delivered. The quality of immobilization with this combination was reported to be good and allowed minor invasive procedures such as blood sampling, skin biopsy, and semen collection to be performed. In addition, a compounded higher concentration of α_2 antagonist, atipamezole (25 mg/ml), and an opioid antagonist, naltrexone (50 mg/ml), can be used to reverse the effects of medetomidine and butorphanol, and shorten the recovery to standing time. Respiratory depression and hypoxemia are common adverse effects associated with BAM, but the availability of the reversal agents to minimize the duration of recumbency and shorten the recovery to standing time have greatly improve the safety of the immobilization process, particularly for wildlife species [18–21].

Xylazine (0.1 mg/kg IV) and diazepam or midazolam (0.2 mg/kg IV) can be combined to produce short-term chemical restraint with recumbency, and this combination was successfully used in a cow to place wires to stabilize a mandibular fracture. The duration of chemical restraint was 30 minutes and the cow stood approximately 60 minutes following drug administration. Additional analgesia with an opioid or a local anesthetic was not required for this procedure [22]. For procedures that require more intense analgesia, xylazine at 0.2 mg/kg and diazepam or midazolam at 0.1 mg/kg can be administered intravenously for a similar duration of recumbency. Tracheal intubation was performed in a calf receiving 0.1 mg/kg of xylazine and 0.2 mg/kg of diazepam (Figure 3.2). Table 3.1 summarizes the doses of drugs and drug combinations used for sedation and chemical restraint in cattle.



Figure 3.2 (a) Chemical restraint in a calf with xylazine (0.1 mg/kg IV) and diazepam (0.2 mg/kg IV). (b) Chemical restraint in a calf with xylazine (0.1 mg/kg IV) and diazepam (0.2 mg/kg IV) followed by endotracheal intubation.

3.2 Small Ruminants and Camelids

Goats are more sensitive to xylazine than sheep and camelids; lower doses of xylazine (0.05–0.1 mg/kg IV) are required to produce a similar degree of sedation to that of sheep (0.1–0.4 mg/kg IV) [23]. Compared to sheep and goats, camelids are less sensitive to xylazine and thus require higher doses (0.1–0.2 mg/kg IV) to produce standing sedation [24]. In sheep, approximately 1 hour of standing sedation was produced by 0.3 mg/kg IM, but recumbency of 1.5 hours occurred when 0.6 mg/kg IM was administered [25]. It is recommended that the dose of xylazine should not exceed 0.15 mg/kg IV due to the concern of significant cardiopulmonary depression [26]. Subanesthetic doses of xylazine (0.025–0.03 mg/kg IV or 1.7–2.2 mg/kg IM) and ketamine (1.1 mg/kg IV or 1.7–2.2 mg/kg IM) can be used to produce chemical restraint with recumbency of 10–25 minutes in camelids. This combination produced better analgesia than that of xylazine alone. Although minor surgical procedures may be performed with subanesthetic doses of xylazine and ketamine combinations, butorphanol (0.05–0.1 mg/kg IV or IM), morphine (0.05–0.1 mg/kg IV or IM), or local or regional anesthetic techniques should be added for more painful procedures [27].

Similar to xylazine, detomidine produces dose-dependent CNS depression. In goats, 0.01–0.02 mg/kg IV of detomidine produces sedation for 30–60 minutes, while severe ataxia and sternal recumbency occur at 0.04 mg/kg administered either intravenously or intramuscularly [28]. Butorphanol (0.05–0.1 mg/kg IV) or morphine (0.01–0.1 mg/kg IV or IM) can be combined with xylazine or detomidine to improve patient cooperation during sedation [3]. Standing sedation occurs when detomidine (0.01 mg/kg IV) is administered concurrently with butorphanol (0.1 mg/kg IV) [29].

Mohammad et al. [30] reported that medetomidine (0.04 mg/kg IM) induced deep sedation with recumbency for a period of 58 minutes in sheep. Good analgesia and muscle relaxation of 30–45 minutes were observed during recumbency [30]. In llamas, medetomidine (0.01 mg/kg IM) induced a brief period of standing sedation with minimal analgesia [31]. Only deep sedation was observed when 0.05 mg/kg of IM medetomidine was combined with 1 mg/kg of IM ketamine in llamas [32].

In sheep and goats, slow injection of diazepam (0.25–0.5 mg/kg IV) produces standing sedation with little analgesia [26, 33]. A transdermal tracheal wash was successfully performed under the mild sedation produced by 0.2 mg/kg IV of diazepam [34]. A period of 10–20 minutes of recumbency occurred when midazolam (0.3 mg/kg IV, 0.4–0.6 mg/kg IM) was administered to sheep and goats [35–37]. Increasing the dose of midazolam to 1.2 mg/kg IV prolonged the duration of recumbency up to 30 minutes [35–37]. Intratesticular injection of xylazine (0.1–0.2 mg/kg) and midazolam (0.1–0.2 mg/kg) has been used successfully for castration in small ruminants [38]. In goats, acepromazine (0.05 mg/kg IM) or midazolam (0.03 mg/kg IM) alone produces significant sedation; however, no significant sedation was observed when combining butorphanol (0.1 mg/kg IM) to acepromazine or midazolam [39].

Butorphanol (0.05 mg/kg IV) can be given alone to sheep and goats to produce light sedation [9, 33, 40]. When xylazine (0.01–0.02 mg/kg IV) and butorphanol (0.01–0.02 mg/kg IV) were administered simultaneously to sheep and goats, deep sedation and recumbency were produced for up to 60 minutes [24]. However, 0.2 mg/kg IV of each drug is required to produce similar sedation in camelids [24]. Barrington et al. [41] described using butorphanol (0.1 mg/kg IM) along with intratesticular injection of 2% lidocaine (2–5 ml) successfully to facilitate standing castration in more than 100 llamas [41]. Diazepam (0.1 mg/kg IV) and butorphanol (0.1 mg/kg IV) are effective in producing short-duration sedation with recumbency in camelids [27].

Johnson [42] recommended adding 1 ml of butorphanol (10 mg) and 1 ml of xylazine (100 mg) to 10 ml of ketamine (1000 mg) (*llama lullaby*) and administering 1 ml/45 kg (99 lb) to camelids for standing sedation. Camelids tend to assume sternal recumbency even under moderate sedation.

Table 3.1 Doses of drugs and drug combinations used for sedation and chemical restraint in cattle

Drug	Dose (mg/kg)	Comments
Acepromazine	0.02, IV	Less ↓ in uterine blood flow Less ↑ in uterine vascular resistance
Acepromazine	0.01–0.02, IV	Chemical restraint
Acepromazine	0.033–0.055, IV or IM	–
Acepromazine	0.03–0.1, IM	–
Acepromazine	0.03, IV	Facilitate penile extension for exam with or without xylazine 0.03 mg/kg IV for sedation
Acepromazine	0.055–0.088, IV or 25–40 mg/450 kg	Standing chemical restraint
Morphine	0.1–0.2, IV, or	
Ketamine	45–90 mg/45 kg CRI: 0.06 mg/kg/hour	
Butorphanol	0.033–0.05, IV	Analgesia, standing restraint
Butorphanol	0.22, IM	–
Butorphanol	20–30 mg/cow IV with or without xylazine 10 mg/cow	Standing analgesia
Butorphanol	0.022–0.05, IV	Sedation
Acepromazine	0.03, IV	Sedation
Butorphanol	0.01, IV	
Acepromazine	0.022, IV	Standing restraint
Butorphanol	0.044, IV	
Butorphanol	10 mg, IV	Standing sedation for Cesarean section in dairy cows
Acepromazine	7.5 mg, IV	
Chloral hydrate	44–66, IV	Standing sedation
Chloral hydrate	30–60 g in 1–2 l water	Sedation with recumbency
Detomidine	0.002–0.005, IV; 0.006–0.01, IM	Standing sedation for tractable cattle
Detomidine	0.005–0.0075, IV; 0.01–0.015, IM	Standing sedation for anxious cattle
Detomidine	0.01–0.015, IV; 0.015–0.02, IM	Standing sedation for unruly cattle
Detomidine	0.0025–0.01, IV	Standing sedation 30–60 minutes
Detomidine	0.01–0.02, IV	Sedation 60 minutes
Detomidine	0.03–0.06, IV	Standing sedation
Detomidine	0.02–0.04, IM	Analgesia 20–120 minutes
Detomidine	0.02–0.05, IM	–
Detomidine	0.04, IV	Profound sedation, recumbency
Detomidine	0.1, IM by dart	Immobilization in free-ranging cattle

(Continued)

Table 3.1 (Continued)

Drug	Dose (mg/kg)	Comments
Detomidine	0.01, IV	Enhanced sedation
Butorphanol	0.05, IV	↓ response to external stimuli Potential significant ptosis, occasional nasopharyngeal edema, and slow nystagmus
Detomidine	15 mg (0.035), IM	Detomidine less likely to cause recumbency than xylazine or medetomidine
Butorphanol	15 mg (0.035), IM For 400–450 kg (880–990 lb)	
Detomidine	0.07, IM	Immobilization in free-ranging cattle
Butorphanol	0.04, IM	
Detomidine	0.011–0.022, IV, or 5–10 mg/450 kg (990 lb)	Standing chemical restraint
Butorphanol	0.011–0.016, IV, or	
Ketamine	5–7 mg/450 kg (990 lb) CRI: 0.6 mg/kg/hour	
Detomidine	Loading dose: 5–10 mg/450 kg (990 lb), IV CRI: 0.022 mg/kg/hour	Standing chemical restraint
Morphine	Loading dose: 45–60 mg/450 kg (990 lb), IV CRI: 0.025–0.05 mg/kg/hour	
Ketamine	Loading dose: 100 mg/450 kg (990 lb), IV CRI: 0.6 mg/kg/hour	Ketamine loading dose may not be required Adjustment CRI to desirable effect
Diazepam	0.25, IM	Inadequate sedation
Diazepam	0.4, IM	–
Diazepam	0.5, IM	–
Diazepam	0.4, IV	5–10-minutes sedation with recumbency
Diazepam	0.2–0.5, IV	–
Diazepam	0.5–1, IM	–
Medetomidine	0.005, IV	Brief standing sedation without analgesia
Medetomidine	0.01, IV	Recumbency
Medetomidine	0.03, IM	Recumbency 60–75 minutes
Morphine	0.1–0.5, IV	Analgesia
Pentobarbital	2, IV, slow	Moderate standing sedation 30 minutes, mild sedation for additional 60 minutes
Romifidine	0.02–0.03, IV	Standing sedation
Romifidine	0.05, IV	Recumbency
Xylazine	0.0075–0.01, IV; 0.015–0.02, IM	Standing sedation, quiet dairy cattle
Xylazine	0.01–0.02, IV; 0.02–0.04, IM	Standing sedation, tractable cattle
Xylazine	0.02–0.03, IV; 0.04–0.06, IM	Standing sedation, anxious cattle

(Continued)

Table 3.1 (Continued)

Drug	Dose (mg/kg)	Comments
Xylazine	0.025–0.05, IV; 0.05–0.1, IM	Standing sedation, unruly cattle
Xylazine	0.015–0.025, IV or IM	Standing sedation
Xylazine	0.02, IV	Standing sedation
Xylazine	0.1, IV, or 0.2, IM	Recumbency 60 minutes
Xylazine	0.055–0.11, IV, or 0.11–0.22, IM	Chemical restraint to light anesthesia
Xylazine	0.02–0.03, IV	Standing sedation
Xylazine	0.1–0.18, IV	Recumbency
Xylazine	0.66–0.88, IM	Capture wild cattle
	Second dose: 0.52–0.53, IM	Recumbency in 3–7 minutes
		Fleeing possible
		Reversal available
Xylazine	10 mg, IV	Standing sedation 10–20 minutes
Acepromazine	10 mg, IV	
Xylazine	0.01–0.02, IV	Standing sedation
Butorphanol	0.01–0.02, IV	Neuroleptanalgesia 60 minutes
Xylazine	0.05–0.1, IV	Deep sedation
Butorphanol	0.01–0.02, IV	
Xylazine	0.03, IV	Standing restraint
Butorphanol	0.033–0.05, IV	
Xylazine	0.055–0.11, IV; 0.11–0.22, IM	Standing sedation
Butorphanol	0.05–0.07, IV	
Xylazine	0.12, IV	Chemical restraint, analgesia
Diazepam	0.1, IV	Recumbency 30 minutes
		Standing in 45–60 minutes
Xylazine	0.1, IV	Chemical restraint
Diazepam	0.2, IV	Standing sedation for tractable cattle
Xylazine	0.2, IV	Chemical restraint, analgesia
Diazepam	0.1, IV	Standing sedation for tractable cattle
Xylazine	0.05, IV	Chemical restraint
Ketamine	0.2–0.4, IV	Recumbency
		Animals appear awake but cooperative
		Half original ketamine to extend duration
Xylazine	0.025–0.05, IM, or 0.05–0.1, IM	Chemical restraint for combative animal
Ketamine	2–4.4, IM	Recumbency, extremely unruly animal may remain standing
Xylazine	0.59 ± 0.02 (0.34–0.86), IM	Free ranging cattle
Ketamine	3.59 ± 0.1 (2.36–5.23), IM	Mean time to recumbency 8 minutes
	Delivered via darts	Yohimbine 0.10 ± 0.01 mg/kg IM
		Mean recumbency time 27 ± 3 minutes

(Continued)

Table 3.1 (Continued)

Drug	Dose (mg/kg)	Comments
<i>Ketamine stun</i>		
Xylazine	0.02–0.0275, IV	Standing sedation
Butorphanol	0.02–0.1, IV	Improve patient cooperation
Ketamine	0.05–0.1, IV	Allow examination for penile injury
<i>Ketamine stun</i>	(5–10–20 technique for 450 kg (990 lb))	Standing sedation, tame Brahman cattle Limit analgesia
Butorphanol	5 mg (0.01), IM, SC	Combine with local anesthesia for surgery
Xylazine	10 mg (0.02), IM, SC	Supplemental dose may cause recumbency
Ketamine	20 mg (0.04), IM, SC	
<i>Ketamine stun</i>	(10–20–40 technique for 450 kg (990 lb))	Standing sedation Combine with local anesthesia
Butorphanol	10 mg (0.02), IM, SC	Can be used in preputial surgery for adult bulls
Xylazine	20 mg (0.04), IM, SC	
Ketamine	40 mg (0.08), IM, SC	
<i>Ketamine stun</i>	(20–40–80 technique for 450 kg (990 lb))	Standing sedation Large, unruly cattle
Butorphanol	20 mg (0.044), IM, SC	
Xylazine	40 mg (0.088), IM, SC	
Ketamine	80 mg (0.18), IM, SC	
<i>Ketamine stun</i>		Recumbency
Xylazine	0.025–0.05, IV	Good analgesia
Butorphanol	0.05–0.1, IV	Random head or limb movement
Ketamine	0.3–0.5, IV	Duration 15 minutes
<i>Ketamine stun</i>		Recumbency, chemical restraint
Xylazine	0.05, IM, SC	Tolerate endotracheal intubation
Butorphanol	0.025, IM, SC	Ambulatory 30–45 minutes
Ketamine	0.1, IM, SC	Combine with local anesthesia, allow umbilical hernia repair; laparotomy in range cattle; endoscopy, head examination for rodeo bulls
Xylazine	0.02, IV, IM	Standing restraint
Butorphanol	0.025, IV, IM	Longer duration if ketamine is administered 10 minutes after xylazine and butorphanol
Ketamine	0.05, IV, IM	Half original ketamine to extend duration
Xylazine	0.05, IV, IM	Recumbency
Butorphanol	0.025, IV, IM	Able to stand and walk on completion
Ketamine	0.2–0.4, IV, IM	
Xylazine	0.02, IV, IM	Standing restraint
Morphine	0.05, IV, IM	Longer duration if ketamine is administered 10 minutes following xylazine and morphine
Ketamine	0.05, IV, IM	Half original ketamine to extend duration

(Continued)

Table 3.1 (Continued)

Drug	Dose (mg/kg)	Comments
<i>Telazol/Ketamine/Xylazine-Ruminants</i>		
Ketamine 2.5 ml (250 mg)	Smaller animals: 1.25–1.5 ml/125 kg (275 lb), IM	Chemical restraint for wild ruminants, large exotic hoofstock
Xylazine 1 ml (100 mg)	Larger animals: 1 ml/125 kg (275 lb), IM	Recumbency in 5–10 minutes
Telazol (500 mg)		Recovery to standing in 40–60 minutes
Final volume 4 ml		Leftover TKX-Ru can be frozen for up to 6 months
Xylazine	0.1–0.2, IM	Capture of wild cattle
Telazol	4, IM	Recumbency
<i>Antagonists</i>		
Doxapram	1, IV	Nonspecific reversal of CNS depression induced by anesthetics to shorten recovery Respiratory stimulant
Atipamezole	0.02–0.05, IV	Reversal of α_2 agonists
Atipamezole	0.02–0.06, IV	
Idazoxan	0.05, IV	Reversal of α_2 agonists
Tolazoline	0.2–2, IV, IM, or SC	Reversal of α_2 agonists
Tolazoline	0.5–2, IV	Hyperesthesia at 2 mg/kg IV
Yohimbine	0.12, IV	Reversal of α_2 agonists Variable efficacy
Yohimbine	0.125–0.2, IV	Partially reverse hypoxemia of xylazine $t_{1/2}$: 53–76 minutes
Nalorphine	0.0088, IV	Reversal of opioid agonist

CRI, constant rate infusion.

Therefore, careful selection of the doses of the drugs used is required to achieve a desirable effect. Different dose combinations of butorphanol, ketamine, and xylazine have been used in small ruminants and camelids and were named *ketamine stun* by Abrahamsen [3, 27]. Administered intravenously, 0.08–0.11 mg/kg of butorphanol, 0.22–0.33 mg/kg of ketamine, and 0.22–0.33 mg/kg of xylazine produced reliable recumbency and analgesia for 15–20 minutes [3, 27]. When administered intramuscularly, 0.055–0.11 mg/kg of butorphanol, 0.22 mg/kg of ketamine, and 0.22–0.55 mg/kg of xylazine extended the duration of recumbency to 45 minutes [3, 27]. Less analgesic effect was observed when lower doses were administered [3, 27]. Animals appear to be stunned but alert, oblivious to surroundings and procedures performed. Extension of the duration of restraint can be achieved by administering half of the original dose of ketamine IV for an additional 5 minutes. If further restraint is desired, then half of the original xylazine and ketamine IV can be administered to extend recumbency for another 7–10 minutes. Procedures such as castration, biopsies, septic joint flushing, casting of fractured limbs, and flank laparotomy for correction of uterine torsion and cesarean section have been performed under IV ketamine stun [27].

A mixture of Telazol (500 mg), ketamine (250 mg, 2.5 ml), and xylazine (250 mg, 2.5 ml) was developed to produce chemical restraint and anesthesia in pigs (Telazol/Ketamine/Xylazine-Pigs).

The use of this three-drug combination [27] was also evaluated in camelids by adding 2.5 ml of ketamine (250 mg) and 1 ml of xylazine (100 mg) into 500 mg of Telazol powder with a final solution of 4 ml. This mixture is referred to as Telazol/Ketamine/Xylazine-Ruminants. Doses to produce recumbency and chemical restraint for 40–60 minutes in camelids are 1–1.5 ml/110–115 kg (220–253 lb). Sedation occurs within 5–10 minutes following IM injection of TKX-Ru, and animals will be awake and assume sternal recumbency by 40–60 minutes and remain in sternal recumbency for another 20–40 minutes [27]. Saddighi et al. [43] studied the nociceptive and selected physiological effects of morphine (0.5 mg/kg IM) and xylazine (0.15 mg/kg IM) on Telazol (2 mg/kg IM) anesthesia in llamas. While the addition of morphine to Telazol at the evaluated dose did not result in a significant antinociception in llamas, the addition of xylazine or xylazine-morphine to Telazol significantly increased the duration of antinociception. However, the addition of xylazine, morphine, or xylazine-morphine caused a significant decrease in arterial O₂ saturation with Telazol-morphine-xylazine having the lowest PaO₂ values among the three combinations studied [43]. Table 3.2 summarizes the doses of drugs and drug combinations used for sedation and chemical restraint in small ruminants and camelids.

Table 3.2 Doses of drugs and drug combinations used for sedation and chemical restraint in sheep, goats, and camelids

Drug	Dose for sheep and goats (mg/kg)	Dose for camelids (mg/kg)	Comments
Acepromazine	0.03–0.05, IV	0.15, IV, IM, SC	Moderate sedation
Acepromazine	0.05–0.1, IM		May ↑ risk for regurgitation
Acepromazine	<50 kg (110 lb): 0.1–0.2, IV >50 kg (110 lb): 0.05–0.1, IV, IM	–	–
Buprenorphine	0.006, IV	–	Sedation, analgesia
Butorphanol	0.05–0.5, IM	0.05–0.1, IV, IM	Sedation and/or ataxia
Butorphanol	0.4, IV	0.02–0.05, IV, IM for larger camels	Enhance sedation and analgesia of xylazine
Butorphanol	–	5 mg/alpaca (0.07), IM 10 mg/llama (0.07), IM	Analgesia, some sedation Tolerant for procedures like hoot trimming, shearing
Butorphanol	0.05–0.5, IM	0.15, IM	Standing castration
Butorphanol	–	0.1–0.2, IM	Add 1–1.5 ml 2% lidocaine to median raphe of scrotum and 2–3 ml to each spermatic cord Give butorphanol 10 minutes prior to local anesthetic
Chloral hydrate	33–55, IV	–	Sedation
Detomidine	0.005–0.02, IV 0.01–0.04, IM	0.01, IM	Sedation for 45–60 minutes

(Continued)

Table 3.2 (Continued)

Drug	Dose for sheep and goats (mg/kg)	Dose for camelids (mg/kg)	Comments
Detomidine	–	0.03–0.06, IM	Immobilization
Detomidine	0.01–0.02, IV	–	Standing sedation for 30–60 minutes
	0.02–0.05, IM		Recumbency
Detomidine	0.03, IV	0.04, IV	Mild sedation, no restraint
Detomidine	0.01, IV	–	Sedation
Butorphanol	0.1, IV		
Diazepam	0.25–0.5, IV, slow	0.1–0.5, IV	Sedation for 30 minutes
Diazepam	0.44–0.66, IV, IM	–	Sedation
Diazepam	0.2–0.5, IV		Sedation
	0.5–1, IM		
Diazepam	1–2, IM	–	Light to moderate sedation
	1, IV		
Diazepam	5 mg IV per goat	–	Calming effect
			Quieting vocalization, movement
			Lack analgesia
Diazepam	–	0.1, IV	Short duration of recumbency
Butorphanol		0.1, IV	Less analgesia versus xylazine–butorphanol
Diazepam	–	0.2, IM	Chemical restraint
Xylazine		0.1, IM	
Butorphanol		0.05, IM	
Dexmedetomidine	0.002–0.005, IV	–	Deep sedation
Medetomidine	0.001–0.007, IV	–	IV sedation
Medetomidine	Goats: 0.01–0.04, IM	–	IM recumbency for 58 minutes
Medetomidine	Sheep: 0.005–0.01, IM	–	
Medetomidine	0.015, IM	–	Recumbency 45 minutes
Medetomidine	0.025, IM	0.01, IM	Standing sedation
Medetomidine	–	0.02–0.03, IM	Recumbency 60–120 minutes
			Analgesia 60 minutes
Medetomidine	0.01–0.02, IM	–	Sedation and analgesia
Butorphanol	0.04, IM		
Medetomidine	0.01, IM	–	Dehorning
Butorphanol	0.1, IM		Block horn buds 0.1–0.2 ml of 1% lidocaine
Meperidine	10, IM	–	–
Midazolam	0.3, IV	–	Sedation with recumbency
	0.4–0.6, IM		10–20 minutes
Midazolam	0.5, IV	–	Moderate sedation

(Continued)

Table 3.2 (Continued)

Drug	Dose for sheep and goats (mg/kg)	Dose for camelids (mg/kg)	Comments
Midazolam	Goats: 0.4, IM; 0.6, IV; 1, IM	–	Profound sedation with recumbency Light surgical anesthesia for nonpainful procedures for 7–15 minutes
Midazolam	1.2, IV	–	Recumbency 30 minutes
Morphine	2, IV	0.05–0.1, IV, IM	↓ Isoflurane minimum alveolar concentration 29%
Romifidine	0.05, IV	–	Recumbency
Xylazine	Goats: 0.05, IV; 0.1, IM, IV Sheep: 0.1–0.2, IV; 0.2–0.3, IM	0.4, IM 0.1–0.2, IV	Standing castration, add 1–1.5-ml 2% lidocaine infiltration to median raphe of scrotum and 2–3 ml to each spermatic cord Light to moderate sedation
Xylazine	–	–	
Xylazine	–	0.3–0.4, IV; 0.5, IV	Recumbency 20–30 minutes Allow tracheal intubation
Xylazine	Goats: 0.05–0.1, IV Sheep: 0.1–0.4, IV	Alpacas: 0.3, IV Llamas: 0.2, IV	Sedation Combine with local infiltration for dehorning
Xylazine	Loading dose: 0.1 mg/kg IM Constant rate infusion: 0.04 mg/kg/hour	–	–
Xylazine	0.3, IM	–	Standing sedation 60 minutes
Xylazine	0.6, IM	–	Recumbency 90 minutes
Xylazine	1.1, IM	–	Analgesia 20–35 minutes Sedation 60–90 minutes
Xylazine	0.01–0.02, IV	Alpacas: 0.1–0.15, IV; 0.2–0.3, IM, SQ	Standing sedation
Xylazine	0.1–0.2, IV; 0.2–0.3, IM	Llamas: 0.075–0.1, IV; 0.15–0.2, IM, SQ	
Xylazine	–	Alpacas: 0.33–0.44, IV; 0.66–0.88, IM, SQ Llamas: 0.22–0.33, IV; 0.44–0.66, IM, SQ	Recumbent sedation
Xylazine	–	1, IM	Immobilization
Xylazine	0.1–0.2, IV	–	Enhance patient cooperation and systemic analgesia
Butorphanol	0.01–0.02, IV		Deep sedation to recumbency 60 minutes

(Continued)

Table 3.2 (Continued)

Drug	Dose for sheep and goats (mg/kg)	Dose for camelids (mg/kg)	Comments
Xylazine	0.1, IM	0.05–0.1, IM	Dehorning
Butorphanol	0.1, IM	0.1, IM	Block horn buds 0.1–0.2 ml of 1% lidocaine
Xylazine	–	0.2, IV	Profound sedation
Butorphanol	–	0.02, IV	Recumbency 20 minutes
Xylazine	–	0.4, IV	Recumbency
Butorphanol	–	0.1, IV	Castration with intratesticular local anesthetic
Xylazine	–	0.2, IM	Standing castration
Butorphanol	–	0.1, IM	
Xylazine	–	0.1, IM	Standing castration
Butorphanol	–	0.051, IM	
Xylazine	–	Alpacas: 0.3, IV; 0.05, IV; 0.1 IM, SC	Standing sedation, analgesia
Butorphanol	–	Llamas: 0.1–0.2, IV; 0.05, IV; 0.07–0.1, IM, SC	
Xylazine	–	0.3–0.4, IV	Castration
Butorphanol	–	0.1, IV	Recumbency 20–30 minutes
Xylazine	0.01–0.02, IV	0.2, IV	Neuroleptanalgesia 60 minutes
Butorphanol	0.01–0.02, IV	0.2, IV	Moderate to deep sedation
Ketamine	20, IM	–	Immobilization
Xylazine	–	0.05, IV	Sedation
Ketamine	–	0.5, IV	
Xylazine	–	0.025–0.03, IV, given first	Recumbent chemical restraint 10–15 minutes
Ketamine	–	1.1, IV, given when xylazine sedation evident	Better analgesia versus xylazine
Xylazine	–	1.7–2.2, IM	Supplemental dose: half of original xylazine and ketamine
Ketamine	–	1.7–2.2, IM	Recumbency 15–25 minutes
<i>Ketamine stun</i>			Recumbency 15–20 minutes (IV), 45 minutes (IM)
Xylazine	–	0.22–0.33, IV	Animals stunned but alert
Ketamine	–	0.22–0.55, IM	Supplemental dose, half of the original ketamine IV extend restraint for 5 minutes; second supplemental dose, half of original xylazine and ketamine IV extend restraint for 7–10 minutes
		0.22–0.33, IV	
		0.22–0.55, IM	
Butorphanol	–	0.08–0.11, IV	
		0.08–0.11, IM	

(Continued)

Table 3.2 (Continued)

Drug	Dose for sheep and goats (mg/kg)	Dose for camelids (mg/kg)	Comments
<i>TKX-Ru</i>			Animals awake and sternal in 40–60 minutes
Telazol (500 mg)	–	4 ml mixture	
Ketamine (2.5 ml, 250 mg)		1.25–1.5 ml/110–115 kg (220–253 lb), IM for small patients	
Xylazine (1 ml, 100 mg)		1 ml/110–115 kg (220–253 lb), IM for larger patients	
<i>Antagonists</i>			
Atipamezole	0–0.05, IV	0.125–0.2, slow IV	Reversal for α_2 agonists
Atipamezole	0.125–0.2, slow IV	0.3–0.5, slow IV	
Tolazoline	1–2, slow IV	1–2, slow IV	Reversal for α_2 agonists Can be given half IV, half IM Some prefer IM
Yohimbine	0.125–0.22, slow IV	0.125–0.22, slow IV	Reversal for α_2 agonists
Doxapram	0.4, IV	0.1, IV	Nonspecific reversal
Flumazenil	–	0.1, IV	Reversal for benzodiazepines
Naloxone	–	0.03, IV	Reversal for opioid agonists

3.3 Swine

Pigs do not tolerate manual restraint, which often is stressful to these animals. IV injection of pigs is difficult not only because they are resistant to restraint but also because they have very few superficial veins. Therefore, IM injection of drugs is considered less stressful and is often preferred in these animals. Acepromazine (0.05–0.5 mg/kg IM, maximum 10 mg), diazepam (0.5–1 mg/kg), midazolam (0.2–0.4 mg/kg IM), azaperone (2–4 mg/kg IM), or ketamine (20–30 mg/kg IM) can be given alone to produce a short duration of sedation (20–30 minutes) [44, 45]. Acepromazine and diazepam are not effective tranquilizers in pigs. Midazolam is another benzodiazepine tranquilizer similar to diazepam but is twice as potent. Unlike diazepam, midazolam is water soluble and it is easily absorbed from the injection site following IM administration. Sedation with midazolam can be achieved with intranasal administration at doses of 0.2–0.4 mg/kg. IM diazepam and midazolam alone tend to be cost prohibitive due to the large volumes of the drugs required to produce effective sedation [46].

Azaperone is the only tranquilizer approved by the Food and Drug Administration (FDA) for use in swine. It can be used to control aggression when mixing commercial pigs. Azaperone should only be given by IM administration, as excitement has been reported when the drug was administered intravenously. In large boars, the dose of azaperone is not recommended to exceed 1 mg/kg to prevent the adverse effect of priapism [46]. For potbellied pigs, azaperone has been used to produce effective tranquilization (2–4 mg/kg IM) and immobilization (8 mg/kg IM) for approximately 20 minutes to perform radiography and tusk trimming [47].

Compared to other domestic species, pigs are the least sensitive to xylazine; deep sedation from xylazine alone is rarely observed in pigs even with high doses. Nonetheless, when mild sedation is adequate, the recommended IM doses of xylazine are 0.5–3 mg/kg. One should keep in mind that xylazine can cause vomiting in pigs, particularly in cases in which fasting is not an option [48]. Diazepam (0.5–1 mg/kg IM) or xylazine (4 mg/kg IM) can be combined with ketamine (10–30 mg/kg IM) to produce an enhanced degree of sedation and analgesia [44]. In Yucatan minipigs, IM medetomidine (0.2 mg/kg) and ketamine (10 mg/kg) combination induced deep sedation characterized by significant but reversible increase in mean arterial pressures and systemic vascular resistance, and a significant decrease in heart rate for 2 hours [49]. However, another report commented that recovery from this combination was rough and prolonged [50], which is conflicting with the observation reported by Nishimura et al. [51]. Linkenhoker et al. [50] compared the sedative effects and several cardiovascular variables of different combinations of ketamine with acepromazine, diazepam, midazolam, or medetomidine. They concluded that midazolam (0.5–0.6 mg/kg SC) with ketamine (25–27 mg/kg SC) produced good sedation for catheterization with little effect on cardiovascular variables. The level of sedation with medetomidine and ketamine combination did not allow for endotracheal intubation; additional mask induction with isoflurane was required to complete endotracheal intubation [50]. In another study, at least 30 minutes of deep sedation was induced with medetomidine (0.2 mg/kg IV) and ketamine (10 mg/kg IV) which was accompanied by hypertension and bradycardia in Yucatan minipigs [49]. This author used xylazine (4 mg/kg IM) and ketamine (5 mg/kg IM) to produce deep sedation in a potbellied pig for radiograph of the pelvis. The pig assumed sternal recumbency and was immobilized within 10 minutes after drug administration. Although the pig appeared to be deeply sedated, it vocalized when manipulated to change positions for radiographic imaging (Figure 3.3). Lehmann et al. [52] reported the use of midazolam (0.2 mg/kg), detomidine (0.1 mg/kg) and butorphanol (0.2 mg/kg) IM or midazolam (0.2 mg/kg), detomidine (0.1 mg/kg) and morphine (0.2 mg/kg) IM with local infiltration of lidocaine (200 mg, total) for castration of 5-month-old boars. There were no significant differences in sedation scores and respiratory rates between the combinations but the pulse rates were higher during midazolam, detomidine, and morphine sedation. Mild hypoxemia was observed

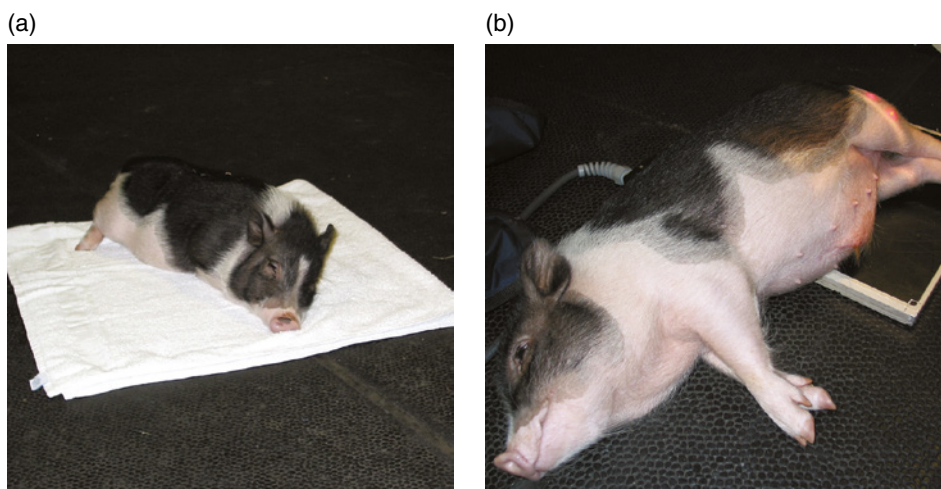


Figure 3.3 Chemical restraint in a potbellied pig with xylazine (4 mg/kg IM) and ketamine (5 mg/kg IM) for radiography.

in both combinations. The time to immobility and then to recovery were similar and all pigs stood at 84 ± 6 minutes. Atipamezole (0.03 mg/kg IM) was administered on 13 occasions (out of 16) 60 minutes after the administration of the drugs but was unnecessary for three pigs in the midazolam, detomidine, and morphine group. While both combinations produced good sedation, the authors concluded that midazolam, detomidine, and butorphanol provided more reliable sedation than midazolam, detomidine, and morphine [52].

Telazol alone (3–5 mg/kg IM) has also been used to produce sedation in potbellied pigs. Although the transition into deep sedation and immobilization is usually smooth, recovery to consciousness tends to be rough with Telazol alone [44, 47]. Similar to TKX-Ru, a mixture of Telazol, ketamine, and xylazine mixture can also be used in pigs by reconstituting 2.5 ml of ketamine and 2.5 ml of 10% xylazine with 500 mg of Telazol powder (TKX-P). The resulting solution contains 50 mg each of tiletamine, ketamine, zolazepam, and xylazine per milliliter, and the final dissociative concentration (i.e. ketamine and tiletamine) is 100 mg/ml, providing a 2 : 1 ratio of dissociative anesthetics to either zolazepam or xylazine. The response induced by this combination is dose dependent. For commercial pigs, the dose range from sedation to anesthesia is 1 ml/35–75 kg (77–165 lb) IM [53, 54]. In potbellied pigs, the doses required to induce sedation and immobilization for a duration of 35–40 minutes are 0.007–0.013 ml/kg IM and 0.012–0.018 ml/kg IM, respectively [53, 54]. When administering multiple drugs to achieve desirable effect in pigs, it is better to combine these drugs and give the mixture as a single IM bolus injection. This technique minimizes the stress caused by restraint during injection and the hyperkinetic reaction to the injection, thus ensuring better and more complete drug absorption and more reliable CNS depression. Table 3.3 summarizes the doses of drugs and drug combinations used for sedation and chemical restraint in pigs.

In general, standing sedation in farm animal species presents more of a challenge than in other domestic species. Ruminants and camelids have a tendency to assume sternal recumbency when they are sedated. Therefore, there is a fine line between the doses of a tranquilizer/sedative for standing sedation or chemical restraint, and carefully adjusting the dose may be necessary to achieve the desired effect, either standing sedation or chemical restraint, for the individual procedure. Furthermore, pigs are more resistant to the CNS-depressing effects of these anesthetics, therefore standing deep sedation is more difficult to achieve and often requires large doses of the drugs. In either case, unintended sternal recumbency may complicate the surgical procedure, and adjustment should be made to accommodate this unexpected situation.

Table 3.3 Doses of drugs and drug combinations used for sedation and chemical restraint in pigs.

Drug	Dose (mg/kg)	Comments
Acepromazine	0.2, IM	Moderate sedation
Acepromazine	0.05–0.5, IM, IV; maximum 15 mg	Sedation
Acepromazine	0.2–0.5, IM	Onset in 20–30 minutes
Acepromazine	0.2–0.11, IM	Duration 30–60 minutes
Acepromazine	1, IM	Light sedation
Ketamine	20–27, IM	

(Continued)

Table 3.3 (Continued)

Drug	Dose (mg/kg)	Comments
Acepromazine	1, IM	Immobilization
Ketamine	22, IM	
Azaperone	0.5–4, IM, IV	Onset in 5–15 minutes
Azaperone	1–2, IM	Duration 60–120 minutes
Azaperone	5, IM	–
Azaperone	8, IM	Moderate to deep sedation
Azaperone	0.25–0.5, IM	Mild sedation, no ataxia
Azaperone	0.5–2, IM	Deep sedation, greatly reduced aggression, ataxia
Azaperone	2–4, IM	Recumbency
Azaperone	1–4, IM	–
Azaperone	2–8, IM	Profound sedation
Ketamine	10–20, IM	
Chloral hydrate	44–66, IV	–
Detomidine	0.1, IM	Deep sedation with recumbency
Midazolam	0.2, IM	Add local infiltration of 200 mg lidocaine for castration
Butorphanol	0.2, IM	Atipamezole given at 60 minutes Standing in 70 minutes
Detomidine	0.1, IM	Deep sedation with recumbency
Midazolam	0.2, IM	Add local infiltration of 200 mg lidocaine for castration
Morphine	0.2, IM	Atipamezole given at 60 minutes Standing in 70 minutes
Diazepam	0.1–0.5, PO	Calming effect
Diazepam	0.1–0.2, IV	Sedation 20–30 minutes
Diazepam	0.5–1.0, IM	Sedation and muscle relaxation
Diazepam	CRI: 0.44–2 mg/kg/hour	Long-duration sedation
Diazepam	1–2, IM	Light to moderate sedation
Diazepam	5.5, IM	Tranquilization, posterior ataxia
Diazepam	8.5, IM	Recumbency Good sedation prior to general anesthesia
Diazepam	0.5–2, IM	Sedation 20–40 minutes
Ketamine	10–15, IM	
Diazepam	1–2, IM	Sedation 20–40 minutes
Ketamine	10–18, IM	
Diazepam	3.5, SC	Adequate sedation for catheterization
Ketamine	27, SC	Time to recovery 70 minutes
Diazepam	0.05–1, IM	Sedation 20–30 minutes
Ketamine	10–30, IM	

(Continued)

Table 3.3 (Continued)

Drug	Dose (mg/kg)	Comments
Ketamine	10–15, IM	Sedation, immobilization
Ketamine	5–20, IM	Chemical restraint Immobilization Rough recovery
Medetomidine	0.02–0.04, IV 0.04–0.08, IM	Sedation
Medetomidine	0.08, IM	Sedation 15–30 minutes
Ketamine	10, IM	
Medetomidine	0.2, IM	Deep sedation
Ketamine	10, IM	↑↑ Mean arterial pressure and systemic vascular resistance, ↓↓ heart rate for 120 minutes
Medetomidine	0.1–0.2, SC	Rough, prolonged recovery
Ketamine	5, SC	Seizure activity in one pig with medetomidine 0.1 mg/kg Bradycardia in one pig with medetomidine 0.2 mg/kg Time to recovery 210–225 minutes
Midazolam	0.1–0.5, IM	Sedation 40–60 minutes
Midazolam	0.2–5, IM	Sedation and muscle relaxation
Midazolam	0.2–0.4, IM	Sedation 20–30 minutes
Midazolam	0.2–0.4, intranasal	Sedation
Midazolam	CRI: 0.6–1.5 mg/kg/hour	Long-duration sedation
Midazolam	0.1–0.3, IM	Sedation
Ketamine	3–5, IM	
Midazolam	0.5–0.6, SC	Deep sedation but not allowed for intubation
Ketamine	25–27, SC	Smooth recovery Time to recovery 165–330 minutes
Midazolam	0.2–0.4, IM	Sedation 20–30 minutes
Ketamine	10–30, IM	
Midazolam	0.1–0.5, IM	Sedation 20–40 minutes
Ketamine	10–20, IM	
Butorphanol	0.18 ± 0.04, IM	Deep sedation to immobilization
Atropine	0.025 ± 0.025, IM	
Medetomidine	0.01 ± 0.006, IM	
Midazolam	0.2 ± 0.07, IM	
Xylazine	1, IM	Sedation
Xylazine	0.5–3, IM	Sedation
Butorphanol	0.18 ± 0.04, IM	Deep sedation
Atropine	0.025 ± 0.025, IM	
Midazolam	0.2 ± 0.07, IM	
Xylazine	0.6 ± 0.7, IM	

(Continued)

Table 3.3 (Continued)

Drug	Dose (mg/kg)	Comments
Xylazine	0.44, IM	Deep sedation 20–40 minutes
Ketamine	2.2, IM	
Xylazine	4, IM	Chemical restraint
Ketamine	4–5, IM	Recumbency
Xylazine	4, IM	Sedation 20–30 minutes
Ketamine	5–10, IM	
Telazol	2–4, IM	Moderate to deep sedation
Telazol	3–5, IM	Sedation 20–30 minutes
Butorphanol	0.18 ± 0.04, IM	Deep sedation to immobilization
Telazol	3.7 ± 0.9, IM	
Ketamine	2.2, IM	Deep sedation 30–35 minutes
Telazol	4.4, IM	Inadequate for tracheal intubation
Xylazine	5 ml 20 mg/ml xylazine	Short-term sedation
Telazol	(100 mg) in 500 mg Telazol 1 ml/27.3 kg (60 lb), IM	
Xylazine	0.5–2.2, IM	Deep sedation
Telazol	3–6, IM	Adequate for tracheal intubation Analgesia Potential apnea
Xylazine/ketamine/ Telazol	2.5 ml 100 mg/ml xylazine (250 mg), 2.5 ml ketamine (250 mg) in 500 mg Telazol 0.006–0.012 ml/kg, IM 1 ml/75 kg (165 lb)	Reconstitute Telazol powder with xylazine and ketamine Low-dose sedation High-dose immobilization
<i>Antagonists</i>		
Flumazenil	1 mg/10–15-mg midazolam IM 0.01 mg/kg, IV	Reversal for benzodiazepines
Atipamezole	0.2, IM	Reversal for α_2 agonists
Tolazoline	1–2, IV, IM	Reversal for α_2 agonists
Yohimbine	0.1–0.2, IV, IM	Reversal for α_2 agonists
Naloxone	0.5–2, IV, IM 4 mg IV, total	Reversal for opioid agonists

CRI, constant rate infusion.

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4

Injectable Anesthetics and Field Anesthesia

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Injectable anesthetics can be used to produce short-term anesthesia for minor diagnostic and surgical procedures, or they can be used for induction of general anesthesia followed by maintenance of inhalation anesthesia for longer procedures. Short-term injectable anesthesia is often preferred for field procedures. Compared to inhalation anesthesia, injectable anesthesia offers the advantages of ease of administration, rapid transition from awake to unconsciousness, and minimal apparatus required for its use. However, it is often difficult to maintain a consistent level of anesthesia with an injectable anesthetic, particularly when it is administered by intermittent repeated dosing. When an injectable anesthetic is used repeatedly to prolong anesthesia, accumulation of the anesthetics may cause prolonged recovery. The goal of balanced anesthesia is to provide narcosis (unconsciousness), analgesia, and muscle relaxation, which ideally can be produced by administration of a single drug. But in reality, the large dose of an injectable anesthetic which is often required to achieve balanced anesthesia and maintain anesthesia for lengthy procedures is often associated with severe adverse effects. The combinations of different classes of anesthetics are frequently used to achieve desirable anesthetic effects with as few side effects as possible. The choice of the anesthetics used for field anesthesia should be based on the intrinsic pharmacological effects of each anesthetic, types of surgery or diagnostic procedures performed, and the duration of the procedure. This chapter describes the pharmacology of commonly used injectable anesthetics and their uses for field anesthesia in farm animal species.

4.1 Injectable Anesthetics

4.1.1 Ketamine

Ketamine is a dissociative anesthetic. Presently, ketamine is the most commonly used injectable anesthetic in large animal practice. It has a rapid onset of action following intravenous (IV) administration with the maximal effect occurring within 1 minute as a result of its small molecular weight, high lipid solubility, and a dissociation constant (pK_a 7.5) value near physiologic pH allowing rapid diffusion of anesthetic across the blood–brain barrier into the central nervous system (CNS). Ketamine produces dose-dependent unconsciousness and analgesia. Termination of the

anesthetic effect after a single dose of ketamine depends on rapid redistribution of the drug from the CNS to peripheral muscle and fat tissues [1]. The primary CNS site of action appears to be mediated through the thalamoneocortical projection system. Ketamine selectively depresses neuronal function of the neocorticothalamic axis and the central nucleus of the thalamus, and at the same time it stimulates parts of the limbic system, including the hippocampus [2, 3]. Therefore, ketamine anesthesia is characterized by unconsciousness while maintaining eye reflexes (palpebral and corneal reflexes) and pharyngeal–laryngeal reflexes (e.g. swallowing reflex). Evidence indicates that antagonism of ketamine on the *N*-methyl-D-aspartate (NMDA) receptors is responsible for most of the anesthetic, analgesic, psychotomimetic, and neuroprotective effects of the drug [4]. On the cellular level, ketamine-induced anesthesia is believed to be mediated through (i) noncompetitive antagonism on the NMDA glutamate receptors, (ii) action on the voltage-dependent sodium and potassium channels and calcium channels, (iii) depression of the acetylcholine receptors, (iv) enhancement and prolongation of the γ -amino-butyric acid (GABA) receptors that link to chloride channels (GABA_A) [5], and (v) depression of nociceptive cells in the medial medullary reticular formation and activity of the laminae I and V of the dorsal horn [6, 7].

Ketamine does not depress cardiovascular function; instead, it causes direct stimulation of the CNS leading to increased sympathetic outflow, resulting in increased heart rate and arterial blood pressures during anesthesia [8]. Several contributing factors for the ketamine-induced increased sympathetic outflow have been identified including (i) sympathomimetic effects mediated within the CNS [9], (ii) inhibition of the neuronal uptake of catecholamines by sympathetic nerve endings [10], (iii) direct vasodilation of the vascular smooth muscle [11], and (iv) an inotropic effect on the myocardium [12]. Plasma concentrations of epinephrine and norepinephrine increase within 2 minutes after IV administration of ketamine and return to control concentrations 15 minutes later; this increase reflects increased sympathetic outflow due to sympathomimetic effect induced by ketamine [13]. As a result, heart rate and arterial blood pressure increase transiently following IV administration of the drug. However, the cardiovascular-stimulating effects of ketamine can be blunted or prevented by prior administration of a benzodiazepine [14, 15], droperidol [16], acepromazine, or α_2 agonist or by concomitant administration of inhalation anesthetics, including nitrous oxide [17, 18]. In the CNS, ketamine induces significant increases in cerebral blood flow (CBF), intracranial pressure (ICP), and cerebrospinal fluid (CSF) pressure as a result of cerebral vasodilation and elevated systemic arterial blood pressure [19–25]. Direct smooth muscle relaxation of bovine middle cerebral arteries via inhibition of calcium uptake has been reported, supporting the finding that ketamine causes cerebral vasodilation [26]. However, the mechanism of ketamine-induced elevated ICP remains controversial. In awake goats, ketamine increases CBF and ICP when the partial pressure of arterial carbon dioxide (PaCO₂) is allowed to rise, but CBF and ICP remain unchanged when PaCO₂ is maintained at a preketamine concentration [27, 28]. In piglets with increased ICP, a further increase in ICP paralleling a rise in PaCO₂ was observed during ketamine anesthesia. When ventilation was controlled, no increase in ICP was observed in piglets with normal or elevated ICP [28]. Increased skeletal, thoracic, and abdominal muscle tone can impede venous return from the head to cause an increase in intracranial blood volume and pressure [28, 29].

Ketamine does not depress ventilatory responses to hypoxia at clinically recommended doses [30]. Hypoxic pulmonary vasoconstriction is preserved during ketamine anesthesia but potentiated during propofol anesthesia in dogs [31]. Nonetheless, arterial oxygenation and functional residual capacity are usually well-maintained during ketamine anesthesia [32–35]. Ketamine is a potent bronchodilator capable of preventing and reversing wheezing in human patients with asthma requiring anesthesia and intubation [36, 37]. At clinically useful doses, this bronchoprotective effect is mediated primarily via depression of neurally (vagally) induced vasoconstriction [38]. In sheep,

ketamine induces a transient decrease in the partial pressure of arterial oxygen (PaO_2) in the presence of decreased or increased respiratory rate [39–41]. The transient apnea induced by ketamine appears to be dose dependent. At higher doses, respiration is characterized by an apneustic, shallow, and irregular pattern [42–44]. Severe ventilatory depression or arrest due to overdosage has been reported in human patients, cats, and ponies [44–46].

Ketamine often causes increased salivation and secretion of mucus in the respiratory tract, which can be reduced by administration of an anticholinergic drug. Laryngeal and pharyngeal reflexes usually are well maintained during ketamine anesthesia. Swallowing reflexes may be present but somewhat obtunded and most animals can be intubated when anesthetized with ketamine [47]. Ruminants normally salivate profusely during ketamine anesthesia. Total amounts of salivary secretion in conscious adult cattle and sheep have been reported to be 50 and 6–16 l per 24 hours, respectively [48, 49]. If the trachea is left unprotected during anesthesia, aspiration of a large amount of saliva can occur and may cause pneumonia.

Ketamine alone does not provide muscle relaxation. Muscle jerking and sometimes rigidity are present following the induction of anesthesia. Acepromazine, diazepam, xylazine, and medetomidine can be used in combination with ketamine to enhance the degree of analgesia and muscle relaxation during anesthesia. Ketamine has been shown to produce intense analgesia even at sub-anesthetic doses [50]. Proposed mechanisms responsible for the analgesic actions of ketamine include blockade of spinoreticular tracts [51, 52], depression of nuclei of the medial medullary reticular formation [6], suppression of lamina in the dorsal horn of the spinal cord [7, 53, 54], interaction with CNS and spinal cord opiate receptors [55–58], and antagonism of NMDA receptors [4]. Studies also indicate that ketamine induces visceral analgesia as evidenced by inhibition of nociceptive responses to graded tests in rats [59–61]. Furthermore, NMDA receptors appear to be more involved in hyperalgesic responses after peripheral tissue injury and inflammation rather than nonnoxious somatic inputs [60, 62]. Ketamine administered at 0.25–0.5 mg/kg intramuscularly every 6–8 hours has been used in combination with opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) to provide pain relief in goats suffering severe pain due to burn injury, polyarthritis, or osteomyelitis [63].

4.1.1.1 Cattle

An IV bolus injection of ketamine (2 mg/kg) followed by continuous infusion of 0.2% (2 mg/ml) ketamine in physiologic saline at a rate of 10 ml/min induces dissociative anesthesia for both minor and major surgeries (toe amputation, laparotomy, etc.) in cows weighing 450 kg (990 lb) [64]. Intramuscular (IM) administration of ketamine alone or in various combinations with other drugs in calves has been used to induce chemical restraint or anesthesia, but this technique is impractical for adult cattle due to the large volume of drug required for the size of the animal. Presently, IV ketamine (2.2 mg/kg) is commonly administered concomitantly with or after IV administration of xylazine (0.1–0.2 mg/kg) for short-term anesthesia in both large and small ruminants. Tracheal intubation is easily achieved in cattle anesthetized with this combination. Anesthesia may be safely prolonged by intermittent IV injection of 1–2 mg/kg of ketamine given slowly to effect. Alternatively, a continuous infusion of 2 mg/ml of ketamine in 0.9% NaCl solution, 5% dextrose solution, or 5% guaifenesin in 5% dextrose solution is administered at a rate of 10 ml/min for animals with a body weight of 450 kg (990 lb) to prolong anesthesia [65].

4.1.1.2 Small Ruminants and Camelids

In sheep, ketamine alone (22 mg/kg IV) may cause side effects such as tachycardia, muscle rigidity, and mild salivation during anesthesia and marked ataxia during recovery [66]. However, at a low

IV bolus dose of 2 mg/kg followed by 4 ml/min of continuous infusion of 0.2% ketamine in 5% glucose solution (2 mg/ml) for up to 2 hours, ketamine produced safe anesthesia in pregnant ewes [67]. In goats, IM ketamine (10 mg/kg, 84 minutes) [68] produced longer duration of anesthesia than in goats that were administered with IV ketamine (6 mg/kg, 15–30 minutes) [69]. Levinson et al. [70] reported that ketamine caused an increase in uterine blood flow but did not produce detrimental effects on fetal cardiovascular or acid–base status. When administered intramuscularly or intravenously to pregnant goats, ketamine rapidly traversed the placental membrane, resulting in an increase in fetal heart rate and blood pressure. Fetal arterial pH value (pHa) and PaO₂ decreased while PaCO₂ increased during anesthesia. The detrimental effects of ketamine on the fetus appeared to be greater with IV administration than with IM administration [71]. When administered to induce general anesthesia, ketamine reportedly increased basal uterine tone as well as the intensity of the contractions in both pregnant and nonpregnant women. Nonetheless, the study showed that human fetal mortality is less with ketamine than with thiopental [72].

Similar to cattle and small ruminants, ketamine (1 mg/ml) is often combined with 5% guaifenesin and given to effect (1.5–2.2 ml/kg IV) to induce and maintain general anesthesia for 15–20 minutes in camelids. When using xylazine and ketamine combination to induce satisfactory anesthesia and to facilitate tracheal intubation, camelids appear to require a higher dose of ketamine (3–5 mg/kg) [73] as opposed to the lower dose of 2.2 mg/kg normally used for cattle and small ruminants [74].

4.1.1.3 Swine

Ketamine administered intramuscularly alone (11 mg/kg) to pigs provides anesthesia that may more appropriately be considered chemical restraint [42]. Although immobilization occurred within 3–5 minutes, muscle relaxation was considered poor with only a brief period of analgesia. IV administration of an additional 2–4 mg/kg of ketamine prolonged immobilization [42]. Violent reactions in pigs to initial IM injection of ketamine with subsequent muscle tremor, extensor rigidity, panting respiration, and erythema have been reported [75]. Other side effects including tachycardia, hypertension, and poor muscle relaxation, as seen in other species, are also observed in pigs. Concurrent administration of diazepam (1 mg/kg IM) or xylazine (2 mg/kg IM) with ketamine provided deep sedation and good muscle relaxation and minimized adverse reactions, but unfortunately pigs still responded to surgical stimulus, for example incision of the abdominal wall [75, 76].

4.1.2 Telazol

Telazol, a proprietary combination of tiletamine (dissociative derivative) and zolazepam (benzodiazepine derivative), produces anesthesia similar to the commonly used anesthetic combination of diazepam and ketamine. Tiletamine and zolazepam are combined in a 1 : 1 ratio by weight of base and marketed as Telazol. The combination of the drugs is supplied in a sterile vial as a lyophilized powder containing 250 mg of tiletamine and 250 mg of zolazepam. It is recommended that the drug be reconstituted immediately before use with 5 ml of sterile water, resulting in a combination of 50 mg of tiletamine and 50 mg of zolazepam per milliliter of the solution. Telazol has a wide margin of safety and has been used to produce safe anesthesia in a wide variety of animal species, including wildlife. The pH of the injectable solution of Telazol is between 2 and 3.5; though acidic, it does not cause tissue irritation and the animal's reactions to IM injection of the drug are minimal. Induction of anesthesia is rapid and smooth, as is recovery in most species. Compared with ketamine, Telazol anesthesia produces better muscle relaxation, more profound analgesia, and longer-lasting effects.

The swallowing and eructation/vomiting reflexes are retained. Muscle relaxation and general lack of response to external stimuli add to Telazol's usefulness. Telazol induces analgesia from interruption of sensory input into the brain, which usually persists after the anesthetic effect has subsided. The animal's eyes remain open, even during surgical anesthesia. Protective reflexes, such as coughing, swallowing, and corneal and pedal reflexes, are maintained. Increased salivation is a common occurrence in most animals administered with Telazol. An anticholinergic drug (e.g. atropine and glycopyrrolate) can be administered with Telazol to reduce salivation [77].

In llamas, Telazol causes no significant changes in heart rate [78]. In calves, Telazol (4 mg/kg IV) induces a transient decrease followed by an increase in heart rate. The mechanism of the transient decrease in heart rate is believed to be caused by tiletamine's negative inotropic and chronotropic effects [79]. The direct depressant effect of tiletamine was clearly demonstrated in denervated myocardium [80]. A decreased amplitude of myocardial contraction was observed when tiletamine (0.5–5 mg) was administered into the coronary circulation of an isolated rabbit heart preparation [81]. The subsequent increase in heart rate is attributed to direct CNS stimulation leading to increased sympathetic tone and perhaps decreased vagal tone [82]. Changes in arterial blood pressure and systemic vascular resistance induced by Telazol are characterized by a decrease followed by an increase after IV injection to calves. Tiletamine may play a major role in the unique biphasic hemodynamic changes occurring after Telazol administration [79]. In calves, the biphasic response in arterial blood pressure induced by Telazol (4 mg/kg IV) is reversed when Telazol is combined with xylazine (0.1 mg/kg IV). The hemodynamic effects of Telazol are offset by the initial vasoconstrictive effect and delayed sympatholytic and parasympathomimetic effects of IV xylazine [83]. In sheep, butorphanol (0.5 mg/kg IV) administered preanesthetically does not influence the decrease in mean systemic and pulmonary arterial pressures induced by Telazol (12 mg/kg IV). Heart rate does not change significantly when butorphanol is administered with or prior to Telazol, although increased systemic vascular resistance is observed [84]. In calves, left ventricular stroke work index and rate pressure product follow a similar biphasic response as seen with blood pressure and systemic vascular resistance after Telazol injection [79]. Cardiac output remains unchanged in calves and llamas [78, 79]. Decreased cardiac output is observed in sheep given butorphanol/Telazol [84]. In calves receiving xylazine and Telazol, cardiac output decreased transiently and was associated with an increase in afterload and a decrease in heart rate [83].

Respiratory rate usually increases in most species following Telazol injection. In calves, low doses (LDs) of Telazol (4–8 mg/kg IV or IM) increase respiratory rate for 30–60 minutes. Apnea may occur when larger doses (10 mg/kg IM) of Telazol are administered, but spontaneous breathing usually soon resumes without respiratory support. In sheep, although respiratory rate remains unchanged, apneustic breathing and decreased inspired minute ventilation and tidal volume are observed after Telazol administration (12 or 24 mg/kg IV) [74]. In llamas, mild respiratory depression accompanied by hypoxemia is also evident [78]. Hypothermia may occur after Telazol injection as a result of profound muscle relaxation. Body temperature should be monitored, as supplemental heat may be required during Telazol anesthesia, particularly in small patients.

4.1.2.1 Cattle

In ruminants, Telazol produces smooth induction of anesthesia rapidly with gradual and prolonged recovery [85]. The pharmacologic effect of Telazol is predominated by tiletamine since zolazepam has very minimal cardiovascular effect, but it is capable of enhancing the anesthetic effect and muscle relaxation of tiletamine. As a result, Telazol causes cardiovascular stimulation rather than depression [85, 86]. In calves, Telazol alone (4 mg/kg IV) induced 45–60 minutes of satisfactory anesthesia with minimal cardiovascular depression [79]. Telazol comes as 500 mg

powder, and it is usually reconstituted with 5 ml of sterile water into 100 mg/ml solution. The drug is very water soluble, thus it can be reconstituted with a smaller volume of sterile water into an injectable solution with higher concentration. For example, adding 2.5 ml of sterile water into 500 mg of Telazol powder results in an injectable solution with final concentration of 200 mg/ml. Because of this, Telazol has been recommended for use to capture free-ranging cattle when a smaller volume is necessary to fill the darts of a tranquilizing gun [65]. Xylazine or detomidine can be used to substitute sterile water to reconstitute Telazol powder to ensure effective chemical restraint of free-ranging cattle. A combination of Telazol, ketamine, and xylazine (TKX-Ru) has been used successfully to capture wild ruminants.

4.1.2.2 Small Ruminants and Camelids

Telazol (8–20 mg/kg IV) has been used successfully to anesthetize sheep undergoing surgical procedures. Induction is rapid and exceptionally smooth, and duration of surgical anesthesia ranges from 40 minutes to 3.7 hours. Excessive salivation can be controlled by administration of 0.066 mg/kg of atropine sulfate [87]. IV doses of 12 or 24 mg/kg of Telazol cause a significant decrease in minute ventilation and respiratory airflow that is characterized by an apneustic breathing pattern [88]. IM administration of 12 mg/kg of Telazol appears to be the optimal dose, with surgical anesthesia lasting approximately 30 minutes. The analgesic effect was found to be most profound around the head, the neck, and the trunk, whereas poor analgesia was found in the distal portion of the limb and perineal area [89]. Hypoventilation and hypothermia have been observed in sheep anesthetized with Telazol alone or with xylazine. Assisted or controlled ventilation with O₂ supplementation may be required in the presence of severe hypoventilation and hypoxemia [90].

In llamas, Telazol (4.4 mg/kg IM) provides good chemical restraint and immobilization for 2 hours, but the degree of muscle relaxation and the quality of analgesia are not sufficient for major surgery [78]. In free-ranging adult guanacos, Telazol (4–6 mg/kg) produced immobilization for an average duration of 7 minutes (1.5–53 minutes) [91]. When xylazine (0.4 mg/kg IM) was combined with Telazol (2 mg/kg IM), longer duration of recumbency (112 ± 9 minutes) and analgesia (51.3 ± 7 minutes) occurred. Hypoxemia with PaO₂ lower than 60 mmHg was observed in these llamas while in lateral recumbency and breathing room air. Nevertheless, arterial oxygen saturation from a pulse oximeter (SpO₂) values remained relatively high (83–95%) in this study [92]. When morphine (0.5 mg/kg IM) was added to xylazine (0.15 mg/kg IM) and Telazol (2 mg/kg IM) combination, the duration of analgesia was longer (48 ± 5 minutes) than that of xylazine (28 ± 5 minutes) or morphine (5 ± 5 minutes) alone with Telazol. Similar to the previous study, hypoxemia (PaO₂ < 60 mmHg) developed 5 minutes after administration of the same drug combinations and soon after the animals were placed in lateral recumbency position regardless of the anesthetic combinations used [93].

4.1.2.3 Swine

Telazol alone in pigs (doses range from 4.4 to 22 mg/kg) induces rapid immobilization but does not produce adequate muscle relaxation and analgesia sufficient for surgery. A hyperresponsive reflex characterized by exaggerated limb withdrawal is common and often persists throughout the course of immobilization. Similar responses have been described in swine receiving ketamine alone [42]. Ganter and Ruppert [94] reported that 10 mg/kg of Telazol given intramuscularly induced rapid immobilization with an average duration of 33.7 ± 15 minutes. Although muscle relaxation was described as good, analgesia was poor. During recovery, the pigs were excited and salivated excessively. It appears that zolazepam in pigs does not induce the same degree of muscle relaxation or suppress hyperresponsiveness as effectively as it does in other species [95–98].

4.1.3 Propofol

Propofol (PropoFlo™) is a unique short-acting anesthetic. Structurally, propofol does not relate to any of the injectable anesthetics currently available in veterinary practice. Propofol is only slightly water soluble and comes as a white, oil-in-water emulsion containing 10 mg of propofol, 100 mg of soybean oil, 22.5 mg of glycerol, and 12 mg of egg lecithin per milliliter in sterile glass ampules. Because this emulsion contains no preservative, after the ampule is opened the contents should be used or discarded within 8 hours. Rapid recovery from propofol is believed to be the result of a combination of rapid redistribution of the drug to peripheral muscle and fat tissues as well as rapid hepatic and extrahepatic metabolism [99, 100]. Complete recovery without residual sedation and ataxia makes propofol a popular choice for outpatient procedures. A single dose of propofol (2 mg/kg IV) produces approximately 10 minutes of anesthesia with complete recovery occurring in 20–30 minutes [101, 102]. Propofol is best used for induction before inhalation anesthesia; it also can be used as a continuous infusion to maintain short-term anesthesia [103–105]. Supplemental analgesic drug should be administered to provide pain relief following surgery since propofol at subanesthetic dose does not provide analgesia [106]. A comparative study was performed to evaluate propofol (3 mg/kg IV), thiopental (8 mg/kg IV), or ketamine (10 mg/kg IV) as induction agents in goats. The result of this study indicated that propofol was superior to thiopental or ketamine as an induction agent because of the rapid and uneventful recovery it produced [107]. A new formulation of propofol, PropoFlo 28, recently has become available. The injectable solution is also a white, water-in-oil emulsion. Instead of 1 mg/ml of benzyl alcohol, 20 mg/ml is added to the original propofol to extend its shelf life up to 28 days. Due to its extremely short duration of action and high cost, the clinical use of propofol and PropoFlo 28 is somewhat limited in farm animal species, especially in adult cattle.

4.1.3.1 Small Ruminants and Camelids

A single dose of propofol (2–6 mg/kg) induces approximately 10 minutes of anesthesia with complete recovery in 20–30 minutes in sheep [102, 103, 108, 109]. Propofol is best used for induction before inhalation anesthesia; it also can be used as a continuous infusion to maintain short-term anesthesia [103–106]. Propofol alone does not provide analgesia. Concurrent administration of an analgesic such as opioids or NSAIDs is beneficial to provide pain relief during painful procedures. At Auburn University College of Veterinary Medicine, morphine (0.2–0.4 mg/kg IV), midazolam (0.2–0.4 mg/kg IV), and propofol (2.5–3 mg/kg IV) combination has been used frequently to induce anesthesia followed by isoflurane maintenance for surgery in goats.

In camelids, 2 mg/kg of propofol does not induce muscle relaxation adequately for tracheal intubation. However, a light plane of anesthesia can be achieved with additional infusion of 24 mg/kg/hour. Llamas were able to maintain a sternal recumbency position 10–15 minutes after the discontinuation of the propofol infusion [110]. For cesarean section, pregnant camelids can be sedated with xylazine (0.1–0.2 mg/kg IM) and butorphanol (0.06–0.12 mg/kg IM), and general anesthesia induced with propofol (3.5 mg/kg IV) with diazepam (0.5 mg/kg IV) or guaifenesin. Though anesthesia can be maintained with propofol infusion for cesarean section, fetal ventilatory function may be better maintained when isoflurane in O₂ is used [111].

4.1.3.2 Swine

In pigs, total IV anesthesia has been maintained with 2 mg/kg of propofol as a loading dose and a continuous infusion of 9, 11, or 13 mg/kg/hour. Decreased heart rate, cardiac index, and dose-dependent ventilatory depression were observed with an infusion of 13 mg/kg/hour. Depending on

the total dose of propofol administered, pigs recovered and assumed sternal recumbency within 30 minutes after being administered lower doses (9 and 11 mg/kg/hour), while 60 minutes was required for pigs that received a high dose (HD) (13 mg/kg/hour) [112]. Endotracheal intubation and positive pressure ventilation may be required immediately following induction as transient apnea occurred frequently with propofol. The cardiovascular effects of propofol administered at 7.5, 15, and 30 mg/kg/hour in newborn piglets were studied. Only mean arterial blood pressure decreased 25% from baseline values; heart rate and left ventricular pressure remained unchanged for all doses [113].

4.1.4 Alfaxalone

Alfaxalone is a synthetic neuroactive steroid anesthetic. The drug is insoluble in water, but it is solubilized in cyclodextrin and marketed as Alfaxan®. Original Alfaxan is presented as an aqueous solution of 10 mg/ml without preservative and it is recommended that the unused portion be discarded after 1 day. In 2018, a preservative was added to Alfaxan and this was marketed as Alfaxan Multidose with a shelf life of 28 days. Alfaxalone produces general anesthesia and muscle relaxation by enhancing the actions on the γ -amino-butyric acid type A (GABAA) receptors [114]. The drug can be administered either by IV or IM injection. Alfaxalone is a short-acting, nonirritant, and noncumulative anesthetic with a wide safety margin. Thus, it is suitable for induction of anesthesia or for maintenance of anesthesia by continuous infusion. No contraindications were indicated when using alfaxalone with preanesthetic sedative, analgesic, or anticholinergic agents, but its administration with other injectable anesthetics is not recommended. Alfaxalone is approved by the Food and Drug Administration (FDA) for use in dogs and cats in the USA, therefore its use in farm animal species is considered as extralabel use.

4.1.4.1 Small Ruminants and Camelids

Alfaxalone (2 mg/kg IV) has been used in sheep to induce short duration of anesthesia [115]. The duration of anesthesia and the time to standing were 6.4 ± 3.6 and 22.0 ± 10.6 minutes, respectively. There were no significant changes in arterial blood pressures and respiratory rate, and apnea was not observed. Heart rate increased significantly immediately following alfaxalone administration, which lasted for 20 minutes before returning to baseline values [115]. A decrease in PaO_2 and an increase in PaCO_2 were accompanied by a significant decrease in SpO_2 and pHa for 15–20 minutes following induction. The authors of the study suggested that the effects of alfaxalone on ventilation and blood gas values were minimal but positioning of the sheep during anesthesia may have greater contribution to the changes in PaO_2 and PaCO_2 [115].

In goats, the quality of induction with alfaxalone was compared to that of ketamine [116]. Goats were sedated with midazolam (0.1 mg/kg IV) and anesthesia was induced with midazolam (0.1 mg/kg IV) and alfaxalone or ketamine at 2 mg/kg IV over 30 seconds. Goats that received alfaxalone did not require an additional dose for endotracheal intubation, whereas five of nine goats that received ketamine required an additional 1 mg/kg of ketamine to facilitate intubation. Anesthesia was maintained with isoflurane in O_2 along with continuous infusion of 0.5–1 mg/kg/hour of ketamine during orthopedic surgery [116]. Heart rate and systolic and mean arterial blood pressures decreased significantly from preinduction values with the alfaxalone group. Apnea occurred in five of nine and three of nine goats for the alfaxalone and ketamine group, respectively. All goats were placed on mechanical ventilation throughout anesthesia [116]. Subjective observation by the investigators suggested that goats receiving alfaxalone were less responsive to the placement of the mouth gag and laryngoscope during the intubation process. Seven of the nine goats in

this group showed transient focal (blinking or facial twitching) or generalized (limb paddling or muscle tremors) muscle movement. These muscle movements were of short duration and did not seem to be related to anesthetic depth [116].

In nonpremedicated alpacas, the mean dose of IV alfaxalone, propofol, and ketamine-diazepam to allow for endotracheal intubation was 2.1 ± 0.1 mg/kg, 3.3 ± 0.4 mg/kg IV, and 4.4 ± 0.6 mg/kg of ketamine and 0.2 ± 0.0 mg/kg of diazepam, respectively [117]. The quality of induction was reported to be good to excellent. Mild excitement or muscle rigidity was observed in one alpaca receiving propofol. No muscle rigidity, twitching, or tremors were observed in those receiving alfaxalone. The mean duration of anesthesia was 12.0 ± 1.9 , 10.9 ± 2.5 , and 10.0 ± 1.5 minutes for alfaxalone, propofol, and ketamine-diazepam, respectively. However, alpacas receiving alfaxalone required longer time to stand (34 ± 7 minutes) than those receiving propofol (19 ± 8.6 minutes) or ketamine-diazepam (25 ± 3.7 minutes) [117]. Heart rate was significantly higher with alfaxalone than with ketamine-diazepam. All alpacas, regardless of the treatment, developed hypoxemia with PaO_2 values below 60 mmHg and required O_2 supplementation and mechanical ventilation. The quality of recovery was worse for those receiving alfaxalone in that alpacas exhibited clinical signs of tremors, paddling, rolling, thrashing, and seizure-like activity during recovery. Nevertheless, all alpacas recovered successfully [117].

4.1.4.2 Pigs

Alfaxalone has been administered IV to azaperone-premedicated pigs at 0.7–0.9 mg/kg for induction of anesthesia. Muscle twitching was observed [118]. When alfaxalone was administered IM (5 mg/kg) with diazepam (0.5 mg/kg), the combination produced faster onset of recumbency (140–260 seconds), deeper sedation, and better muscle relaxation with minimal side effects. Tracheal intubation can be performed with either alfaxalone alone or alfaxalone with diazepam [119]. Respiratory rate decreased significantly for 5 minutes following induction, but apnea was not observed [119]. When compared to ketamine (10 mg/kg IM) and dexmedetomidine (0.01 mg/kg IM), alfaxalone (5 mg/kg IM) and dexmedetomidine (0.01 mg/kg IM) produced deeper sedation and better quality of induction of anesthesia [120]. Muscle twitching and limb movement were observed in some pigs receiving alfaxalone and dexmedetomidine, whereas slight excitement with grunting occurred in those receiving ketamine and dexmedetomidine [120].

Alfaxalone in combination with sedatives and analgesics can be used to produce safe anesthesia in pigs. However, the volume of the drug required for larger pigs (1% solution in cyclodextrin, >10 ml for pigs up to 22 kg [48.4 lb] body weight) may be a limiting factor for widespread use of alfaxalone in pigs.

4.1.5 Guaifenesin

Guaifenesin is a central muscle relaxant frequently used in large animal practice. The drug acts by interrupting impulse transmission in the internuncial neurons of the spinal cord, brain stem, and subcortical areas of the brain. Unlike neuromuscular blocking drugs, guaifenesin produces muscle relaxation, not muscle paralysis. In cattle, IV guaifenesin administered at 50 mg/kg induced ataxia and muscle relaxation. Recumbency occurred at a dose of 100 mg/kg [121]. Only minimal changes on respiratory muscle activity and respiratory and cardiovascular functions were observed when guaifenesin was administered at the therapeutic dose [122]. However, a significant decrease in arterial blood pressure and acute respiratory acidosis occurred following the administration of guaifenesin (165 mg/kg) to buffalo calves [123]. Guaifenesin doses three to four times higher than the dose required to induce recumbency can result in respiratory paralysis [124]. Guaifenesin is not an

anesthetic, and it does not produce anesthesia or analgesia. Therefore, guaifenesin should always be used in combination with anesthetic(s), for example ketamine, thiopental, or propofol, for good muscle relaxation during anesthesia [65]. Nevertheless, guaifenesin alone at 15–25 mg/kg IV induces mild standing sedation in large ruminants and camelids, but the amount of drug administered should be carefully titrated to avoid excessive muscle relaxation and recumbency [125]. Guaifenesin comes as a powder and can be reconstituted with 5% dextrose to make up 5% (50 mg/ml) or 10% (100 mg/ml) injectable solution by a compounding pharmacist. Thrombophlebitis has occurred following the administration of 5% guaifenesin solution [126]. However, hemolysis, hemoglobinuria, and venous thrombosis are more likely to occur with solution of 10% or greater [127]. Guaifenesin, xylazine, and ketamine combination, referred to as Triple Drip, is a popular injectable anesthetic combination for short-term anesthesia in large and small ruminants, camelids, and pigs. Because of the breed and species variation in sensitivity to xylazine and individual difference for the anesthetic dose requirement, adjustment of the concentration of each drug in Triple Drip and the rate of infusion of the mixture is very important to ensure safe anesthesia.

4.2 Field Anesthesia

4.2.1 Cattle

Acepromazine, diazepam, xylazine, and medetomidine can be used in combination with ketamine to enhance analgesia and muscle relaxation during anesthesia. IV administration of xylazine (0.1–0.2 mg/kg) prior to or concomitantly with ketamine (2–3 mg/kg) is the most commonly used combination to induce short-term anesthesia in cattle of all ages. Lowering the dose of xylazine in cattle weighing more than 600 kg (1320 lb) may be appropriate [128]. While IM xylazine (0.1–0.2 mg/kg) and ketamine (10–15 mg/kg) can be used in young calves, this is impractical for adult cattle because of the large amount of ketamine required [101]. Tracheal intubation is easily achieved in cattle anesthetized with this combination (Figure 4.1). Duration of anesthesia with IV xylazine and ketamine is approximately 20–30 minutes in most cases. Anesthesia may be safely prolonged by IV administration of a third to half of the original dose of each drug or 1–2 mg/kg of ketamine given slowly to effect for additional 15 minutes [65]. In calves anesthetized with xylazine and ketamine, the decrease in heart rate induced by xylazine is offset by the increased sympathetic tone from subsequent administration of ketamine. When xylazine and ketamine are administered simultaneously, no significant changes in heart rate, cardiac output, and arterial blood pressure are observed [129, 130]. Thus, it appears that administration of xylazine prior to or simultaneously with ketamine offers the advantage of minimizing the decrease in heart rate and arterial blood pressure induced by xylazine alone [131]. Respiratory rate often increases after xylazine and ketamine administration, but it is usually accompanied by a decrease in PaO_2 and an increase in PaCO_2 [132, 133]. Arterial pH decreases slightly as a result of accumulation of PaCO_2 . Only minor changes in base excess and bicarbonate are observed during xylazine and ketamine anesthesia, indicating hypoventilation is minor without the need for metabolic compensation [132]. Alternatively, anesthesia can be maintained with a continuous infusion of ketamine (2 mg/ml) in 0.9% NaCl solution or 5% dextrose solution at a rate of 10 ml/min [65]. A bolus injection of ketamine (2 mg/kg IV) followed by continuous IV infusion of 0.2% (2 mg/ml) ketamine in 0.9% NaCl solution at a rate of 10 ml/min in cows produces anesthesia appropriate for minor and major surgeries (e.g. toe amputation, laparotomy, etc.) [64]. LDs of xylazine (0.05 mg/kg IV or 0.05–0.1 mg/kg IM) and ketamine (2 mg/kg IV or 4 mg/kg IM) combined have been used to produce anesthesia with less



Figure 4.1 Endotracheal intubation using the digital palpation technique in a bull anesthetized with xylazine (0.1 mg/kg IV) and ketamine (2.2 mg/kg IV).

intensity of analgesia and shorter duration of recumbency [125]. As mentioned in Chapter 3, IV xylazine (0.1–0.2 mg/kg) and diazepam (0.1–0.2 mg/kg) induce approximately 30 minutes of immobilization with analgesia in adult cattle [134]. Depending on the desired level of analgesia, HD of xylazine with LD of diazepam is suitable for procedures requiring a greater degree of analgesia, whereas LD of xylazine with HD of diazepam is preferred for animals with high anesthetic risk.

Ketamine (1 mg/ml) can be mixed with 5% guaifenesin (50 mg/ml) solution to maintain short duration of anesthesia in ruminants [86]. A combination of guaifenesin (50 mg/ml), ketamine (1–2 mg/ml), and xylazine (0.1 mg/ml), often referred to as *Bovine Triple Drip* or *GKX*, can be used for procedures that require longer duration of anesthesia [135]. Anesthesia using *Bovine Triple Drip* can be induced with 0.55–1.1 ml/kg initially and maintained with 2.2 ml/kg/hour in adult cattle and 1.65 ml/kg/hour in calves. Onset of anesthesia is gradual but smooth, muscle relaxation is excellent, and tracheal intubation is easy. Supplementation with O₂ (5–10 l/min) during prolonged procedures may help prevent hypoxemia. Mild hypoventilation is observed when this anesthetic mixture is used. Recovery to standing with *Bovine Triple Trip* usually occurs within 40–45 minutes after discontinuation of the infusion. Surgical procedures that have been performed in cattle anesthetized with *Bovine Triple Trip* include femoral fracture plating and pinning, penile surgery, umbilical hernia repair, cesarean section, and celiotomy [74]. The concentration of xylazine and/or ketamine should be reduced to 0.05 and 1 mg/ml, respectively, for procedures lasting longer than 2 hours to prevent accumulation of the drugs and prolonged recovery. Because cattle anesthetized with *Bovine Triple Drip* may regurgitate due to profound muscle relaxation, tracheal intubation is recommended immediately following induction [101].

A combination of higher doses of ketamine, xylazine, and butorphanol (*Ketamine Stun*) than those used for standing sedation and chemical restraint can be used to produce a short duration of recumbency and anesthesia. Onset of recumbency occurs within 1 minute following IV

bolus injection of ketamine (0.3–0.5 mg/kg), xylazine (0.025–0.05 mg/kg), and butorphanol (0.05–0.1 mg/kg). Animals may appear to be “awake” but are not responsive to external stimulations. Many minor surgical procedures can be performed under this level of light anesthesia. Mild involuntary head or limb movements can occur which are not a response to surgical stimulation. Purposeful movement or vocalization indicates inadequate depth of anesthesia, and half of the initial doses of xylazine and ketamine should be administered to produce appropriate depth of anesthesia. Surgical anesthesia is produced with this combination; however, local anesthetic can be administered to the surgical field to enhance analgesia. A short period of anesthesia (15–20 minutes) is achieved with this combination. IM or subcutaneous (SC) administration of the same combination, ketamine (0.1 mg/kg), xylazine (0.05 mg/kg), and butorphanol (0.025 mg/kg), produces recumbency but with less analgesia as compared to that produced when administered by IV injection. Recumbency occurs within 3–10 minutes and lasts for 45 minutes following SC injection. Endotracheal intubation can be accomplished with this technique [125]. Initially, the combination of butorphanol (0.0375 mg/kg), ketamine (3.75 mg/kg), and xylazine (0.375 mg/kg) was described by Dr. Larue Johnson at Colorado State University. The combination was made by adding 1 ml of xylazine (100 mg) and 1 ml of butorphanol (10 mg) to 10 ml (1000 mg) of ketamine and administering the combination at a dose of 1 ml/20 kg (44 lb) IM. Recumbency occurs within 3–5 minutes with 20–30 minutes of anesthesia. Half of the original dose of each drug can be administered to extend the duration of anesthesia. This dose combination is recommended only for healthy animals as the combination contains a higher dose of xylazine [136] than that described by Abrahamsen [125]. Recovery to standing time is expected to be longer with this dose combination. In clinical practice, IV butorphanol (0.025–0.05 mg/kg), xylazine (0.1–0.15 mg/kg), and ketamine (0.5–1 mg/kg) has been used to produce 30 minutes of surgical anesthesia for complicated umbilical surgery. Xylazine and butorphanol are administered to produce profound sedation and followed by ketamine to induce anesthesia. Miesner [137] indicated that endotracheal intubation during these surgical procedures greatly improved the quality and duration of the anesthesia. If surgery requires an hour or longer, IV infusion of Bovine Triple Drip can be used to extend the duration of anesthesia.

IV administration of medetomidine (0.02 mg/kg) and ketamine (2.2 mg/kg) induced lateral recumbency for 94 ± 25 minutes in Holstein calves [138]. Muscle relaxation was adequate for endotracheal intubation in all calves. During anesthesia, heart rate remained unchanged, but arterial blood pressure increased significantly. Respiratory rate increased significantly immediately following drug administration, but mean values for PaO_2 , PaCO_2 , and pH_a remained within normal ranges. Atipamezole and tolazoline were each effective in reversing medetomidine and ketamine anesthesia with recovery to standing occurring in 4 ± 3 and 16 ± 9 minutes, respectively, after injection. Yohimbine is the least effective of the three α_2 antagonists in shortening the duration of medetomidine and ketamine anesthesia; calves did not stand for 48 ± 20 minutes after the injection [138]. Medetomidine (0.02 mg/kg IV) combined with a lower dose of ketamine (0.5 mg/kg IV) was reported to produce anesthesia of 32 minutes for calves undergoing umbilical hernia surgery. The intensity of analgesia produced by the lower dose of ketamine in this combination was not sufficient to prevent signs of pain during surgery, and administration of a local anesthetic solution at the incision site was required. Similar to xylazine and ketamine combination, anesthesia can be prolonged with administration of half of the initial dose of each drug if needed [139]. In cattle, diazepam (0.1 mg/kg IV) administered prior to ketamine (4.5 mg/kg IV) produces 10–15 minutes of surgical anesthesia. Endotracheal intubation can be achieved with this combination, but swallowing reflex may still be present. Animals usually stand 30 minutes after this combination of drugs is administered [101, 128].

In calves, Telazol (4 mg/kg IV) induces 45–60 minutes of satisfactory anesthesia with minimal cardiovascular depression [79], and induces rapid immobilization when administered in doses of 4–12 mg/kg intramuscularly. When Telazol is administered at a dose of 10 mg/kg or greater, apnea occurs. Muscle relaxation is profound, but analgesia is minimal. The overall response is characteristic of general anesthesia. Xylazine can be administered at a dose of 0.1–0.2 mg/kg IM in combination with Telazol (4 mg/kg IV) to increase the duration of anesthesia for an additional 15 and 25 minutes for 0.1 and 0.2 mg/kg, respectively. However, higher doses of xylazine tend to increase the incidence of apnea [140]. By administering a combination of xylazine (0.1 mg/kg IV) with Telazol (4 mg/kg IV), a longer duration of profound muscle relaxation and analgesia was observed when compared to Telazol (4 mg/kg IV) administered alone [83, 140].

A combination of TKX-Ru has been used successfully to capture wild ruminants. When 500 mg of Telazol is reconstituted with 2.5 ml of ketamine (100 mg/ml) and 1 ml of xylazine (100 mg/ml) with a final volume of 4 ml, the concentration of each drug is 125 mg/ml of Telazol, 62.5 mg/ml of ketamine, and 25 mg/ml of xylazine, respectively. The recommended IM dose of the mixture is 1.25–1.5 ml/125 kg (275 lb) for small cattle and 1 ml/125 kg (275 lb) for larger, adult cattle. Recumbency usually occurs within 5–10 minutes following IM administration of TKX-Ru. Twenty minutes is required for the initial administration to reach peak anesthetic effect before repeat dosing is considered. Recovery to standing with this combination usually occurs within 40–60 minutes following TKX-Ru administration. Ketamine and guaifenesin mixture or Bovine Triple Drip described previously can be administered following TKX-Ru to maintain longer duration of anesthesia [141].

A combination of tiletamine–zolazepam (Telazol), ketamine and detomidine (TZKD) has been administered to induce anesthesia in calves and free-ranging cattle [142, 143]. The TZKD mixture is created by adding 5 ml of 100 mg/ml of ketamine and 4 ml of 10 mg/ml of detomidine into 500 mg of Telazol, resulting in a final concentration of 55.5 mg/ml of ketamine, 55.5 mg/ml of Telazol, and 4.4 mg/ml of detomidine. Three doses of TZKD, 1 ml/100 kg (220 lb) (LD), 1.3 ml/100 kg (220 lb) (medium dose, MD), and 1.5 ml/100 kg (220 lb) (HD) were given to calves in separate occasions. The onset to recumbency was 6 ± 2 , 5 ± 2 , and 4 ± 1 minutes for LD, MD, and HD, respectively. The duration of anesthesia was 30 ± 8 , 32 ± 6 , and 52 ± 7 minutes and the duration of total recumbency time was 83 ± 19 , 113 ± 13 , and 128 ± 13 minutes, for LD, MD, and HD, respectively [142]. The duration of analgesia, as evidenced by lack of response to pin prick stimulus, was 5 minutes for LD and 35 minutes for MD and HD. Similarly, a significant reduction in response to electrical stimulus was also observed at 35 and 55 minutes for MD and HD, respectively [142]. Mild bradycardia was observed with all doses. The most notable side effects of this combination were respiratory depression and hypoxemia which was accompanied by significant decreases in PaO_2 and O_2 saturations [142]. It is believed that the adverse effect of detomidine, an α_2 agonist, is responsible for the respiratory depression and hypoxemia observed with this combination. TZKD has been used to immobilize and anesthetize 53 free-ranging cattle for minor surgical procedures (e.g. subconjunctival infiltration, orchiectomy, goring repair, abdominal herniorrhaphy) or medical treatment (e.g. stroma treatment, joint infiltration) [143]. Most of these procedures are considered to cause minimal to moderate pain and local or regional anesthetic techniques can be applied to enhance the analgesic effect. The mean IM dose of the combination used was 1.07 ml/100 kg (220 lb). Most procedures required less than 1 hour to complete with the exception of two abdominal herniorrhaphy and one goring injury, which required one repeated dosing at 42 ± 3 minutes after the initial administration. One of the herniorrhaphy surgery was prolonged and required three repeated dosings with a final dose of 2.9 ml/100 kg (200 lb). Good analgesia occurred in 51 animals but was fair in two animals. The onset of anesthesia occurred at 6.1 ± 2.8 minutes following drug administration. The duration of

anesthesia ranged from 5 to 119 minutes [143]. Atipamezole (0.02–0.06 mg/kg IM), an α_2 antagonist, was administered at 6–41 minutes to those requiring only one single dose of TZKD. In those receiving repeated dosing, atipamezole was administered at 75–124 minutes after the initial dose [143]. Animals receiving a single dose of TZKD stood at 12.1 ± 8.4 minutes, whereas those who received repeated doses stood at 23.0 ± 14.4 minutes after the administration of atipamezole [143]. None of these animals were fasted, but no incident of regurgitation or bloating occurred even though 18 animals were placed in lateral recumbency and two were in dorsal recumbency [143]. TZKD combination is an effective drug combination and can be used to produce reversible immobilization and anesthesia. The adverse effect of respiratory depression and hypoxemia should be kept in mind and supplemental O₂ provided if possible [143].

Table 4.1 summarizes the doses of injectable anesthetic and anesthetic combinations used in cattle.

Table 4.1 Doses of injectable anesthetic and anesthetic combinations used in cattle.

Drug	Dose (mg/kg)	Comments
Ketamine	Loading dose: 2, IV CRI: 600 ml/hour of 2 mg/ml K in saline for BW 450 kg (990 lb)	–
Diazepam	0.1, IV	Immobilization with good analgesia
Xylazine	0.2, IV	
Diazepam	0.1, IV	Adequate muscle relaxation for tracheal intubation
Ketamine	4.5, IV immediately after diazepam	Anesthesia 10–15 minutes Total recumbency 30 minutes
Medetomidine	0.02, IV	Used in calves
Ketamine	0.5, IV	Incomplete analgesia, requires local anesthetic at the incision site
Medetomidine	0.02, IV	Anesthesia 70–120 minutes in calves
Ketamine	2.2, IV	
Xylazine	0.1–0.2, IM	Used in calves
Ketamine	10–15, IM	Anesthesia for 45 minutes Supplemental dose: ketamine 3–5, IM, or 1–2, IV
Xylazine	0.05–0.1, IM	Anesthesia 30–40 minutes, half of each IM for additional 15–20 minutes
Ketamine	4, IM	
Xylazine	0.05, IV, wait for sedation or recumbency or mix with ketamine, 2, IV	Surgical analgesia 15–20 minutes Half dose of ketamine to extend duration for 10 minutes
Ketamine	3–5, IV	Anesthesia 15–20 minutes
Xylazine	0.1–0.2, IV; 0.1 for >600 kg (1320 lb)	Preferred combination for adult large ruminants Can be given together as a bolus injection or separately with ketamine following xylazine
Ketamine	2, IV	Anesthesia 30 minutes Additional ketamine 0.75–1.25 mg/kg for another 15 minutes

(Continued)

Table 4.1 (Continued)

Drug	Dose (mg/kg)	Comments
Xylazine	0.1–0.15, IV	Anesthesia 30 minutes
Butorphanol	0.025–0.05, IV	Surgery for umbilical hernia repair
Ketamine	0.5–1, IV, after sign of sedation with xylazine and butorphanol	
<i>BKX</i>		Anesthesia 20–30 min
Butorphanol	0.0375, IM	Mixture: add 1 ml xylazine (100 mg) and 1 ml butorphanol (10 mg) into 10 ml ketamine (1000 mg); give 1 ml/20 kg (44 lb) IM
Ketamine	3.75, IM	
Xylazine	0.375, IM	Additional half dose of butorphanol/ketamine/xylazine for total duration of 25–35 minutes
<i>Double Drip</i>		Morphine 0.05–0.3 mg/kg IM or butorphanol 0.05–0.2 mg/kg IM for analgesia
Ketamine	1 mg/ml ketamine in 5% guaifenesin	
Guaifenesin	1.5–2.2 ml/kg, IV	
<i>Bovine Triple Drip (GKX)</i>		Adjustable dose for induction
Xylazine (0.1 mg/ml)	Induction: 0.67–1.1 ml/kg	Stable plane of anesthesia
Ketamine (1–2 mg/ml) in guaifenesin (5%)	Maintenance: 2.2 ml/kg/hour	Maintenance CRI to effect (1.5 ml/kg/hour for calves; 2 ml/kg/hour for adult cattle)
Telazol	4, IV	Smooth recovery
		Minimal cardiovascular depression in healthy calves
		Anesthesia 45–60 minutes
		Zolazepam lasts longer than tiletamine, smooth but gradual recovery
<i>TZKD</i>	1 ml/100 kg BW	Immobilization
Telazol	500 mg	Anesthesia 40 minutes
Ketamine	500 mg (5 ml)	Analgesia for minor surgery
Detomidine	40 mg (4 ml)	Atipamezole 0.02–0.06 mg/kg to shorten recovery
Xylazine	0.1, IM	Anesthesia 60 minutes
Telazol	4, IM	Standing in 130 minutes
Xylazine	0.05, IV	Shorter duration than IM
Telazol	1, IV	
Propofol	4–6, IV	Anesthesia 5–10 minutes
		Transient apnea may occur
		CRI 0.4 mg/kg/min for maintenance of light anesthesia

BW, body weight; CRI, constant rate infusion.

4.2.2 Small Ruminants and Camelids

Ketamine (1 mg/ml) and guaifenesin mixture can be used to induce and maintain anesthesia in small ruminants and camelids. Bovine Triple Drip is a commonly used anesthetic combination for induction and maintenance of anesthesia in these animals [135]. Xylazine and ketamine is another effective and widely used anesthetic combination for these two species. In general, doses of

xylazine (0.1–0.2 mg/kg IV) and ketamine (2–3 mg/kg IV) used in cattle produce similar short-term anesthesia in sheep and goats. This combination can be administered either intravenously or intramuscularly. IM xylazine (0.1–0.2 mg/kg) and ketamine (6.6–11 mg/kg) is a more convenient way to induce anesthesia in less cooperative animals [144]. Camelids are less sensitive to xylazine than are sheep and goats, thus the dose of xylazine required in the xylazine and ketamine combination is higher when used in camelids. Short duration of anesthesia can be achieved with 0.15–0.25 mg/kg IV or 0.25–0.35 mg/kg IM of xylazine combined with 3–5 mg/kg IV or 5–8 mg/kg IM of ketamine. Longer duration of anesthesia (30–45 minutes) is produced when higher IM doses of xylazine (0.5–0.7 mg/kg) and ketamine (5–7 mg/kg) are administered. Castration can be performed successfully with 0.6 mg/kg of xylazine and 6 mg/kg of ketamine for llamas and 0.7 mg/kg of xylazine and 7 mg/kg of ketamine for alpacas [145]. Alpacas tend to be temperamental compared to llamas, thus high-dose ranges of xylazine and ketamine are needed to produce desirable anesthesia (Figure 4.2). *Llama Lullaby* or *BKX*, a combination of butorphanol, ketamine, and xylazine, has been used effectively to produce short-term anesthesia in alpacas and llamas [136]. The injectable solution of the combination is made up by adding 1 ml of xylazine (100 mg) and 1 ml of butorphanol (10 mg) into 10 ml of ketamine (1000 mg) with the concentration of each drug being 0.83, 83.3, and 8.3 mg/ml for butorphanol, ketamine, and xylazine, respectively. The dose to produce 20–30 minutes of anesthesia for llamas is 1 ml/23 kg (50.6 lb) IM and for alpacas is 1 ml/18 kg (39.6 lb) IM. The resulting individual dose of each drug in this mixture for llamas is 0.036, 3.6, and 0.36 mg/kg for butorphanol, ketamine, and xylazine, respectively, and 0.046, 4.6, and 0.46 mg/kg, respectively, for alpacas [136, 146]. The same *Llama Lullaby* or *BKX* combination has also been administered at 1 ml/91 kg (200.2 lb) IM to goats to produce anesthesia. More rapid and complete anesthetic response occurs when the IM injection is made in the triceps muscles [136, 147]. Lateral recumbency generally occurs within 4–7 minutes after BKX administration with anesthetic effect sufficient for minor surgical procedures. However, endotracheal intubation may be difficult to accomplish with this combination at this dose. Addition of infiltration of local anesthetic to the

Figure 4.2 Endotracheal intubation in an alpaca anesthetized with xylazine (0.35 mg/kg IM) and ketamine (8 mg/kg IM).



incision site may be required for more painful surgery, for example castration. The times to return to sternal recumbency and standing in llamas and alpacas anesthetized with BKX were 43 ± 14.6 and 62.9 ± 12.6 minutes, respectively, for llamas and 18.4 ± 7.7 and 21.9 ± 10.4 minutes, respectively, for alpacas [147]. This shows that at this dosage range the duration of anesthesia is shorter in alpacas and repeat dosing to prolong anesthesia is more likely to be needed for alpacas. A *modified BKX* has been described, using 8 mg of xylazine, 8 mg of butorphanol, and 400 mg of ketamine mixture with the final concentration of each drug being 1.6, 8, and 1.6 mg/ml for butorphanol, ketamine, and xylazine, respectively. Safe anesthesia is produced in sheep when the combination is given at 0.022 ml/kg IV (xylazine 0.03 mg/kg, ketamine 1.6 mg/kg, butorphanol 0.03 mg/kg) [136]. Anderson [148] reported that a combination of xylazine (0.2 mg/kg IV, 0.4 mg/kg IM), butorphanol (0.1 mg/kg IV or IM), and ketamine (2 mg/kg IV, 4 mg/kg IM) provided 20 minutes of surgical anesthesia for minor surgical procedures, such as castration, in camelids. However, careful titration of the IV dose of ketamine is required as respiratory depression or even arrest has been observed after bolus IV injection of 2 mg/kg of ketamine.

Other α_2 agonists such as detomidine and medetomidine have also been used in combination with ketamine to produce short-term anesthesia. A combination of detomidine (0.02–0.04 mg/kg IM) and ketamine (2–4 mg/kg IM) has been used in New World camelids with subsequent administration of atipamezole to shorten the recovery time [91]. Only deep sedation was observed when 0.05 mg/kg of medetomidine was combined with 1 mg/kg of ketamine and administered intramuscularly to llamas. Surgical anesthesia was produced when a higher dose of ketamine (2 mg/kg IV) was administered with medetomidine (0.02 mg/kg IV) in sheep and goats. For more vigorous small ruminants, diazepam (0.44 mg/kg) and ketamine (6.6 mg/kg) combination can be administered intravenously as a bolus injection to induce short-term anesthesia [149]. α_2 agonists such as xylazine, detomidine, and medetomidine are associated with a significant increase in urine output and may be contraindicated in animals with urethral obstruction. Hyperkalemia with characteristic bradycardia, arrhythmias, and occasional cardiac arrest has been observed in goats with urethral obstruction (personal observation), therefore the minimal cardiovascular depression produced by diazepam makes this drug a good substitution for α_2 agonists to combine with ketamine for use in severely compromised animals. Diazepam (5 mg/ml) can be mixed with ketamine (100 mg/ml) at equal volumes and administered at 1 ml/18–22 kg (39.6–48.4 lb) to sheep and goats for short-term anesthesia of 15–20 minutes. Administration of an analgesic such as butorphanol (0.05–0.1 mg/kg IV or IM) or morphine (0.05–0.1 mg/kg IV or IM) may be needed for painful procedures [125].

Telazol (2.2–6.6 mg/kg IM) can be administered to small ruminants to induce general anesthesia lasting 60–100 minutes. When given intravenously, higher doses of Telazol (8–20 mg/kg) produce surgical anesthesia. The induction is reported to be exceptionally smooth with surgical anesthesia ranging from 40 minutes to 3.7 hours. Significant decrease in minute ventilation and respiratory airflow that is characterized by an apneustic breathing pattern occurred with Telazol when administered at an IV dose of 12 or 24 mg/kg [150]. In addition, 12 mg/kg of Telazol administered intramuscularly appears to be the optimal dose to produce surgical anesthesia lasting approximately 30 minutes. Administering butorphanol (0.5 mg/kg IV) along with Telazol (12 mg/kg IV) anesthesia simultaneously or prior to administration of Telazol provides good analgesia for 25–50 minutes [84]. In goats, Telazol (5 mg/kg IV) with or without butorphanol (0.1 mg/kg IV) has been used for laparotomy and embryo collecting procedures. Supplemental doses of Telazol (0.5–1 mg/kg IV) were administered to extend anesthesia. At the completion of the surgery, the average total dose of Telazol was 10.46 ± 1.64 mg/kg when administered alone and 10.53 ± 2.0 mg/kg when administered with butorphanol. Interestingly, Carroll et al. [151] reported that adding butorphanol to Telazol anesthesia did not improve visceral analgesia or prolong the duration of Telazol-induced anesthesia. Compared

to Telazol alone, xylazine (0.11 mg/kg IV) combined with Telazol (13.2 mg/kg IV) produces a longer duration of analgesia in sheep, 41.6 and 101.7 minutes, respectively. Apnea may occur after administering this combination, and sheep may require assisted ventilation immediately after IV injection of the combination. Nonetheless, apnea is short-lived, with spontaneous breathing returning within 2 minutes [90]. In llamas, Telazol (4.4 mg/kg IM) provides good chemical restraint, but muscle relaxation and analgesia are not sufficient for surgery [78].

Propofol is best used for induction before inhalation anesthesia, and it is also used as a continuous infusion to maintain longer duration of anesthesia in small ruminants [103–105]. A single dose of propofol (2 mg/kg) produces approximately 10 minutes of anesthesia with complete recovery occurring within 20–30 minutes [101, 102]. Duke et al. [110] evaluated the cardiopulmonary effects of propofol infusion in llamas. Anesthesia was induced with 2 mg/kg IV and maintained using two different infusion rates, 12 and 24 mg/kg/hour, for 1 hour. Only the higher infusion rate induced adequate anesthesia. Increased heart rate and mean carotid arterial pressure were observed during anesthesia. Three llamas became dyspneic and required nasotracheal intubation to maintain a patent airway even though PaCO₂ in these llamas remained within the normal range. All llamas recovered and stood at 13–20 minutes after discontinuation of infusion with little to no ataxia [110]. In goats, a combination of detomidine, butorphanol, and propofol has been used for induction followed by continuous IV infusion for maintenance to provide surgical anesthesia for castration or ovariectomy [152]. Comparing propofol (3 mg/kg IV), thiopental (8 mg/kg IV), or ketamine (10 mg/kg IV) as induction agents in goats, propofol was reported to be superior to thiopental or ketamine because recovery was rapid and uneventful [107]. Total intravenous anesthesia (TIVA) with ketamine and propofol infusion has been used successfully to maintain immobilization and anesthesia in goats undergoing magnetic resonance imaging procedure. These goats were sedated with midazolam (0.4 mg/kg IV), and anesthesia was induced with propofol (1 mg/kg IV) and ketamine (3 mg/kg IV) and maintained with constant infusion rates of propofol (18 mg/kg/hour) and ketamine (1.8 mg/kg/hour) with or without sevoflurane [153].

Table 4.2 summarizes the doses of injectable anesthetic and anesthetic combinations used in sheep, goats, and camelids.

4.2.3 Swine

Pigs do not tolerate restraint well, and they often protest strongly with loud noises and vigorous struggling. Gentle handling with little restraint should be practiced to minimize stress. Thus, IM administration of anesthetic drugs is preferred over more stressful IV injection. Adverse effects such as muscle tremor and extensor rigidity observed with IM ketamine alone can be minimized by combining ketamine (10–20 mg/kg IM) with drugs that produce central muscle relaxation such as diazepam (1 mg/kg IM) or xylazine (2–3 mg/kg IM). Addition of diazepam or xylazine to ketamine also reduces the potential for excitement to occur during recovery. IM diazepam (1 mg/kg) or xylazine (2 mg/kg) can be combined with ketamine (11–17.6 mg/kg) for minor procedures of short duration. Though deep sedation and good muscle relaxation occur with these combinations, pigs may still respond to noxious stimuli such as incision of the abdominal wall [75, 76, 149]. Supplemental dosing with half of the original dose of xylazine and ketamine may be required for tracheal intubation [76]. This author (Lin) prefers simultaneous administration of xylazine (2.2 mg/kg IV) and ketamine (2.2 mg/kg IV) to induce a short period of satisfactory anesthesia when IV injection is possible. Alternatively, a combination of oxymorphone (0.075 mg/kg), xylazine (2 mg/kg), and ketamine (2 mg/kg) mixed in the same syringe and given intravenously induces surgical anesthesia with good analgesia and muscle relaxation. When given intramuscularly, satisfactory response can be achieved by doubling the dose

Table 4.2 Doses of injectable anesthetic and anesthetic combinations for sheep, goats, and camelids.

Drug	Dosage in sheep and goats (mg/kg)	Dosage in camelids (mg/kg)	Comments
Alfaxalone	2, IV in sheep	–	Duration of anesthesia 6.4 ± 3.6 minutes Time to standing 22 ± 10.6 minutes Decreased in PaO ₂ and SpO ₂
Alfaxalone Midazolam	2, IV in goats 0.1, IV over 30 seconds	2, IV in alpacas	Preinduction midazolam 0.1 mg/kg IV in goats Intubation Apnea following induction Transient muscle movement Poor recovery in alpacas
Ketamine (1 mg/ml) in 5% guaifenesin	Induction: 2 ml/kg, 50–75% of calculated dose first Maintenance: 2.2 ml/kg/hour or to effect	Induction: 2 ml/kg, 65–75% of calculated dose first Maintenance: 2.2 ml/kg/hour or to effect	–
Acepromazine	0.55, IV	N/A	–
Ketamine	2.2, IV		
Detomidine	0.022, IV	0.02, IV	–
Ketamine	2.2, IV	2.2, IV	
Butorphanol	0.4, IV	0.4, IV	
Diazepam Ketamine	Mix 1 ml diazepam (5 mg) and 1 ml ketamine (100 mg); give 1 ml/18–22 kg (40–48 lb), IV	–	Anesthesia 15–20 minutes Additional analgesia: butorphanol 0.05–0.1 mg/kg IV, IM, or morphine 0.05–0.1 mg/kg, IV, IM
Diazepam	1–2, IM	0.2–0.3, IM	Light to moderate anesthesia
Ketamine	10–15, IM	5–8, IM	20–30 minutes
Diazepam	0.5–1, IV	–	Anesthesia 15–20 minutes
Ketamine	4, IV		Recumbency 30 minutes
Diazepam	0.25–0.5, IV	–	Anesthesia 15–20 minutes
Ketamine	4–7.5, IV		Recumbency 30 minutes
Diazepam	–	0.1, IV	Anesthesia 5–10 minutes
Ketamine		2.2–4.4, IV	
Diazepam	–	0.05–0.2, IV	Anesthesia 10–20 minutes
Ketamine		4, IV	
Diazepam	0.11, IV	0.2–0.3, IM	Anesthesia 10–20 minutes
Ketamine	4.4, IV	5–8, IM	

(Continued)

Table 4.2 (Continued)

Drug	Dosage in sheep and goats (mg/kg)	Dosage in camelids (mg/kg)	Comments
Diazepam	–	0.1, IV	Anesthesia 5–10 minutes
Ketamine		2.2, IV	
Diazepam	0.25–0.5, IV	0.05–0.2, IV	Anesthesia 5–10 minutes
Ketamine	4–7.5, IV	4, IV	
Ketamine	–	1.6, IV	Anesthesia 15–20 minutes
Guaifenesin (5%)		80, IV	
Medetomidine	0.015, IM	–	Anesthesia 45 minutes
Ketamine	5, IM		
Medetomidine	0.02, IV	0.05, IM	Deep sedation in camelids
Ketamine	2, IV	1, IM	
Medetomidine	0.025, IV	0.025–0.035, IM	Light anesthesia 30–60 minutes
Ketamine	1, IV	1–1.5, IM	
Midazolam	0.4, IM	–	Anesthesia 15 minutes
Ketamine	4, IV		
Xylazine	0.1, IV	0.22–0.44 IV	Anesthesia 30–60 minutes
Ketamine	2.2, IV	2.2–2.5, IV	
Xylazine	Goats: 0.1, IM; 3–5, IM	0.03–0.05, IV	High range for alpacas Anesthesia 15–20 minutes
Ketamine		3–5, IV	
Xylazine	Sheep: 0.2, IM; 3–5, IM	0.5, IM	–
Ketamine		2.2, IV	
Xylazine	–	0.44, IV	Anesthesia 15–25 minutes
Ketamine		4.4, IV	
Xylazine	–	0.25–0.35, IM	Recumbency 30–60 minutes
Ketamine		6–10, IM	
Xylazine	0.11–0.22, IM, wait for 10 minutes	0.35, IM	Induction of anesthesia and intubation
Ketamine	10–15, IM	5–8, IM	
Xylazine	–	0.8, IM	Analgesia 15–45 minutes
Ketamine		8, IM	Anesthesia 30 minutes
Xylazine	–	1.2, IM	Analgesia 50–70 minutes
Ketamine		12, IM	
Xylazine	0.2, IM	0.22, IM, wait for 10 minutes	High-dose range for alpacas
Ketamine	15, IM	10–15, IM	
Xylazine	–	Add 1 ml xylazine (100 mg/ml) to 10 ml (100 mg/ml) ketamine, 1 ml/23 kg (51 lb) IV, IM	Anesthesia 15–25 minutes
Ketamine			

(Continued)

Table 4.2 (Continued)

Drug	Dosage in sheep and goats (mg/kg)	Dosage in camelids (mg/kg)	Comments
Xylazine	–	0.5–0.7, IM	Low-dose range for llamas
Ketamine		5–7, IM	High-dose range for alpacas
BKX (Llama Lullaby)	1 ml/91 kg (200 lb), IM	Llamas: 1 ml/23 kg (51 lb), IM	Anesthesia 30–45 minutes
Butorphanol	0.009, IM	0.037, IM	Llama Lullaby: Add 1 ml of xylazine (100 mg/ml) and 1 ml of butorphanol (10 mg/ml) to 10 ml of ketamine (100 mg/ml)
Ketamine	0.92, IM	3.7, IM	
Xylazine	0.09, IM	0.37, IM	Concentration of mixture: 8.3 mg/ml xylazine, 83.3 mg/ml ketamine, and 0.83 mg/ml butorphanol
	1 ml/23 kg (51 lb), IM; 1 ml/45 kg (99 lb), IV	Alpacas: 1 ml/18 kg (40 lb), IM	
Butorphanol	0.037, IM; 0.018, IV	0.046, IM	Recumbency 18–43 minutes
Ketamine	3.7, IM; 1.8, IV	4.6, IM	
Xylazine	0.37, IM; 0.18, IV	0.46, IM	
Modified BKX	0.02 ml/kg, IV	–	Modified BKX: Add 8 mg of xylazine, 8 mg of butorphanol to 400 mg (4 ml) of ketamine; total volume 5 ml; concentration of mixture: 1.6 mg/ml xylazine, 80 mg/ml ketamine, and 1.6 mg/ml butorphanol
Xylazine	0.03, IV		Reduce xylazine dose
Ketamine	1.6, IV		
Butorphanol	0.03, IV		
Xylazine	–	0.22–0.33, IV	Recumbency 15–20 minutes
Ketamine		0.077–0.11, IV	Analgesia
Butorphanol		0.22–0.33, IV	
Xylazine	–	0.22–0.55, IM	Recumbency 45 minutes
Ketamine		0.22–0.55, IM	
Butorphanol		0.055–0.11, IM	
Butorphanol	–	0.1	Anesthesia 20 minutes
Ketamine		1.5	Castration
Xylazine		0.2	
<i>Bovine Triple Drip (GKX)</i>			
Xylazine (0.1 mg/ml)	Induction:	Induction:	Adjustable dose for induction
Ketamine	0.67–1.1 ml/kg	0.67–1.1 ml/kg	Stable plane of anesthesia
(1–2 mg/ml) in 5% guaifenesin	Maintenance: 2.2 ml/kg/hour	Maintenance: 2.2 ml/kg/hour	Maintenance constant rate infusion to effect
			Smooth recovery
Propofol	4–6, IV	–	Light anesthesia 5–10 minutes
Propofol	Induction: 3–4, IV or	Induction: 2–3.5, IV	Rapid induction
	Induction: 4–8, IV	Maintenance: 24 mg/kg/hour	Rapid recovery
	Maintenance: 18–40 mg/kg/hour IV infusion or to effect		

(Continued)

Table 4.2 (Continued)

Drug	Dosage in sheep and goats (mg/kg)	Dosage in camelids (mg/kg)	Comments
Xylazine	–	0.1–0.2, SC, IM	For cesarean section
Butorphanol		0.06–0.12, IM	Anesthesia maintained with isoflurane
Diazepam		0.5, IV	Minimal fetal effect
Propofol		3.5, IV	
Telazol	–	2, IV	Anesthesia 15–20 minutes Recumbency 25–35 minutes Poor muscle relaxation
Telazol	2–4, IV or 5.5, IV	4.4, IM	Anesthesia 100 minutes Butorphanol 0.1, IV, can be added
Telazol	2–5, IV	2–5, IV	Anesthesia
Butorphanol	0.1, IV	0.1, IV	
Dexmedetomidine	–	0.015–0.02, IM	Analgesia 30–40 minutes
Telazol		2, IM	Hypoxemia, returned to normal in 15–20 minutes Recovery to standing 81 minutes
Xylazine	–	0.4, IM	Recumbency 112 ± 9 minutes
Telazol		2, IM	Analgesia 51.3 ± 7 minutes Hypoxemia
Atropine	–	0.04, IV	Anesthesia for laparotomy
Xylazine		0.25, IV	
Telazol		1, IV	
Morphine	–	0.5, IM	Analgesia 48 ± 5 minutes
Xylazine		0.15, IM	Hypoxemia
Telazol		2, IM	

of each drug [65, 154]. Short-term anesthesia in pigs can also be achieved by administering either of the following two combinations: butorphanol (0.2 mg/kg IM), xylazine (2 mg/kg IM), and ketamine (10 mg/kg IM) or butorphanol (0.2 mg/kg IM), medetomidine (0.08 mg/kg IM), and ketamine (10 mg/kg IM). Rapid induction of anesthesia occurs with either combination. The combination of butorphanol, medetomidine, and ketamine induces more adequate anesthesia for 98.8 ± 22.5 minutes, which is characterized by good muscle relaxation appropriate for endotracheal intubation. Atipamezole (0.24 mg/kg IV or IM) can be administered to shorten the duration of anesthesia from either combination [155]. Alternatively, dexmedetomidine (0.04 mg/kg IM) or detomidine (0.06 mg/kg IM) can be used to substitute medetomidine to combine with butorphanol (0.2 mg/kg IM) and ketamine (10 mg/kg IM) for short-term anesthesia [156, 157]. Another report shows that medetomidine and ketamine combination induces longer duration of muscle relaxation (43.6 ± 12.7 vs. 21.0 ± 14 minutes) and anesthesia (49.4 ± 13.5 vs. 34.6 ± 17.2 minutes) than xylazine and ketamine combination in pigs. Slight cardiovascular stimulation with minimal respiratory effect is observed during medetomidine and ketamine anesthesia [158]. Intratesticular injection of xylazine (1–2 mg/kg) and ketamine (3–5 mg/kg) has been used to induce immobilization and anesthesia for castration of mature boars. Half the calculated dose of the combination is injected into each testicle. Surgical removal of the testicle removes the drugs not yet absorbed from the testicle, which, as a result, shortens the duration of immobilization and hastens the recovery from anesthesia [65].

As in horses and ruminants, the combination of guaifenesin (50 mg/ml), xylazine (1 mg/ml), and ketamine (1–2 mg/ml) (Swine Triple Drip) is a very useful anesthetic regimen for pigs of all ages. It should be recognized that the concentration of xylazine in this mixture is twice that used in horses and 10 times that used in ruminants. With this combination, anesthesia can be induced rapidly when administered at 0.67–1.1 ml/kg via a catheterized auricular vein. For prolonged procedures, anesthesia can be maintained by continuous infusion at 2.2–4.4 ml/kg/hour. Mean arterial pressure and systemic vascular resistance increase in pigs anesthetized with Swine Triple Drip. During anesthesia, heart rate decreases but the rate remains within an acceptable range. The PaCO_2 decreases, while PaO_2 remains unaffected. In general, continuous infusion of Swine Triple Drip induces minimal cardiopulmonary changes similar to those observed in pigs anesthetized with inhalation anesthetics. This mixture has been used to induce satisfactory anesthesia in healthy swine for up to 2 hours [159].

In miniature swine, acepromazine (0.39 mg/kg IM) and ketamine (15 mg/kg IM) combination produces anesthesia for 65–80 minutes [160]. IM administration of droperidol (1.3 mg/kg), fentanyl (0.03 mg/kg), and ketamine (12–16 mg/kg) induces surgical anesthesia of 30–40 minutes. Prolongation of anesthesia can be achieved with supplemental ketamine (2.2 mg/kg IV or 6.6 mg/kg IM) [161].

Xylazine (2 mg/kg IM), ketamine (5 mg/kg IM), and butorphanol (0.1 mg/kg IM) have been used successfully to produce light anesthesia in Vietnamese potbellied pigs for electroejaculation and artificial insemination [162]. Ketamine has also been combined with diazepam (0.5–1 mg/kg IM) or midazolam (0.2–0.4 mg/kg IM) to produce short-term anesthesia [149, 163, 164]. In miniature pigs, the anesthetic effect produced by xylazine (2 mg/kg IM), ketamine (5 mg/kg IM), and butorphanol (0.22 mg/kg IM) is reported to be better, more potent, and longer lasting (62 ± 13 vs. 28 ± 19 minutes) than that of xylazine (2 mg/kg IM) and ketamine (15 mg/kg IM). The quality of recovery is also believed to be better and smoother when the xylazine, ketamine, and butorphanol combination is administered [165].

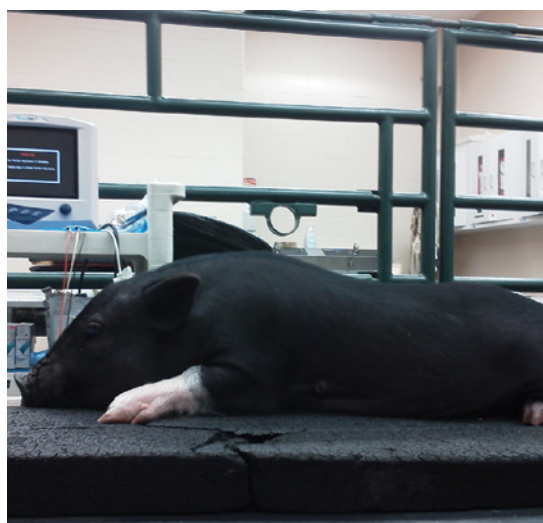
Romifidine, an α_2 agonist similar to xylazine, detomidine, and medetomidine, has been combined with butorphanol and ketamine and administered IV or IM to produce anesthesia for 20–30 minutes for castration, herniorrhaphy, or radiography procedures in pigs. Anesthesia can be prolonged for up to 2 hours with continuous infusion at 2 ml/kg/hour with the combination (5 mg of romifidine, 5.6 mg of butorphanol, and 200 mg of ketamine in 100 ml of 0.9% NaCl solution). All pigs in this study recovered uneventfully. Smaller pigs are able to stand in 50–60 minutes after the bolus injection, while 70–90 minutes is required for larger pigs with a body weight greater than 80 kg (176 lb) [166].

Telazol alone (2–4 mg/kg) can be administered intramuscularly to induce immobilization and anesthesia adequate for minor diagnostic procedures in pigs, but muscle relaxation and analgesia are deemed insufficient for surgery. Butorphanol (0.2 mg/kg) can be given concomitantly for more painful procedures. Combining xylazine (1.1 or 2.2 mg/kg IM) with Telazol (6 mg/kg IM) induces effective and safe anesthesia with good muscle relaxation for approximately 1 hour. Pigs become recumbent within 1–2 minutes following xylazine and Telazol injection. Heart rate increases but decreases gradually below baseline values at 45 minutes. Respiratory rate also increases but returns to baseline 15 minutes later. Duration of analgesia is prolonged when higher doses of xylazine are administered (68 vs. 47 minutes) [167]. IV administration of xylazine (2.2 mg/kg) and Telazol (2.2 mg/kg) combination has been recommended for short-term anesthesia or for induction where anesthesia is to be maintained with an inhalation anesthetic. Repeat dosing of Telazol to extend the duration of anesthesia is not recommended since prolonged recovery may occur, especially in older pigs. Xylazine and ketamine combination may be a better option to extend the duration of xylazine and Telazol anesthesia if needed. In feral swine (*Sus scrofa*) and wild collard peccaries

(*Tayassu tajacu*), IM xylazine and Telazol combination has been a very effective immobilizing drug combination. The combination is given at 4–5 mg/kg of each drug or by mixing 1 ml of Telazol (100 mg/ml) with 1 ml of xylazine (100 mg/ml) and administering 0.04–0.05 ml/kg of the mixture. Immobilization occurs within 5 minutes, with the pigs recovering to standing in 54–78 minutes after administration of the drugs [168]. Female babirusa (*Babirusa babirusa*: deer hog of Indonesia) was shown to require higher doses of xylazine and Telazol (xylazine 1.88 ± 0.37 mg/kg IM, Telazol 2.2 mg/kg IM) than males (xylazine 1.22 ± 0.16 mg/kg IM, Telazol 1.7 mg/kg IM). Rapid immobilization with good analgesia and muscle relaxation are the characteristic anesthetic effects of this combination. In this report, yohimbine (0.15 mg/kg IM) and flumazenil (1 mg/20 mg of zolazepam IM) are administered to antagonize the pharmacological effects of xylazine and zolazepam, respectively. Compared to yohimbine, atipamezole (0.2–0.3 mg/kg IM) appears to be more effective in reversing xylazine's effects [169].

Prolonged recovery associated with Telazol anesthesia in swine is believed to be due to zolazepam. When using Telazol alone, it is impossible to increase the concentration of tiletamine without increasing the concentration of zolazepam since the drug is a proprietary combination. In an effort to reduce the dose of zolazepam used for Telazol anesthesia and to shorten recovery, 2.5 ml of ketamine and 2.5 ml of 10% xylazine were used to reconstitute TKX-P. The resulting solution contains 50 mg each of tiletamine, ketamine, zolazepam, and xylazine per milliliter, and the final dissociative concentration (i.e. ketamine and tiletamine) is 100 mg/ml, providing a 2 : 1 ratio of dissociative anesthetics to either zolazepam or xylazine. The addition of xylazine and ketamine in this combination increases the anesthetic action and dissociative anesthetic concentrations relative to the concentration of zolazepam. The dose volume necessary to produce anesthesia is decreased, as is the dose component of zolazepam. Consequently, the prolonged recovery often observed when Telazol is administered alone is shortened with TKX-P [65, 164, 170, 171]. The anesthetic effect induced by this combination is dose dependent. For commercial pigs, the dose recommended for sedation to anesthesia is 1 ml/35–75 kg (77–165 lb) IM. In potbellied pigs, the dose required to induce sedation and immobilization for a duration of 35–40 minutes is 0.007–0.013 ml/kg IM. Doses of 0.02–0.026 ml/kg IM induce muscle relaxation adequate for tracheal intubation and surgical anesthesia for 25–35 minutes (Figure 4.3). Anesthesia can be safely extended by a supplemental IV dose of 0.006 ml/kg of TKX-P given slowly over 60 seconds. When this combination is used to

Figure 4.3 A potbellied pig anesthetized with Telazol, ketamine, and xylazine (TKX-P) combination.



induce anesthesia, the inhalation anesthetic requirement for maintenance is decreased by approximately 40–50%. The anesthetic effects of IM TKX-P (Telazol 4.4 mg/kg, ketamine 2.2 mg/kg, and xylazine 2.2 mg/kg), xylazine (4 mg/kg) and ketamine (8 mg/kg) combination, and xylazine (2.2–4.4 mg/kg) and Telazol (4.4 mg/kg) combination were studied [172]. The results showed that all four combinations produced safe and satisfactory anesthesia. However, TKX-P and xylazine and Telazol (xylazine 4.4 mg/kg, Telazol 4.4 mg/kg) were preferred drug combinations for injectable anesthesia. Many practitioners commented that TKX-P produced reliable anesthesia with good analgesia and muscle relaxation. In addition, only one single IM injection of TKX-P was needed to induce anesthesia as compared to the need of IV catheter for administration of Swine Triple Drip [65, 170, 173].

Four IM anesthetic combinations, TKX (Telazol [4.4 mg/kg, max. 8.8 mg/kg], ketamine [2.2 mg/kg, max. 4.4 mg/kg], and xylazine [4.4 mg/kg, max. 8.8 mg/kg]), TKA (Telazol [4.4 mg/kg, max. 10 mg/kg], ketamine [2.2 mg/kg, max. 5 mg/kg], and acepromazine [0.03 mg/kg, max. 0.07 mg/kg]), TAL (Telazol [4.4 mg/kg, max 11 mg/kg], acepromazine [0.3 mg/kg, max. 0.5 mg/kg], and lumbosacral epidural lidocaine [2.2 mg/kg, max. 10 ml/kg]), and KAL (Ketamine [5 mg/kg, max. 33 mg/kg], acepromazine [0.5 mg/kg, max. 1.2 mg/kg], and lumbosacral epidural lidocaine [2.2 mg/kg, max. 10 ml/kg]) were studied for percutaneous synovial fluid aspiration in healthy pigs [174]. Pigs were monitored for adequate depth of anesthesia following the administration of the initial doses of each combination. One half to all of the original dose of each drug was administered 5–10 minutes after the initial administration depending on whether the pigs were recumbent and unconscious (half of the dose) or conscious and ambulatory (full dose). Mean time to joint fluid collection was 13 ± 9 , 40 ± 7 , and 82 ± 2 minutes for TKX, TAL, and TKA, respectively. Sufficient depth of anesthesia for joint fluid collection occurred only in one pig with KAL. Mean time of recovery to sternal recumbency was 125 ± 26 , 198 ± 28 , and 363 ± 258 minutes and mean time to ambulatory was 266 ± 73 , 378 ± 79 , and 267 minutes for TKX, TAL, and TKA, respectively [174]. One pig receiving TKA died after reaching sternal recumbency and attempting to stand during recovery. Post-mortem revealed pulmonary congestion in both lungs and grossly enlarged heart with ventricular dilation. TKX and TAL both induced adequate depth of anesthesia, but only TKX consistently induced anesthetic depth suitable for synovial fluid collection [174].

When xylazine (2.2 mg/kg IM) or medetomidine (0.04 mg/kg IM) was administered with Telazol (4.4 mg/kg IM) to Landrace–Yorkshire mixed-breed pigs, both combinations produced smooth induction and good immobilization [175]. Heart rate decreased significantly throughout anesthesia for both groups. The medetomidine–Telazol group was able to maintain higher arterial blood pressures than the xylazine–Telazol group. The initial hypertension induced by medetomidine was more significant than that induced by xylazine. Mild hypoventilation and hypoxemia were observed in both groups. However, the values for PaCO_2 remained below 49 mmHg and PaO_2 above 60 mmHg. The mean time to induction was 3.0 ± 0.8 and 1.5 ± 0.6 minutes, mean time to sternal recumbency was 97.5 ± 15.5 and 106.5 ± 15 minutes, and the duration of anesthesia was 72.5 ± 10.4 and 73.6 ± 12.5 minutes for xylazine–Telazol and medetomidine–Telazol, respectively [175].

Chang et al. [176] compared the anesthetic effects of pigs using three IM combinations: Telazol (3 mg/kg), detomidine (0.18 mg/kg), and butorphanol (0.12 mg/kg) (TDB); Telazol (4 mg/kg), xylazine (4 mg/kg), and butorphanol (0.2 mg/kg) (TXB); and ketamine (8 mg/kg), detomidine (0.18 mg/kg), and butorphanol (0.3 mg/kg) (KDB). There were no significant differences in heart rate and blood pressure between combinations. Respiratory rate was significantly lower with TXB combination. However, SpO_2 did not change from baseline values for all three combinations. Endotracheal intubation was performed in all pigs except two pigs that received KDB. The duration of anesthesia was 55.3 ± 4.8 , 83.8 ± 15.8 , and 28.2 ± 4.5 minutes for TDB, TXB, and KDB,

respectively. Administration of tolazoline (2 mg/kg IM) shortened the duration of anesthesia in all pigs [176]. When combining methadone (0.2 mg/kg IM) with dexmedetomidine (0.02 mg/kg IM) and ketamine (8 mg/kg IM) or Telazol (8 mg/kg IM), Telazol and methadone combination produced faster onset of lateral recumbency (132.1 ± 30.5 seconds) with a duration from drug administration to first head movement occurring in 57.8 ± 11.4 minutes, as compared to 249.2 ± 84.0 seconds and 45.1 ± 10.5 minutes with methadone, dexmedetomidine, and ketamine combination [177]. Lower PaO_2 and SaO_2 and higher shunt fraction and alveolar to arterial O_2 differences were observed with methadone and Telazol combination. The authors concluded that both combinations produced anesthetic effects adequate for minor procedures, and the methadone and Telazol combination was associated with poor quality of recovery and oxygenation [177].

Kim et al. [178] reported that the administration of an α_2 antagonist, yohimbine (0.1 mg/kg IM), 20 minutes after IM injection of xylazine (2.2 mg/kg IM) and Telazol (4.4 mg/kg IM) significantly shortened the recovery time to standing (77 ± 9.8 vs 98.7 ± 15.8 minutes). Hyaluronidase has been used to enhance the absorption of a concurrently administered injectable drugs by its ability to degrade hyaluronic acid, which is a mucopolysaccharide widely distributed in the connective tissues [179]. The addition of hyaluronidase to reduce capture times had been reported in black rhinoceros (*Diceros bicornis*) [180]. Interestingly, Bisetto et al. [181] reported that the addition of hyaluronidase to xylazine-Telazol injection did not affect the onset and the duration of anesthesia but it shortened the recovery time (i.e. time from return of pedal withdrawal reflex to assumption of sternal recumbency) by 72% (9 ± 6 vs. 32 ± 16 minutes) in pigs. Apparently, a shorter duration of recovery from anesthesia is beneficial for the animal's wellbeing because it allows physiologic status to return more quickly to the preanesthetic values and limit the impact of potential anesthetic complications, e.g. hypothermia and postanesthetic neuromyopathy [181].

In pigs weighing 30–60 kg, medetomidine (0.02–0.04 mg/kg) and propofol (2–4 mg/kg) combination induces a light plane of anesthesia. Though medetomidine may provide some degree of analgesia, adding a potent analgesic may be necessary for painful procedures [182]. Martin-Cancho et al. [183] reported that combining propofol (11 mg/kg IV) with an opioid analgesic, fentanyl (2.5 mg/kg IV, every 30 minutes), produced surgical anesthesia for abdominal surgery [183]. The need for IV administration of propofol limits its use in pigs.

IM administration of alfaxalone (5 mg/kg) and diazepam (0.5 mg/kg) produces faster onset of recumbency (140–260 seconds), deeper sedation, and better muscle relaxation than that of alfaxalone (5 mg/kg) alone [119]. Tracheal intubation was performed successfully with alfaxalone alone or alfaxalone with diazepam [119]. When compared to ketamine (10 mg/kg IM) and dexmedetomidine (0.01 mg/kg IM), alfaxalone (5 mg/kg IM) and dexmedetomidine (0.01 mg/kg IM) produced deeper sedation and better quality of induction of anesthesia [120]. Muscle twitching and limb movement were observed in some pigs receiving alfaxalone and dexmedetomidine, whereas slight excitement with grunting occurred in those receiving ketamine and dexmedetomidine [120]. It seems that diazepam is more capable of suppressing the muscle twitching or movement associated with alfaxalone anesthesia than dexmedetomidine [119, 120].

When alfaxalone (2 mg/kg), medetomidine (0.02 mg/kg), and hydromorphone (0.1 mg/kg) combination was administered IM to pigs, it failed to produce sedation [184]. On increasing the IM doses of alfaxalone and medetomidine to 3 mg/kg and 0.03 mg/kg, respectively, and combining with hydromorphone (0.1 mg/kg IM), sedation with sternal or lateral recumbency occurred within 5–10 minutes in three pigs. However, there was variability in the quality of sedation and the degree of skin twitching and muscle movement made it difficult to place an epidural catheter in these pigs. Successful placement of a lumbosacral epidural catheter was achieved when increasing alfaxalone and medetomidine doses to 4 mg/kg and 0.04 mg/kg, respectively, and combined with

0.4 mg/kg of butorphanol to produce sedation followed by IV alfaxalone to induce anesthesia and continuous infusion of alfaxalone (0.05–2 mg/kg/min) for maintenance. Profound sedation was produced with the combination and tracheal intubation was performed without induction dose of alfaxalone in three of the nine pigs. A low IV induction dose of alfaxalone, 0.9 (0.0–2.3) mg/kg, was administered to facilitate intubation for the remainder of the pigs. The induction quality was smooth and there was no incidence of excitement, paddling, or difficulty in intubation [184]. Anesthesia was maintained with 0.1 (0.07–0.27) mg/kg/min of alfaxalone infusion for an average of 48 (37–62) minutes [184]. In another study, IM 2 mg/kg of alfaxalone, 0.02 mg/kg of dexmedetomidine, and 0.2 mg/kg of butorphanol was reported to produce better sedation than IM ketamine-dexmedetomidine-butorphanol in male pigs [185].

Three dosage combinations of alfaxalone and lidocaine have been studied, HD: alfaxalone 8 mg/kg and lidocaine 2.5 mg/kg; MD: alfaxalone 6 mg/kg and lidocaine 2 mg/kg; and LD: alfaxalone 4 mg/kg and lidocaine 1.5 mg/kg have been administered intratesticularly for castration in 2–10 days old piglets. Induction time was 2.2, 2.3, and 3.7 minutes for HD, MD, and LD, respectively [186]. Recovery to sternal position was significantly shorter with LD (16.5 minutes) than MD (21.4 minutes) and HD (21.9 minutes). Time to standing was 34.1, 31.6, and 29.6 minutes for HD, MD, and LD, respectively. Seven of the 30 pigs (23%) demonstrated shaking or twitching movement and two exhibited paddling of the limbs [186]. All treatments caused a significant decrease in heart rate, but the respiratory rate only increased in the MD and LD groups. Overall, deep sedation can be produced with all three dose combinations, and 6 mg/kg of alfaxalone and 2 mg/kg of lidocaine appears to produce sedation and analgesia suitable for castration in piglets [186].

Table 4.3 summarizes the doses of injectable anesthetic and anesthetic combinations used in pigs.

Field anesthesia with injectable anesthetics provides a convenient method allowing many minor procedures to be completed in the field. Knowledge of the pharmacologic effects of the anesthetic used alone and in combination, the type of procedure to be performed, and the duration required to complete the procedure is important for selecting an appropriate anesthetic or anesthetic combination to ensure safe anesthesia and uneventful recovery of the patient.

Table 4.3 Doses of injectable anesthetic and anesthetic combinations used in pigs.

Drug	Dose (mg/kg)	Comments
Alfaxalone	0.7–0.9, IV	Muscle twitching
Azaperone		
Alfaxalone	5, IM	Recumbency in 2–4 minutes
Diazepam	0.5, IM	Intubation
Alfaxalone	5, IM	Deep sedation
Dexmedetomidine	0.01, IM	Muscle twitching, limb movement
Alfaxalone	3, IM	Sedation in 5–10 minutes
Medetomidine	0.03, IM	Recumbency
Butorphanol	0.4, IM	Muscle twitching
Alfaxalone	4, IM	Profound sedation with alfaxalone (0.9 mg/kg IV) for induction and intubation if needed
Medetomidine	0.04, IM	
Hydromorphone	0.1, IM	Alfaxalone CRI (0.1 mg/kg/min) for maintenance of anesthesia

(Continued)

Table 4.3 (Continued)

Drug	Dose (mg/kg)	Comments
Alfaxalone	6, intratesticular	Adequate sedation and analgesia for castration
Lidocaine	2, intratesticular	Induction time: 2.3 minutes Recovery to sternal recumbency 21.4 minutes Recovery to standing 31.6 minutes
Ketamine	10–20, IM	–
Acepromazine	0.1–0.4, IM	Anesthesia 15–30 minutes
Ketamine	10–20, IM	
Acepromazine	0.5, IM	Recumbency 18 minutes
Ketamine	15, IM	
Acepromazine	1.1, IM	Light anesthesia 20–30 minutes
Ketamine	10, IM	
Azaperone	2, IM	Maintenance of anesthesia: isoflurane
Ketamine	10, IM	
Propofol	1.87 ± 0.6, IV	
Azaperone	2, IM	40–60 minutes
Xylazine	0.2, IM	
Ketamine	2, IM	
Azaperone	2.2, IM	Ketamine–morphine 20 minutes after azaperone–meperidine
Meperidine	2.2, IM	
Morphine	1.7, IM	Surgical anesthesia 60–120 minutes
Ketamine	22, IM	
Detomidine	0.125, IM	Anesthesia
Butorphanol	0.3, IM	
Midazolam	0.3, IM	
Detomidine	0.1, IM	–
Butorphanol	0.1–0.2, IM	
Ketamine	5, IM	
Detomidine	0.18, IM	Anesthesia 25–32 minutes
Butorphanol	0.3, IM	
Ketamine	8, IM	
Dexmedetomidine	0.02, IM	Anesthesia for 35–55 minutes
Methadone	0.2, IM	
Ketamine	8, IM	
Diazepam	1–2, IM	Duration 20–40 minutes
Ketamine	12–20, IM	
Diazepam	2, IM	–
Ketamine	15, IM	
Diazepam	1.1, IM	Short-term anesthesia
Ketamine	11–17.6, IM	
Diazepam	1 : 2 ratio of diazepam:ketamine	–
Ketamine	1 ml/10 kg (22 lb), IV	

(Continued)

Table 4.3 (Continued)

Drug	Dose (mg/kg)	Comments
Medetomidine	0.1, IM	–
Ketamine	1, IM	
Medetomidine	0.08, IM	Light anesthesia for 40–90 minutes
Ketamine	10, IM	
Medetomidine	0.03–0.08, IM	Anesthesia for 60–120 minutes
Butorphanol	0.1–0.2, IM	
Ketamine	5, IM	
Medetomidine	0.08, IM	Anesthesia for 60–120 minutes
Butorphanol	0.2, IM	
Ketamine	2, IM	
Medetomidine	0.08, IM	Anesthesia for 75–100 minutes
Butorphanol	0.2, IM	
Ketamine	10, IM	
Medetomidine	0.04–0.07, IM	–
Midazolam	0.08–0.3, IM	
Butorphanol	0.15–0.3, IM	
Medetomidine	0.06, IM	Good anesthesia
Midazolam	0.3, IM	Analgesia
Butorphanol	0.3, IM	
Midazolam	0.1–0.5, IM	Duration 20–40 minutes
Ketamine	10–15, IM	
Midazolam	0.5–2, IM	Light anesthesia for 20–30 minutes
Ketamine	10–15, IM	
Midazolam	0.5, SC	Effective anesthesia for instrumentation for cardiovascular catheterization
Ketamine	25, SC	
Midazolam	0.5, IM	–
Ketamine	33, IM	
Romifidine	5 mg	Maintenance of anesthesia
Butorphanol	5.6 mg	Standing in 50–60 minutes in smaller pigs, 70–90 minutes in BW > 80 kg
Ketamine	200 mg	
	In 100 ml saline	
	CRI at 2 ml/kg/hour	
Propofol	2.5–3.5, IV	Surgical anesthesia for 5–10 minutes
Propofol	2–5, IV	Duration 2–5 minutes
Propofol	6.6–8.8, IV	–
Propofol	9–11, IV	–
Fentanyl	2.5, IV	Fentanyl every 30 minutes
Propofol	CRI: 11 mg/kg/hour	
Medetomidine	0.02–0.04, IM, IV	Light anesthesia
Propofol	2–4, IV	

(Continued)

Table 4.3 (Continued)

Drug	Dose (mg/kg)	Comments
Xylazine	1–2, IM, IV	Light anesthesia
Propofol	2–4, IV	
Romifidine	0.12, IM	–
Butorphanol	0.1, IM	
Ketamine	5–8, IM	
Xylazine	0.2, IM	Recumbency 25 minutes
Ketamine	11, IM	
Xylazine	0.5, IM	Anesthesia 5–15 minutes
Ketamine	5, IM	
Xylazine	2, intratesticularly	Castration
Ketamine	6, intratesticularly	
Xylazine	2, IM	Duration 20–40 minutes
Ketamine	20, IM	Half of each drug needed for tracheal intubation
Xylazine	2.2, IM	Anesthesia extended with 2–4 mg/kg K IV
Ketamine	12–20, IM	
Xylazine	1.1, IM	Short-term anesthesia
Ketamine	11–17.6, IM	
Azaperone	2, IM	Duration 40–60 minutes
Xylazine	0.2, IM	
Ketamine	2, IM	
Xylazine	2, IM	Short-term anesthesia for abdominal surgery
Butorphanol	0.22, IM	Duration 60–120 minutes
Ketamine	10–11, IM	
Xylazine	0.2, IM	Duration 60–120 minutes
Medetomidine	0.08, IM	
Ketamine	2, IM	
Xylazine	2, IM	Anesthesia 70–100 minutes
Midazolam	0.25, IM	
Ketamine	20, IM	
<i>Swine Triple Drip (GKX)</i>	Add 1 mg/ml xylazine, 1–2 mg/ml ketamine in 5% guaifenesin	–
Guaifenesin (5%)		
Xylazine	Induction: 0.67–1.1 ml/kg, IV	
Ketamine	CRI maintenance: 2.2 ml/kg/hour, IV	
Xylazine	4, IM	Anesthesia 40–60 minutes
Ketamine	4, IM	
Oxymorphone	0.15, IM	
Xylazine	2.2, IV	Anesthesia 20–30 minutes
Ketamine	2, IV	
Oxymorphone	0.075, IV	

(Continued)

Table 4.3 (Continued)

Drug	Dose (mg/kg)	Comments
Xylazine	2.5, IM	Anesthesia 30–60 minutes
Ketamine	25, IM	
Tramadol	5, IM	
Telazol	2.2, IV	–
Telazol	2–4, IM	Short-term anesthesia for 20–30 minutes
Telazol	1–5, IM	Diagnostic procedures
Telazol	6.6, IM	Smooth induction, poor muscle relaxation and recovery
Telazol	6–8, IM	Light anesthesia for 20–30 minutes
Butorphanol	0.2, IM	Painful procedures
Telazol	2–4, IM	
Detomidine	0.18, IM	Anesthesia for 50–60 minutes
Butorphanol	0.12, IM	
Telazol	3, IM	
Medetomidine	0.04, IM	Smooth induction
Telazol	4.4, IM	Immobilization
		Induction in 1.5 ± 0.6 minutes
		Anesthesia 73.6 ± 12.5 minutes
		Recovery to sternal recumbency 106.5 ± 15 minutes
Methadone	0.2, IM	Anesthesia for 45–70 minutes
Telazol	8, IM	
Xylazine	0.2–1, IM	Light to medium anesthesia for 30–40 minutes
Telazol	2–7, IM	
Xylazine	0.5–2.2, IM	Anesthesia for 30–50 minutes
Telazol	3–6, IM	
Xylazine	0.22–2.2, IM	Xylazine improves muscle relaxation and ease of recovery
Telazol	6.6, IM	
Xylazine	1–4, IM	Anesthesia for 30–60 minutes
Telazol	4–6, IM	
Xylazine	5 ml of 100 mg/ml	Anesthesia
Telazol	xylazine (500 mg) in 500 mg telazol 1 ml/45 kg (99 lb)	
Xylazine	4, IM	Anesthesia for 65–98 minutes
Butorphanol	0.2, IM	
Telazol	4, IM	
Xylazine	1.2, IM	Anesthesia for 78 minutes
Telazol	3, IM	Excellent muscle relaxation and analgesia
Tramadol	1.6, IM	
Acepromazine	0.03–0.1, IM	Anesthesia 40–50 minutes
Ketamine	2.2, IM	
Telazol	4.4, IM	

(Continued)

Table 4.3 (Continued)

Drug	Dose (mg/kg)	Comments
Xylazine	2.5 ml of 100 mg/ml	Smooth induction
Ketamine	xylazine (250 mg) and	Immobilization
Telazol	2.5 ml ketamine	Good muscle relaxation for tracheal intubation
	(250 mg) in 500 mg	Duration 20–35 minutes
	telazol	Duration 45–60 minutes
	0.012–0.018 ml/kg, IM	
	1 ml/83–56 kg	
	(183–123 lb), IM	
	0.018–0.024 ml/kg, IM	
	1 ml/56–42 kg	
	(123–92 lb), IM	
	1 ml/35 kg (77 lb), IM	
Xylazine	2.2, IM	Anesthesia for 47–60 minutes
Ketamine	2.2, IM	
Telazol	4.4, IM	
Xylazine	4.4, IM	Anesthesia for 60–75 minutes
Ketamine	2.2, IM	
Telazol	4.4, IM	

CRI, constant rate infusion.

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Neuromuscular Blocking Agents

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Neuromuscular blocking agents (NMBAs) are a class of drugs used to produce skeletal muscle relaxation and paralysis most commonly to facilitate surgical and diagnostic procedure in anesthetized animals. Skeletal muscle paralysis can be useful for procedures that require precision and do not tolerate patient movement, such as ophthalmic surgery involving an intraorbital approach or repair of the cornea. Profound muscle relaxation achieved with the use of NMBAs can be helpful where muscle contraction impedes the progress of surgical repair, such as realignment of long bone fracture fragments. Animals having abdominal procedures may benefit from neuromuscular blockade through reduction of abdominal muscular tone that allows for easier apposition of the body wall for suturing. It is critical to understand that use of NMBAs results in paralysis of all skeletal muscle, including the diaphragm and intercostal muscles. This necessitates the use of assisted/mechanical ventilation to allow for gas exchange.

It is important to remember that NMBAs do not induce unconsciousness nor do they provide any analgesia. Therefore, anesthetic and analgesic agents must be used in conjunction with these drugs. The use of this class of drugs without rendering an animal unconscious first is inhumane and unacceptable under any circumstances.

5.1 Physiology of the Neuromuscular Junction

A detailed review of neuromuscular physiology is beyond the scope of this chapter. For further detail, the reader is referred to medical textbooks. The neuromuscular junction is the synapse between a presynaptic motor nerve endplate and the corresponding postsynaptic muscle fiber. The neuromuscular junction is the site of action where a motor nerve transmits a signal to muscle to initiate the process of contraction. Most motor nerves are of the alpha subtype and are heavily myelinated and have high conduction velocities. After making initial contact with a muscle group, motor nerves divide into small terminal nerve fibers and innervate a small number of skeletal muscle fibers. Terminal fibers tend to innervate large numbers of fibers in muscle responsible for gross movement (e.g. postural muscles), whereas terminal fibers tend to innervate few fibers in muscles responsible for fine movement (e.g. extraocular muscles).

Acetylcholine (ACh) is the chemical messenger that traverses the neuromuscular junction to relay information from the nerve to the muscle fiber [1]. Most ACh is synthesized in the terminal end of the nerve and packaged in vesicles. When an action potential reaches the terminal end of the motor neuron, calcium enters the cell and helps mobilize ACh vesicles through a voltage-gated calcium-dependent exocytosis. This results in multiple quanta (packets) of ACh entering the synaptic cleft. The released ACh diffuses across the synaptic cleft in order to interact with receptors on the postsynaptic muscle. Only about half of the ACh molecules will reach their receptors as acetylcholinesterase (AChE), present in the synapse, rapidly hydrolyzes any ACh molecule it meets to choline and acetate.

The primary receptor for ACh on the postsynaptic muscle is the nicotinic cholinergic receptor. These receptors are part of a pentameric protein ion channel. Two ACh molecules must bind with the receptor to allow for activation (opening) of the ion channel (ligand-gated ion channel). Once the ion channel is open, sodium and other cations flow into the cell, resulting in membrane depolarization and subsequent muscle contraction.

The binding of ACh to a receptor is short-lived and ACh disassociates from the receptor and diffuses back into the synaptic cleft. Abundant AChE within the synaptic cleft quickly deactivates the ACh and the free choline is taken up by the presynaptic nerve for synthesis of new ACh.

5.2 Mechanism of Action of NMBAs

A clear understanding of the physiologic events occurring at the neuromuscular junction is essential, as it is the site of action for drugs used to prevent muscular contraction. NMBAs can be broadly classified into two categories based on their mechanism of action: depolarizing NMBAs and nondepolarizing NMBAs.

5.2.1 Depolarizing NMBAs

Depolarizing NMBA drugs are limited in clinical use to only succinylcholine. When administered, succinylcholine binds to postsynaptic nicotinic receptors in a similar way to ACh. This results in opening of the ion channel and muscle membrane depolarization. However, this depolarization results in disorganized muscle contraction, which then manifests mainly as short-lived fasciculation. Succinylcholine does not dissociate from the receptor as quickly as ACh, thus prolonging the period of time that the ion channel is open. This prevents repolarization of the muscle and readying of the receptor to accept further ACh to initiate a subsequent muscle contraction. Skeletal muscle remains in a flaccid, depolarized state. Additionally, succinylcholine is not degraded by AChE, thus succinylcholine resides in the synaptic cleft longer, resulting in a prolonged effect. Succinylcholine has an onset of action of 30–60 seconds with a duration of action of 5–15 minutes. Although onset of action is quick and therefore useful for assistance with intubation, the short-lived duration of action limits the drug's clinical usefulness. Additionally, administration of succinylcholine can cause liberation of large quantities of potassium from muscle cells, particularly in animals with extensive muscle trauma, and can lead to life-threatening arrhythmias.

5.2.2 Nondepolarizing NMBAs

Nondepolarizing NMBA drugs are the current standard for patient paralysis in human and veterinary medicine. Drugs in this class work through competitive antagonism at the postsynaptic ACh receptors. These drugs do not cause depolarization of the muscle membranes but simply block the

ACh receptors from being available to be bound by ACh. Because two ACh receptors must be bound by ACh to open the ion channel, nondepolarizing NMBAs only need to bind one of the receptors to render the ion channel inoperative. After administration, NMBA concentration quickly becomes higher than that of ACh at the receptors and thus the NMBA outcompetes ACh for receptor binding and exerts its clinical effect. Muscle relaxation occurs because ACh cannot evoke a response. The neuromuscular junction has an intrinsic wide safety margin due to high numbers of ligand-gated ion channels and thus a large number of ACh receptors. This can be seen clinically, as greater than 70% of the postsynaptic ACh receptors must be blocked by an NMBA before any clinical effect will be seen. This necessitates a higher initial dosage of NMBA to get the desired effect but fractional dosages are all that are necessary to prolong the effect. Continued high dosages of drug will prolong the effect further but will not necessarily deepen the degree of muscle relaxation.

5.3 Clinically Useful NMBAs

There is very little published research into the use of NMBAs in food and fiber species. Much of the published literature relates to the use in sheep and swine for human research purposes. Thus, much of what is executed clinically is based on extrapolation from research in small animals and horses, and clinical observation of veterinary anesthesiologists. Currently, the most commonly used nondepolarizing NMBAs are atracurium, cis-atracurium, vecuronium, and rocuronium. They can be divided into two categories based on their chemical structure, benzyliisoquinolines and aminosteroids.

5.3.1 Atracurium

Atracurium is a benzyliisoquinolinium compound that has been clinically available since the early 1980s. It is composed of 10 different isomers that are variable in potency [2]. Additionally, atracurium is removed from circulation via nonspecific enzyme metabolism and Hoffman elimination, a nonenzymatic degradation related to pH and patient temperature [3]. In humans, atracurium causes release of histamine on injection and results in a decrease in blood pressure and an increase in heart rate [4]. However, although documented in laboratory species, the effect of atracurium causing release of histamine in food and fiber animals has not been reported.

Onset of action of atracurium is variable based on dosage and pH but can be expected to range between 5 and 15 minutes with increased dosage and lower blood pH shortening the time to onset [5, 6]. Duration of action is also variable and is dependent on dosage, pH, patient temperature, patient age, and type of inhalation anesthetic used [2, 5–7]. Higher dosage, lower pH, increased patient temperature and age, and use of isoflurane may result in a longer duration of blockade.

Atracurium dosages reported in sheep are 0.4 and 0.5 mg/kg and for swine are 0.4 and 2.5 mg/kg [6, 8–10]. It should be noted that higher dosages than used in other species appear to be necessary in swine to achieve clinically useful paralysis. Dosages for other ruminant species have not been reported. However, reported and clinically useful dosages in horses, dogs, and cats range from 0.11 to 0.6 mg/kg [2, 11, 12]. The author has used atracurium in several ruminant species successfully at an initial dose of 0.4 mg/kg IV and subsequent doses when needed at 0.2 mg/kg IV.

5.3.2 Cis-atracurium

Cis-atracurium is one of the isomers of atracurium and is considerably more potent. Thus, a fraction of the dosage compared to atracurium is necessary for clinical use. There are no published

reports of *cis*-aracurium use in ruminants. In horses, complete blockade has been achieved with 0.04 mg/kg. Onset and duration of action are considered to be similar to atracurium.

5.3.3 Vecuronium

Vecuronium, an aminosteroid, became clinically available around the same time as atracurium. Vecuronium has a similar clinical profile as atracurium without histamine release and has become a useful alternative to atracurium. However, in horses there are reports of resistance to its neuromuscular blocking abilities [13]. Vecuronium has been described in sheep and it appears that this species has much higher sensitivity to vecuronium than small animals and humans [14]. An appropriate dosage for small ruminants is likely around 0.025 mg/kg [15]. For swine, a vecuronium dosage of 0.4 mg/kg has been reported to be useful [16].

5.3.4 Rocuronium

To date, the newest NMBA available to veterinary medicine is the aminosteroid rocuronium. Rocuronium was developed in response to a need in human medicine for a nondepolarizing NMBA with a short onset of action time similar to succinylcholine. In humans, onset of action is less than 2 minutes after a dosage of 0.6 mg/kg, considerably shorter than equipotent dosages of atracurium (3.2 minutes) or *cis*-atracurium (5.2 minutes) [17, 18]. After a dosage of 1.2 mg/kg in swine, onset of action was less than 1 minute with a duration of action time to complete recovery of approximately 55 minutes [19]. There is minimal published data on the use of rocuronium in ruminant species. In horses, dosages between 0.2 and 0.6 mg/kg resulted in an onset of action of 2.5 minutes and a duration of action of 20 minutes to 1 hour depending on the dosage used [2]. It is important to note that anecdotal clinical impression of rocuronium in food and fiber species is that while rapid onset of action is predictable, duration of action appears to be wildly variable. The author has used rocuronium in multiple ruminants, and at a similar dosage rocuronium in one individual animal may have a duration of action of less than 15 minutes and in another individual animal of the same species have a duration of action of greater than 1 hour. For this reason, it may be more clinically practical to use conservative dosages and use top-up doses as necessary rather than a large dosage that may result in prolonged unwanted blockade. Continuous rate infusion of rocuronium has been described in dogs at 0.2 mg/kg/hour to provide a more predictable duration of blockade [20].

5.4 Monitoring of NMBA Action

Neuromuscular function monitoring of a patient receiving NMBA during a procedure should be regular practice. Residual neuromuscular blockade, unidentified persisting low levels of neuromuscular block, is a complication that can result from use of NMBAs during an anesthetic protocol. In humans, residual neuromuscular blockade results in increased postoperative morbidity and mortality in the 24 hours after anesthesia. This results from impaired contraction of ventilatory muscles with atelectasis formation, inability to cough, impaired swallowing, and accumulation of airway secretions and aspiration of gastric contents [21]. In dogs, laryngeal function appears to recover at a much slower rate than muscle of the pelvic limb, suggesting that pulmonary system compromise can occur even when full recovery of external muscle groups appears apparent [22]. Residual neuromuscular blockade has not been studied in ruminant or swine species and the

extent to which it causes problems is unknown. However, it should be assumed that residual neuromuscular blockade can lead to health concerns similar to those in humans in any species and appropriate monitoring and care should be performed.

Neuromuscular function is assessed with the use of a peripheral nerve stimulator (Figure 5.1). This device, in essence, stimulates a peripheral motor nerve and the response of the associated muscle is measured. Typically, motor nerves located in the pelvic or thoracic limbs are utilized for NMBA monitoring. This allows for measuring limb movement in response to nerve stimulation. While not described in scientific literature for food animals, the radial nerve in the thoracic limb and the peroneal nerve in the pelvic limb have been described for use in horses [2]. The author has used both of these sites for monitoring NMBAs in ruminant species (Figure 5.2).

Peripheral nerve stimulators can produce several different patterns of nerve stimulation for monitoring neuromuscular junction function. Most peripheral nerve stimulators can be programmed to deliver a single twitch, train of four, double burst, or tetanic patterns. However, only the train of four is commonly used in veterinary medicine. The train of four delivers four supramaximal electrical stimulations to the targeted motor nerve over 2 seconds (2 Hz) or one stimulation every 0.5 seconds. This evokes four muscular contractions that can be measured to determine the level of the function of the neuromuscular junction of the targeted motor neuron. A train of four can be repeated every 10–15 seconds for continuous monitoring. More frequent stimulation (less than 10 seconds between stimulations) can result in stimulation-evoked responses that suggest adequate blockade when in fact adequate blockade has not been achieved [23]. A supramaximal stimulation (having strength significantly above that which is required to activate all nerve fibers in contact with the electrodes) is used to ensure that all fibers within the target muscle have an evoked response.

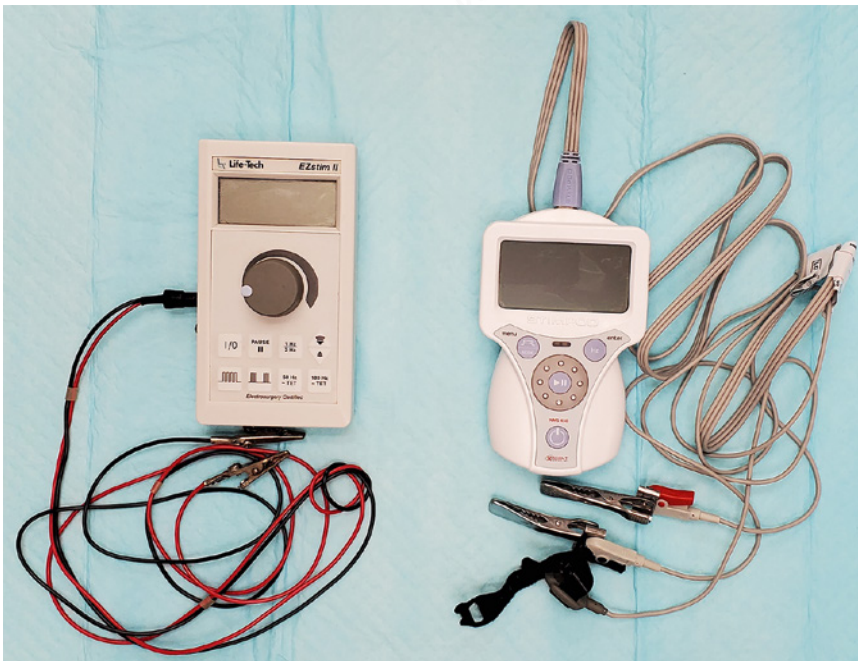


Figure 5.1 Examples of peripheral nerve stimulators used to assess the function of the neuromuscular junction.



Figure 5.2 Placement of a peripheral nerve stimulator on the pelvic limb of an anesthetized goat. The electrodes are placed with clips to stimulate the peroneal nerve. The proximal (positive) electrode is placed on the lateral aspect of the stifle and the distal (negative) electrode is placed on the lateral aspect of the hock. An accelerometer is fixed around the distal end of the limb just above the foot. This allows for measurement of changes in acceleration during nerve stimulation. Stimulation of the peroneal nerve results in an evoked muscular response that causes flexion of the hock.

When utilizing the train-of-four pattern to assess neuromuscular function, the first evoked response is compared to the fourth evoked response. When the first and the fourth twitches are of equal strength, the ratio (twitch 4/twitch 1, T4/T1) is equal to 1.0 (or 100%) and indicates a complete absence of paralysis and one can be assured that neuromuscular function is at baseline. However, as NMBAs take effect after administration, fade will be observed. Fade is a decrease in the ratio and an indication of the presence of neuromuscular blockade. For patient safety, some degree of blockade is assumed to be present at a ratio less than 0.9. The number of ACh receptors that are blocked by the NMBA can be roughly assessed by the number of evoked responses during a train-of-four stimulation. Approximately 70–75% of receptors must be blocked for fade to start to develop (loss of strength in the fourth twitch). Once 75–80% of receptors are blocked, there may be complete absence of the fourth twitch. At 85% blockade of receptors, the third twitch may be lost, at 90% blockade of receptors, the second twitch may be lost, and at 95% blockade, there may be complete absence of any twitches [24]. The train-of-four pattern can be assessed in several ways. The easiest way is to visually view the four evoked contractile responses and subjectively compare the first and the fourth twitches. If the fourth twitch or more is not present, then it can be assumed that the animal is effectively paralyzed. Absence of two or more twitches indicates paralysis suitable for surgical intervention is adequate. A train-of-four ratio cannot be calculated and only fade corresponding to a ratio of 0.5 or less can be visually detected. This can result in residual or subtle paralysis not being detected and has the potential to lead to patient complications [2]. Objective monitoring of the train-of-four can be accomplished with mechanomyography, electromyography, or acceleromyography. Mechanomyography is the measurement of the force applied by the evoked muscle. Although highly accurate, it necessitates specialized equipment that is not practical for daily use. Electromyography records the electrical activity of muscle tissue during the response to a train-of-four stimulation. Recording this activity at the cellular level has advantages in not needing actual limb movement and thus an animal can be fully secured to a surgical table. However,

Figure 5.3 A peripheral nerve stimulator that utilizes acceleromyography. The display shows the output of a train-of-four stimulation pattern of a nerve and the evoked muscular response of an anesthetized patient prior to receiving an NMBA. The first and fourth responses are of equal strength, resulting in a T4/T1 ratio of 1 (100%), indicating no presence of neuromuscular blockade.



electromyography equipment is not readily available and there are no units described for use in food or fiber animals. Acceleromyography is likely the most commonly used objective measurement device for assessing neuromuscular function in humans and animals. An accelerometer transducer is fixed to a distal location of the muscle to be stimulated (usually at the end of a limb) and acceleration is measured (Figure 5.2). Measurements from the transducer are graphically displayed on the peripheral nerve stimulator screen and a ratio of the fourth to the first acceleration is calculated and displayed (Figure 5.3). After administration of NMBA and increase in the level of blockade, fade will occur and subsequent train-of-four stimulations will reflect decreased strength and the presence of twitches (Figures 5.4–5.6).

5.5 Reversal of NMBAs

Reversal of blockade from NMBAs can be done by simply waiting out the time necessary for the drugs to dissociate from the neuromuscular junction and the return of normal function of ACh. Use of a peripheral nerve stimulator is necessary to demonstrate a T4/T1 ratio of at least 0.9 prior to discontinuing oxygen and ventilator support. However, pharmacological reversal of the effects of NMBA administration can be performed to accelerate return of neuromuscular function. As previously stated, NMBAs act through competition with ACh for postsynaptic ACh receptors of the neuromuscular junction. Essentially, the substance with the highest concentration will have the highest likelihood of interacting with a receptor. Thus, shortly after injection, the NMBA concentration will be higher than that of ACh. For reversal of effect, increasing the concentration of ACh will allow it to outcompete for the receptors. It is not possible to administer ACh as it is not

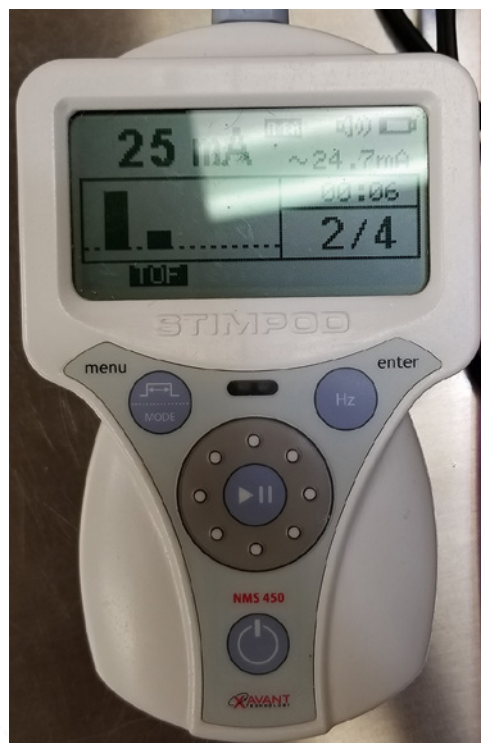


Figure 5.4 A peripheral nerve stimulator that utilizes acceleromyography. The display shows the output of a train-of-four stimulation pattern of a nerve and the evoked muscular response of an anesthetized patient after receiving an NMBA. The T4/T1 ratio of 0.56 (56%) indicates that 70–75% of the ACh receptors are blocked.



Figure 5.5 A peripheral nerve stimulator that utilizes acceleromyography. The display shows the output of a train-of-four stimulation pattern of a nerve and the evoked muscular response of an anesthetized patient after receiving an NMBA. The T4/T1 ratio of 0.11 (11%) with the fourth twitch nearly absent indicates that 75–80% of the ACh receptors are blocked.

Figure 5.6 A peripheral nerve stimulator that utilizes acceleromyography. The display shows the output of a train-of-four stimulation pattern of a nerve and the evoked muscular response of an anesthetized patient after receiving an NMBA. The T4/T1 ratio is not calculated as there is complete absence of twitches 3 and 4, indicating that at least 90% of the ACh receptors are blocked.



commercially available and would result in serious side effects as ACh is used in many systems throughout the body. Thus, prevention of degradation at the neuromuscular junction will allow for ACh concentration to rise above that of an exogenously administered substance (NMBA). Inhibition of acetylcholinesterase, and thus a concomitant rise in ACh concentrations, can be performed by administration of a drug such as neostigmine, a potent acetylcholinesterase inhibitor. Neostigmine dosage of 0.04 mg/kg IV has been described for other veterinary species and has been used by the author in ruminants [2, 25]. The acetylcholinesterase inhibiting activity of neostigmine is not limited to the neuromuscular junction. As such, because the parasympathetic nervous system utilized ACh as its main neurotransmitter, inhibition of acetylcholinesterase and a concomitant rise in ACh result in a sharp increase in parasympathetic activity (muscarinic effects). This is mainly clinically observed as bradycardia, sometimes profound, and bronchospasm after administration of neostigmine [26]. Thus, neostigmine is often combined with an anticholinergic drug (atropine) in human and small animal patients [26, 27]. Administration of anticholinergic drugs, particularly to horses, is not without risk (mainly colic), therefore very slow administration of neostigmine without an anticholinergic has been shown to result in limited side effects in horses and may be the preferred method of NMBA reversal by many veterinary anesthesiologists [2].

Unlike the other nondepolarizing NMBAs, rocuronium can not only be antagonized with neostigmine, but it also has a reversal agent, sugammadex, that is specific for it. Sugammadex is a cyclodextrin complex that binds nearly irreversibly to rocuronium, making it unavailable to bind with an ACh receptor. There are no reports of the use of sugammadex in food or fiber animals and its availability is very limited currently. However, sugammadex represents a new technology for NMBA reversal that may be more available for the veterinary market in the future.

When considering using pharmacological means to reverse the effects of NMBA, it is important that the animals show some degree of recovery (it is recommended that a minimum of two responses from a train-of-four pattern from a peripheral nerve stimulator be present). If neostigmine is administered to an animal that has complete blockade (no response to a peripheral nerve stimulator), a lack of recovery can occur. This is because neostigmine cannot increase the amount of ACh in the neuromuscular junction; it can only prevent the degradation. Thus, even with inhibition of acetylcholinesterase, the concentration of NMBA during profound blockade will still be sufficient to outcompete the available ACh for receptors.

NMBAs are a unique class of drugs that are helpful in providing profound muscle relaxation and immobilization of patients during anesthesia. Use of NMBAs requires an ability to provide mechanical ventilation and monitoring of neuromuscular function. Currently, there is little available research into the clinical use of NMBAs in food and fiber species, with much of the information extrapolated from research in other species and clinical experience. Given what is known at this time, atracurium appears to be the most predictable NMBA and thus maybe be a best first choice of NMBA for use in ruminants and swine.

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6

Inhalation Anesthesia and Use of Ventilators

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When general anesthesia is considered in farm animal species, factors that affect the decision between injectable and inhalation anesthesia include the type of procedure to be performed, anticipated duration of the procedure, inhalation anesthetic equipment availability, familiarity of the veterinarians with the anesthetic technique, and anesthetic costs. Injectable anesthesia has the advantages of easy drug administration and relatively low cost of specific anesthetic equipment or accessories required for delivery and monitoring. Delivery of an inhalation anesthetic requires expensive and specialized equipment and accessories to be able to deliver the anesthetic to the patient. However, accumulation of injectable anesthetics in the patient following repeated dosing or extended infusion required for completion of a procedure can result in delayed drug elimination and prolonged recovery. Because of the ease and speed in adjusting the depth of anesthesia with the currently available inhalation anesthetics (e.g. isoflurane, sevoflurane, and desflurane), inhalation anesthesia is often preferred for use in long procedures and also for patients that are considered at higher anesthetic risk as a result of preexisting systemic conditions. Isoflurane was first synthesized in 1965 and subsequently became a popular inhalation anesthetic in human patients in 1981. It is still a very commonly utilized inhalation anesthetic in veterinary practice. Sevoflurane was synthesized in the early 1970s. At that time, it was difficult to synthesize the drug and therefore it was expensive to manufacture. It was not until the late 1980s that sevoflurane was introduced in Japan and was later marketed in the USA in 1995 [1]. Special preanesthetic considerations and preparations with respect to laryngeal and gastrointestinal anatomy and physiology prior to general anesthesia in farm animal species are discussed in detail in Chapter 1.

The goal of delivering surgical anesthesia with an inhalation anesthetic is to maintain a constant and optimal partial pressure of the anesthetic in the alveoli of the lungs and central nervous systems (CNS). Currently available inhalation anesthetics, isoflurane, sevoflurane, and desflurane, have low blood solubility (isoflurane 1.46, sevoflurane 0.68, desflurane 0.42) and minimal hepatic metabolism (isoflurane 0.2%, sevoflurane 3–5%, desflurane 0.02%) [2]. Blood solubility of an inhalation anesthetic is referred to as blood–gas partition coefficient, which is the ratio of the distribution of an inhalation anesthetic between the blood and the gas. The partition coefficient is the concentration ratio of an anesthetic between the solvent and gas phase, for example blood and gas, or between two tissue solvents, for example brain and blood. As an example, an inhalation anesthetic with a blood–gas partition coefficient of 10 at equilibrium (i.e. the partial pressure of

that anesthetic is identical in the blood and gas phases) implies that the concentration of that anesthetic is 10 in the blood and 1 in the gas phase. An anesthetic with a lower blood solubility has a lower blood–gas partition coefficient. In other words, a smaller amount of the anesthetic is dissolved in the blood than in the gas phase when their partial pressures reach equilibrium. Therefore, the speed of achieving surgical plane of anesthesia, the rate of anesthetic depth variation, and the time until consciousness is returned and recovery is achieved are normally faster for an inhalation anesthetic with a lower blood solubility than anesthetics with higher blood solubility. In this case, the time of induction to surgical plane of anesthesia and the time to recovery of full motor function of a patient are faster with desflurane (0.42), intermediate with sevoflurane (0.69), and slower with isoflurane (1.41) [2].

Under ideal conditions, the partial pressure of an anesthetic from the alveoli (P_A) to the pulmonary arterial blood (P_a) and then to the brain (P_{br}) should be close, if not equal, to the inspired anesthetic partial pressure (P_I), that is, $P_I \approx P_A \approx P_a \approx P_{br}$, at equilibrium. Changes in P_I , alveolar ventilation, and the characteristics of an anesthetic breathing system will affect the uptake of the anesthetic from the inspired anesthetic gas flow delivered by the anesthesia machine to the alveoli. Variation of the blood–gas partition coefficient of the anesthetics, the cardiac output of the patients, and the alveoli to venous partial pressure difference affect the transfer of an inhalation anesthetic from the alveolar tissues to pulmonary arterial blood. Factors that determine how quickly the inhalation anesthetic accumulates in the brain include the brain–blood partition coefficient, the cerebral blood flow, and the cerebral arterial to venous partial pressure difference. Because the brain–blood partition coefficients for isoflurane (1.6) and sevoflurane (1.7) are very similar, there should be no significant difference in the speed of the transfer from blood to brain between these two anesthetics [1]. Therefore, increasing P_I and alveolar ventilation and reducing anesthesia breathing system volume decreases the time of the partial pressure of an inhalation anesthetic to equilibrium between alveoli and pulmonary arterial blood, and therefore results in a faster induction of anesthesia for that anesthetic. Vice versa, decreasing P_I and alveolar ventilation and increasing the volume of the anesthesia breathing system prolongs the time to equilibrium and results in a slower induction of anesthesia. Furthermore, anesthetics with a low blood–gas partition coefficient, patients with a low cardiac output, and small differences between alveolar and venous partial pressures tend to result in faster induction than an anesthetic with greater blood–gas partition coefficient, patients with an increased cardiac output, and larger differences between alveolar and venous partial pressures. Similarly, an anesthetic with a low brain–blood partition coefficient, patients with increased cerebral blood flow, and small differences between cerebral arterial and venous partial pressures tend to result in a faster induction than those with a greater brain–blood partition coefficient, patients with decreased cerebral blood flow, and larger differences between cerebral arterial and venous partial pressures. These tend to result in a slower induction of anesthesia [1, 3]. Return of consciousness and recovery from inhalation anesthesia is an inverse process of induction, which is a result of the elimination of the anesthetic from the CNS. Therefore, factors that affect the speed of induction, for example alveolar ventilation, cardiac output, and blood and tissue solubility, also affect the speed of recovery. In the presence of normal alveolar ventilation and cardiac output, recovery is generally faster for an anesthetic with lower blood and tissue solubility. Hence, recovery from desflurane (0.42) and sevoflurane (0.69) tends to be faster than from isoflurane (1.41).

Isoflurane and sevoflurane are the two most commonly used inhalation anesthetics in current veterinary practice (Figures 6.1 and 6.2). Both anesthetics can be used safely and effectively for general anesthesia in farm animal species. Desflurane is a newer inhalation anesthetic with a chemical structure similar to isoflurane with the exception of the substitution of a fluorine for the



Figure 6.1 Anesthesia machine with isoflurane vaporizer.



Figure 6.2 Anesthesia machine with sevoflurane vaporizer.

chlorine on the alpha-ethyl carbon. Desflurane is unique among the conventional inhaled anesthetics. It has a vapor pressure of 681 mmHg at 20 °C, which is very close to the atmospheric pressure (760 mmHg) and a boiling point of 22.8 °C. At normal operating room temperature, desflurane can boil with a saturated vapor concentration of 87% (681 mmHg/760 mmHg), which is approximately 10 times the minimum alveolar concentration (MAC) of desflurane for humans (6.6%). Because of these unique characteristics, desflurane requires a specially designed vaporizer that is pressurized and heated to provide precise control of anesthetic output from the vaporizer and prevent over anesthetizing the patient [4]. Because of this special vaporizer requirement, desflurane has not been used as commonly as isoflurane and sevoflurane. Isoflurane and sevoflurane require a standard vaporizer calibrated specifically for each anesthetic. Compared to older inhalation anesthetics, isoflurane and sevoflurane have lower potency with MAC values of 1.29% and 2.33%, respectively [5]. The MAC value of an inhalation anesthetic is the minimum alveolar anesthetic

concentration required to prevent gross purposeful movement in 50% of patients in response to obnoxious stimuli such as surgical incision. The MAC value is used as an indicator of the potency of the anesthetic. The higher the MAC value, the lower the potency of the anesthetic. From the physico-chemical properties of the inhalation anesthetics, MAC values are inversely related to the blood solubility of the anesthetic. Therefore, an inhalation anesthetic with high potency normally has a high blood solubility but a low MAC value. On the contrary, an inhalation anesthetic with low potency generally has a low blood solubility but a high MAC value [1]. Sevoflurane is less potent than isoflurane, as reflected in the higher MAC values (2.33% vs. 1.29%), and lower blood solubility (0.69 vs. 1.41). One should always keep in mind that at 1 MAC ($1 \times \text{MAC}$), only 50% of patients will not respond to obnoxious stimulation. In other words, the remainder of the patients may respond to an obnoxious stimulation, resulting in gross purposeful movement. In general, surgical anesthesia requires maintaining anesthetic concentration at 1.3 MAC to prevent 95% of the patients from responding to surgical stimulation. Thus, 1.3 MAC of an inhalation anesthetic is referred to as ED_{95} or surgical anesthesia [1, 3]. For very painful procedures, 1.5 MAC of an inhalation anesthetic concentration may be required to maintain surgical anesthesia. The MAC value is measured and determined in normal healthy patients anesthetized with that inhalation anesthetic alone with no other CNS-depressing drugs such as tranquilizers, sedatives, analgesics, and injectable anesthetics administered at the time of measurement. The MAC values can be influenced by concurrent administration of anesthetic-related drugs, alterations of the physiological conditions of the patient, or concurrent administration of medications for the treatment of other conditions or illness. Factors that may increase the MAC value of an inhalation anesthetic for a particular patient include hyperthermia (fever), hyponatremia, and drug-induced increased CNS catecholamine levels. Increased age, hypothermia, hyponatremia, pregnancy, and concurrent administration of tranquilizers, sedatives, analgesics, injectable anesthetics, local anesthetics, neuromuscular blocking drugs, and drugs that decrease CNS catecholamine levels tend to decrease the MAC value. Duration of anesthesia and magnitude of individual anesthetic metabolism have no effect on the MAC value [6, 7]. Table 6.1 summarizes the blood–gas partition coefficient, metabolism, and MAC values of isoflurane, sevoflurane, and desflurane in farm animal species.

Eger [23] and Malan et al. [24] reported that the circulatory effects produced by desflurane closely resemble those produced by isoflurane. Sevoflurane-induced circulatory effects have the characteristics of both isoflurane and halothane. In humans, isoflurane and sevoflurane produce a dose-dependent decrease in mean arterial pressure primarily due to the decrease in systemic vascular resistance produced by these anesthetics. Heart rate tends to increase up to 1 MAC (1.29%) during isoflurane anesthesia, while heart rate does not increase until the concentration of sevoflurane anesthesia is greater than 1.5 MAC ($1.5 \times 2.3\% = 3.5\%$). An abrupt increase in alveolar concentration of isoflurane from 0.55 to 1.66 MAC produces an increase in sympathetic nervous system and renin–angiotensin activities. As a result, transient increases in heart rate and mean arterial blood pressure occur, which may cause the anesthetist to misinterpret insufficient anesthetic depth and further increase the anesthetic concentration delivered to the patient [25]. The transient increase in heart rate and mean arterial pressure associated with an abrupt increase in anesthetic concentration has not been observed during sevoflurane anesthesia [26]. It is believed that the neurocirculatory excitatory effect of isoflurane is caused by stimulation of the sympathetic nervous system located in the upper airway and in the lung in response to a sudden increase in alveolar concentration of the anesthetic. This effect is more likely to occur for inhalation anesthetics with low blood solubility that is capable of causing a rapid rise in alveolar concentration by increasing the inspired concentration delivered to the patient [27]. However, prior administration of fentanyl, alfentanil, or clonidine has been shown to blunt the neurocirculatory excitatory response to abrupt

Table 6.1 Blood–gas solubility, metabolism, and MAC of isoflurane, sevoflurane, and desflurane in farm animal species.

	Isoflurane	Sevoflurane	Desflurane
Blood–gas solubility [7]	1.46	0.68	0.42
Hepatic metabolism [7]	0.2%	3–5%	0.02%
<i>MAC values (%)</i>			
Cattle	Calves: 1.47 [8]	N/A	N/A
Goats	1.13 ± 0.03 [9]	2.3–2.7 [10]	N/A
	1.29 ± 0.11 [5]	2.33 ± 0.15 [5]	
	1.63 ± 0.17 [11]		
Sheep	1.01–1.58 [12, 13]	3.3 [14]	9.5 [15]
	1.51 [16]		
Llamas/alpacas	1.05 ± 0.17 [17]	Llamas: 2.29 ± 0.14 [18] Alpacas: 2.33 ± 0.09 [18]	Llamas: 7.99 ± 0.58 [19] Alpacas: 7.83 ± 0.51 [19]
Pigs	1.65 ± 0.36– 2.04 ± 0.19 [20]	4.1 (3.65–4.5) [21] 3.5 ± 0.1 [22]	8.28 ± 1.34%– 10 ± 0.94 [20]

N/A, not applicable.

increase of desflurane concentration [28, 29]. A similar suppression response may occur if these drugs are administered prior to isoflurane anesthesia. In general, isoflurane does not affect cardiac output as much as sevoflurane. Cardiac output decreases significantly at 1 and 1.5 MAC of sevoflurane but returns to near-awake values at 2 MAC [30]. It is believed that isoflurane may possess mild β agonist effects and the resultant sympathomimetic effect is reflected as an increased heart rate, decreased systemic vascular resistance, and overall unchanged cardiac output in human patients [30]. However, this theory has not been supported by animal data [31]. Neither isoflurane nor sevoflurane overly sensitizes the myocardium to circulating catecholamines, thus they are unlikely to cause cardiac dysrhythmias in susceptible patients [30].

Hypoventilation and increased PaCO_2 are often observed during inhalation anesthesia as a result of medullary respiratory center depression and reduced chest wall expansion due to anesthetic-induced intercostal muscle relaxation [4]. Furthermore, positioning of ruminant patients in lateral or dorsal recumbency for surgery results in compression of the diaphragm, which collapses the caudal lung lobes by the cranial shifting of the rumen and further debilitates the ventilation function of an anesthetized ruminant patient [32, 33]. Sevoflurane produces a dose-dependent increase in respiratory rate in human volunteers. Isoflurane increases the respiratory rate up to a concentration of 1 MAC. A further increase in isoflurane concentration is not associated with a further increase in the respiratory rate. Awake patients may be able to compensate for a decrease in respiratory rate by increasing the tidal volume to maintain normal minute ventilation and prevent the increase in PaCO_2 . However, dose-dependent depression of the response of the medullary respiratory center to the increased PaCO_2 is often observed, which prohibits central compensatory mechanism by increasing respiratory rate or tidal volume in an effort to maintain normal PaCO_2 during isoflurane or sevoflurane anesthesia [23, 34]. Isoflurane and sevoflurane both produce

bronchodilation in patients suffering from chronic obstructive pulmonary disease. Isoflurane vapor has a special pungent odor and has been shown to cause airway irritation, coughing, and breath holding during induction. On the contrary, sevoflurane has been described as “pleasant smelling,” and does not irritate the airway. Therefore, sevoflurane is often preferred for mask inductions [35].

Isoflurane, sevoflurane, and desflurane have little effect in overall hepatic and renal function in healthy patients. Isoflurane has been reported to decrease portal venous blood flow at 1.5 MAC, but total hepatic blood flow and hepatic arterial blood flow are shown to be within normal range. Therefore, hepatic perfusion is well maintained, which when combined with isoflurane-induced vasodilation ensures adequate hepatic O₂ delivery [36]. Of the three most popular inhalation anesthetics, isoflurane is probably the one that better maintains hepatic O₂ supply and is least likely to cause hepatic injury. Nevertheless, sevoflurane and desflurane produce hepatic effects similar to isoflurane [37–39]. The elimination of these inhalation anesthetics depends primarily on ventilation rather than the hepatic metabolism. Sevoflurane has a higher hepatic metabolism (3%) than isoflurane (0.2%) and desflurane (0.02%). Apparently, sevoflurane is 10 times more vulnerable than isoflurane and 100 times more than desflurane to hepatic metabolism and the subsequent production of inorganic and organic fluoride [23]. Fluoride-induced renal toxicity and renal dysfunction with a fluoride concentration of 50 μmol/l or greater have been previously documented with the administration of one of the older-generation inhalation anesthetics, methoxyflurane [40]. Clinical studies in humans showed that plasma fluoride concentrations can be maintained below 80 μmol/l, even though peak plasma fluoride concentration is rarely reached due to methoxyflurane’s high blood solubility and slow rise in blood concentration [41]. Further evidence shows that renal dysfunction rarely occurs even with a peak plasma fluoride concentration of greater than 50 μmol/l, but less than 80 μmol/l, in the presence of high sevoflurane concentration and prolonged duration of anesthesia [41–46]. That being said, sevoflurane-induced cardiovascular depression may enhance the renal toxicity effect by detrimental hepatic or renal effects, for example hepatocellular injury due to reduced hepatic blood flow and decreased O₂ delivery and diminished renal function as a result of the decreased renal blood flow and glomerular filtration rate. Therefore, it is important to maintain normal cardiovascular function and ensure adequate hepatic and renal perfusion in anesthetized patients.

Compound A is a vinyl ether produced as one of the degradation products of sevoflurane presented in the CO₂-absorbent canister as a trace contaminant. Breakdown of sevoflurane to compound A has been associated with administration of high sevoflurane concentrations, the presence of the dry alkaline CO₂ absorbent (e.g. soda lime or baralyme), the use of the low O₂ flow in the breathing circuit, and the production of high temperature from the chemical interaction of exhaled CO₂ with the CO₂ absorbent [47–56]. In rats, inhalation of high compound A concentrations has been shown to cause fatal renal injuries [56]. However, it is believed that compound A is less toxic in humans due to lower β-lyase enzyme activity compared to rats [57]. When a fresh O₂ flow rate of 2 l/min was used in rats during sevoflurane anesthesia, which provided much higher O₂ than the minimum metabolic O₂ requirement of the rats, a very low concentration of compound A in the breathing circuit of the anesthetic machine was analyzed, and renal toxicity to the rats was not reported [34]. Increased production of compound A has been associated with higher CO₂ absorbent temperatures up to 46 °C. Also, studies have shown that CO₂ absorbent that contained NaOH and/or KOH often resulted in higher compound A production. No compound A was produced when NaOH- and KOH-free CO₂ absorbent was used [55, 58]. In rats, the concentrations of compound A that are associated with renal toxicity and median lethal concentration following 1 hour of sevoflurane anesthesia are reported to be 100–300 ppm [59] and 1050–1090 ppm [60], respectively. In humans, peak compound A concentration of less than 40 ppm was reported even after

prolonged duration of sevoflurane anesthesia [49, 61]. Similarly, a peak compound A concentration of 61 ppm was reported in dogs anesthetized with sevoflurane using a low flow (fresh O₂ flow rate 3 ml/kg/min), closed circuit system for 1 hour [62]. Kandel et al. [60] reported that renal injury in rats only occurred in the presence of a compound A concentration of at least 200 ppm with a maximum of 1 hour of exposure time. Fortunately, there is no report of compound A-related renal toxicity under normal clinical conditions in humans or domestic animals.

All halogenated inhalation anesthetics are known triggers for malignant hyperthermia. Halothane appears to be the most potent and the most frequently reported in pigs. Isoflurane has been reported to trigger malignant hyperthermia in susceptible pigs like Pietrain or Pietrain-mixed pigs [63]. Incidences of isoflurane-induced malignant hyperthermia have been reported in a pot-bellied pig [64] and a bull [65]. Sevoflurane-induced malignant hyperthermia has been reported in purebred Poland China pigs [66]. Episodes of malignant hyperthermia induced by desflurane have been reported in Large White, Pietrain, and Pietrain-mixed pigs [63, 67]. Compared to well-documented halothane-induced malignant hyperthermia, the episodes induced by desflurane and isoflurane were reported to have a slower onset than halothane [63]. Please refer to Chapters 1 and 7 for detailed discussion and treatment of malignant hyperthermia.

6.1 Cattle

In steers anesthetized for rumenotomy with atropine/guaifenesin/thiamylal for induction and either isoflurane or halothane for maintenance, higher heart rate and lower respiratory rates were observed during isoflurane than those observed during halothane anesthesia. Mean arterial blood pressure was not significantly different between the two anesthetics. Surprisingly, the end-tidal isoflurane concentration required for rumenotomy surgery (1.7% at 15 minutes and 1.3% at 90 minutes) was lower than that of halothane (2.6% at 15 minutes and 1.7% at 90 minutes) [68]. In most of the other domestic species, isoflurane is reported to be less potent than halothane with 1.5 MAC values being 1.95% (1.5 × 1.3%) and 1.35% (1.5 × 0.9%) vapor concentration for isoflurane and halothane, respectively. The reason for this discrepancy remains unknown [68]. Both anesthetics produced a similar degree of respiratory depression which was reflected in the same level of PaCO₂ accumulation during anesthesia. However, it seems that animals anesthetized with isoflurane tend to breathe with greater tidal volume to compensate for the lower respiratory rate caused by isoflurane. On the contrary, a decreased tidal volume accompanied by an increased respiratory rate in isoflurane-anesthetized calves was not able to prevent hypoventilation, as evidenced by a significant increase in PaCO₂ throughout the anesthesia period. In normal, awake animals, an increase in PaCO₂ (hypoventilation) and a decrease in PaO₂ (hypoxia) are the primary stimulants for the medullary respiratory center and peripheral chemoreceptors to increase respiratory rate or tidal volume to maintain normal PaCO₂ and PaO₂. When the medullary respiratory center and peripheral chemoreceptors are depressed by isoflurane during anesthesia, hypoxia becomes the primary stimulant responsible to improve ventilation. However, 100% O₂, typically used as the carrier gas for all the inhalation anesthetics, more specifically isoflurane in this case, eliminated the ventilatory drive that normally responds to hypoxia, resulting in an accumulation and subsequent increase in PaCO₂ despite an increased respiratory rate [69, 70]. Nonetheless, calves induced with xylazine (0.1 mg/kg IM) and ketamine (2 mg/kg IV) and maintained with isoflurane in O₂ for repair of umbilical hernia had better arterial oxygenation, less degree of pulmonary vascular shunting, and better quality of anesthesia than those induced with xylazine (0.2 mg/kg IM) and ketamine (5 mg/kg IV) and maintained with intermittent IV ketamine (2.5 mg/kg) [71].

In calves, mask induction with desflurane to tracheal intubation only required 151 ± 32.8 seconds. No struggling, breath holding, or coughing was observed during the induction period, indicating lack of upper airway irritation from desflurane. Anesthesia was maintained at mean end-tidal desflurane concentration of $10 \pm 0.76\%$ with control ventilation. No surgery was performed in these calves during desflurane anesthesia. The only cardiovascular changes observed were significant decreases in arterial blood pressures and systemic vascular resistance. Heart rate and cardiac output did not change from baseline values, suggesting that the decrease in systemic vascular resistance was responsible for the decrease in arterial blood pressure observed in these calves, similar to that seen with isoflurane and sevoflurane. Desflurane anesthesia was discontinued after 45 minutes of recording of cardiovascular variables, and isoflurane was then used to maintain anesthesia for surgical placement of a duodenal cannula and thymectomy. All calves in this study recovered uneventfully. Compared to isoflurane and sevoflurane, desflurane, due to its low blood solubility, has the advantage of having a very rapid induction and recovery, and ease of adjustment of anesthetic depth [72]. There is no report on the alveolar concentration of desflurane required during surgical anesthesia in calves. In other domestic animals, the MAC value of desflurane is 7.6% in horses [73], 9.5% in sheep [74], and 10% in pigs [20]. The authors of the study in calves suggested that the 10% end-tidal desflurane concentration used resulted in the maintenance of a light plane of anesthesia which was sufficient for the nonpainful procedures, but higher concentrations will be required for painful surgery [72].

In Holstein cows induced with thiopental and guaifenesin and maintained under sevoflurane anesthesia, heart rate increased above preanesthetic values throughout the anesthesia period. Atropine administered during the preanesthetic period may be responsible for the increased heart rate observed in this study. Arterial blood pressure and respiratory rate remained unchanged during sevoflurane anesthesia. However, a decrease in pH_a and an increase in PaCO₂ were reported in these cows, indicating the presence of respiratory depression produced by sevoflurane. Cows in this study recovered from anesthesia smoothly and rapidly. All cows had normal aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and creatinine for 7 days, suggesting a normal hepatic and renal function following 75 minutes of sevoflurane anesthesia [75]. A comparison study in Holstein calves anesthetized with either isoflurane or sevoflurane reported no significant difference in cardiopulmonary parameters between the two anesthetics. However, recovery from sevoflurane appeared to be more rapid, and more attempts to stand unassisted were required for the calves than for those recovering from isoflurane anesthesia [76].

A case of malignant hyperthermia in cattle was reported in an isoflurane-anesthetized Angus bull [65]. Xylazine (0.1 mg/kg IV) was administered for sedation, which was followed in 5 minutes with 5% guaifenesin (34 mg/kg IV) and ketamine (3 mg/kg IV) for induction of anesthesia. The bull was placed in dorsal recumbency for surgery and control ventilation with a respiratory rate of 7 breaths/minute and a tidal volume of 4 l/minute was instituted. At 30 minutes after induction, the results of arterial blood gas were within normal ranges. However, progressive increase of heart rate from 55 to 70 beats/minute and end-tidal CO₂ from 38 to 60 mmHg occurred at 75 minutes after induction. The result of arterial blood gas indicated a respiratory acidosis (pH_a 7.268) with moderate increase of PaCO₂ (from 29.7 to 66.4 mmHg) and a decrease in PaO₂ (from 449 to 267 mmHg). At this time, isoflurane was discontinued and replaced with a different anesthesia machine. However, heart rate (from 70 to 155 beats/minute) and end-tidal CO₂ (from 60 to 218 mmHg) continued to increase at 140 minutes postinduction. Body temperatures recorded from a nasopharyngeal probe increased from 39.5°C (103.1°F) at 75 minutes and 43.5°C (110.3°F) at 140 minutes. Unfortunately, the bull developed ventricular fibrillation which progressed to asystole and attempts

at cardiopulmonary resuscitation was unsuccessful [65]. This is the first reported malignant hyperthermia case in cattle. Unlike malignant hyperthermia in pigs [77, 78], muscle rigidity, one of the typical clinical signs of malignant hyperthermia, was not observed in this bull. In addition, clinical signs of malignant hyperthermia in pigs developed within minutes of exposure to the triggering agent, whereas progression of the clinical signs in this bull did not occur until 75 minutes after initiation of isoflurane. The delay onset of clinical signs has also been observed in horses [79], dogs [80], and cats [81]. Please refer to Chapters 1 and 7 for discussion and treatment of malignant hyperthermia.

6.2 Small Ruminants and Camelids

In newborn lambs, isoflurane induced significant decreases in heart rate, stroke volume, cardiac output, and mean arterial blood pressures when compared to baseline values, but only cardiac output and mean arterial blood pressure decreased in a dose-dependent manner [16]. Conflicting results were reported by Hikasa et al. [5], in that isoflurane and sevoflurane both induced a dose-dependent decrease in arterial blood pressure and systemic vascular resistance, but the cardiac index (cardiac output/body weight in kg), a reflection of cardiac output, did not decrease further with increasing either isoflurane or sevoflurane concentration in adult goats. Isoflurane induced a rapid and smooth induction and recovery in llamas and alpacas. At 1 MAC ($1.05 \pm 0.17\%$), arterial blood pressure increased significantly from the baseline value in isoflurane-anesthetized llamas and alpacas. A trend of increase in heart rates was observed, although the values were not statistically significant. Respiratory rate and PaCO_2 remained unchanged during anesthesia [17]. A dose-dependent increase in heart rate and PaCO_2 and decrease in mean arterial blood pressure occurred when the concentration of isoflurane was increased up to two times of the MAC value [82]. The anesthetic effects of isoflurane, sevoflurane, and desflurane for maintenance were studied in sheep following induction of anesthesia with xylazine (0.1 mg/kg IM), ketamine (2 mg/kg IV), and midazolam (0.03 mg/kg IV). Buprenorphine (0.008 mg/kg IM) was administered to these sheep for additional analgesia [83]. All three inhalation anesthetics produced adequate and stable anesthesia during experimental orthopedic surgeries. There were no significant differences in heart rate and arterial blood pressures between anesthetics, and the values remained within normal ranges. Respiration was characterized by an irregular breathing pattern with intermittent rapid breaths followed by a short period of apnea. No significant difference was observed on the end-tidal CO_2 , suggesting a similar ventilatory effect for the three anesthetics. Considering the blood solubility of these anesthetics, the speed of recovery in theory from fastest to slowest should be in the order of desflurane > sevoflurane > isoflurane in the absence of other anesthetics. The result of this study showed that the time of recovery for sheep capable of keeping their head lifted for 5 minutes was fastest with desflurane (29.8 ± 11.5 minutes), slowest with sevoflurane (38.8 ± 16.6 minutes), and intermediate with isoflurane (32.8 ± 18.1 minutes). Two sheep receiving sevoflurane experienced rough recoveries, but all other sheep recovered uneventfully [83]. In lambs ranging from 3 to 6 weeks of age undergoing experimental spinal surgery, medetomidine (0.01 mg/kg IM) was administered to produce sedation, and anesthesia was induced with either isoflurane or sevoflurane. All lambs received meloxicam (0.6 mg/kg IV), morphine (0.5 mg/kg IV), a constant rate infusion of ketamine (loading dose 1 mg/kg, infusion 0.01 mg/kg IV), and atracurium (0.5 mg/kg IV) during surgery. In this study, lambs receiving sevoflurane maintained higher mean and diastolic arterial blood pressure than those receiving isoflurane. The duration from the end of anesthesia to the time the lambs were reunited with their ewes was shorter with sevoflurane [84]. In goats, the

speed of recovery was faster for those receiving desflurane and sevoflurane than those receiving isoflurane [10]. Administration of injectable anesthetics to induce anesthesia, addition of supplemental analgesics to enhance analgesia during surgery, and the duration of anesthesia with inhalation anesthetics are very likely to affect the speed of recovery, which explains the differences observed between studies.

6.3 Swine

Isoflurane and sevoflurane can be used to produce effective and safe anesthesia in pigs. Both anesthetics can be used for mask induction as no breath holding or coughing is observed when these anesthetics are used to anesthetize piglets for castration on the farm or in the field using a mask and a specially designed anesthetic inhaler [85]. Lerman et al. [86] reported that the heart rate decreased 19% and 31%, and systolic arterial blood pressure decreased 43% and 36%, respectively, at 1.5 MAC of isoflurane and sevoflurane anesthesia in pigs when compared to awake values. Interestingly, isoflurane caused a 43% decrease in cardiac index (cardiac output/body weight in kg), but there was no difference observed with sevoflurane. It is apparent that sevoflurane depresses arterial blood pressure and cardiac output to a lesser degree than isoflurane in pigs [86]. Decrease in PaO_2 during inhalation anesthesia is a common complication, particularly in large adult commercial pigs. Depression of the medullary ventilatory center, inhibition of hypoxic pulmonary vasoconstriction, and alteration of the distribution of pulmonary blood and thus a decrease in the PaO_2 value have been well documented during halothane anesthesia [87, 88]. In pigs with a preexisting gas exchange defect, sevoflurane may further impair pulmonary gas exchange, while isoflurane does not [89]. Therefore, close monitoring and efforts to maintain normal PaO_2 should be practiced when using sevoflurane in animals with pulmonary disease.

It seems that pig age may have a great influence on the MAC value of sevoflurane. Different MAC values have been reported for different age groups of pigs such as 1.97% for 4–10 days of age, 2.5% for 12–13 weeks of age, 2.66% for 22–25 weeks of age, 3.5% for 9 weeks of age, and 4.4% for juvenile pigs [22, 86, 90–92]. In general, increasing age does not increase the anesthetic requirements or the MAC value for inhalation anesthetics in swine. However, concurrent administration of preanesthetics, injectable anesthetics, or opioid analgesics, and different types of stimulus such as electrical stimulation, tail clamping, or dewclaw clamping will influence the requirement for inhalation anesthetic concentration.

6.4 Use of Ventilators

Respiratory depression is a common complication in anesthetized animals and is often a result of anesthetic-induced respiratory depression and the abnormal position (e.g. lateral or dorsal recumbency) required for surgical procedures. This is particularly true in farm animals due to their unique anatomic and physiological features. Please refer to Chapters 1 and 7 for a discussion on preanesthetic considerations and anesthetic monitoring and complications. Significant ventilation/perfusion mismatch with subsequent increase in PaCO_2 and decrease in PaO_2 are common complications with potential severe consequence during anesthesia in farm animals. Assisted or mechanical control ventilation during anesthesia is often necessary to ensure adequate ventilation and to maintain normal PaCO_2 and PaO_2 values. However, assisted ventilation by periodically squeezing the rebreathing bag with higher peak inspiratory pressure in an attempt to inflate the

compressed/collapsed lung lobes to improve ventilation may not be effective to correct ventilation/perfusion mismatch and to decrease PaCO_2 and increase PaO_2 values. Therefore, mechanical control ventilation needs to be used to facilitate appropriate and effective ventilation for the anesthetized animals.

Mechanical control ventilation utilizes an automated ventilator to effectively deliver adequate tidal volume to the anesthetized patients. Most of the commercially available veterinary use ventilators are designed to use a bellows-in-a-box design. The bellows, which replace the rebreathing bag during mechanical ventilation, are placed inside a clear or transparent cylinder that is electrically powered, pneumatically powered, or pneumatically powered with electrical control. Most ventilators are designed to have dials to preset different respiratory parameters such as respiratory rate, tidal volume, peak inspiratory fresh gas flow rate or peak inspiratory pressure, and/or inspiratory to expiratory ratios (I:E ratio) (Figures 6.3 and 6.4). In simple terms, each breath delivered by the ventilator has four stages: (i) inspiratory flow, (ii) inspiratory pause, (iii) expiratory flow, and (iv) expiratory pause. Anesthetic gas in 100% O_2 flows into the patients from the bellows during inspiratory flow and out of the patient into the bellows during expiration flow. There is no gas movement during inspiratory pause and expiratory pause [93]. During effective mechanical ventilation, patients cease to breath spontaneously, allowing the ventilator to take over the breathing and maintain adequate gas exchange and oxygenation during anesthesia.

The most commonly used ventilators in veterinary anesthesia machines are classified into two types, volume-limited and pressure-limited. Volume-limited ventilators are allowed to preset the tidal volume delivered to the patient regardless of the pressure required to deliver the preset tidal volume. However, in cases of excessive high pressure presented in the ventilator, there is a built-in pressure relief valve or alarm system in the anesthesia machines or breathing circuits which will be activated and limit the pressure the ventilator can deliver to the patient [94, 95]. Pressure-limited ventilators are allowed to preset the peak inspiratory pressure and tidal volume delivered. Once the pressure in the breathing circuit reaches the preset value, the delivery of tidal volume is terminated regardless of the volume delivered [94, 95]. Changes in the compliance of a patient's



Figure 6.3 Preset respiratory parameters, respiratory rate, tidal volume, peak inspiratory fresh gas flow rate or peak inspiratory pressure, and/or inspiratory to expiratory ratios (I:E ratio) or inspiratory time of a ventilator (SurgiVet).

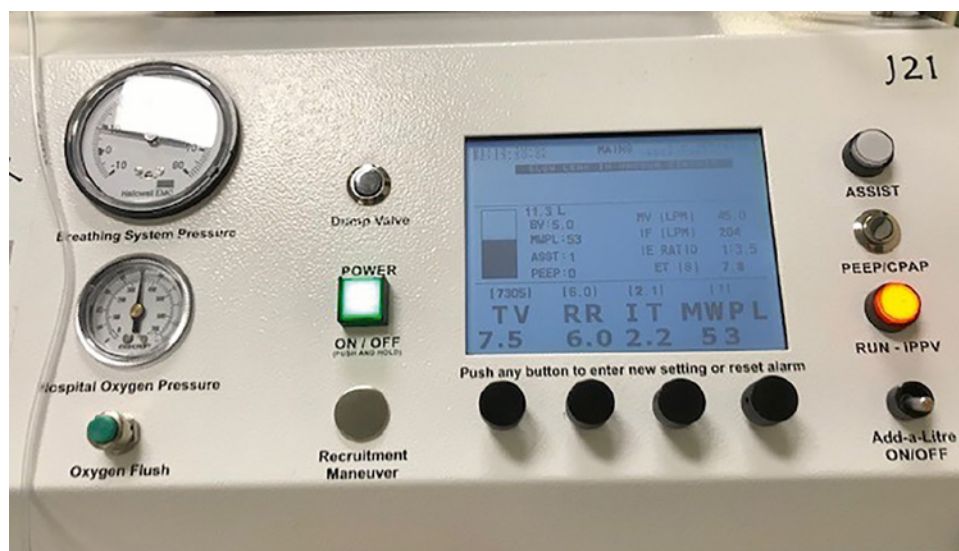


Figure 6.4 Preset respiratory parameters, respiratory rate, tidal volume, peak inspiratory fresh gas flow rate or peak inspiratory pressure, and/or inspiratory to expiratory ratios (I:E ratio) or inspiratory time of a ventilator (Tafonius).

Figure 6.5 Ventilator with standing bellows for small pediatric animals (Hallowell).



airway and in the breathing circuit, changes in inspiratory flow rates and inspiratory time, or a leak in the breathing system can affect the tidal volume delivered in either type of ventilator [94, 95].

The bellows in a ventilator are classified as ascending or descending depending on the location they are attached to in the cylinder [94, 95]. Ascending bellows (also referred to as standing bellows) are attached to the bottom of the cylinder and ascend toward the top of the cylinder during exhalation (Figure 6.5). Descending bellows (also referred to as hanging bellows) are attached to the top of the cylinder and descend toward the bottom of the cylinder during exhalation [94, 95]



Figure 6.6 Ventilator with hanging bellows for large animals (SurgiVet).

(Figure 6.6). The driving force of a ventilator can be electrically powered, pneumatically powered, or pneumatically powered with electric control. Electrically powered ventilators require plugging into a wall outlet or a battery pack to provide the power to drive the ventilator. Pneumatically powered ventilators require a high-pressure driving gas to drive them. O_2 , compressed air, or a mixture of O_2 and air are used to drive pneumatically powered ventilators [94, 95]. The bellows in the ventilators are usually situated within a clear, transparent cylinder and the anesthetist can monitor the movement of the bellows and estimate the tidal volume delivered by observing the movement of the bellows and the scale in milliliters (ml) or liters (l) marked outside the cylinder that contains the bellows (Figures 6.5 and 6.6). Modern piston-driven ventilators utilize an electric motor to drive the piston and deliver the preset tidal volume to the patient. Piston-driven ventilators have a fixed volume and all the pieces in the ventilator are rigid. The tidal volume delivered is directly related to the linear movement of the piston in the piston chamber and the volume delivered by the piston-driven ventilator is very accurate and approximates the preset tidal volume each time [94, 95]. Piston-style ventilators are electrically powered and require plugging into a wall outlet. The ventilator is enclosed in a nontransparent cylinder (Figure 6.7) and the anesthetist is not able to see the movement of the piston. The ventilator is quiet during operation therefore the anesthetist has to pay close attention to the patient's physiological reflexes and anesthesia monitor to detect any potential ventilator malfunctions [94, 95]. There is only one piston-driven ventilator available for use in large animal species, the Tefonius (Hallowell, MA), which is equipped with computer controlled ventilatory parameters (Figure 6.7).

In comparison, pneumatically powered ventilators used in veterinary anesthesia appear to be less accurate than piston-driven ventilators [96]. A study comparing the accuracy of the tidal volume delivered by five different large animal ventilators showed that all the ventilators studied had a delivered volume error (percentage of the difference between preset and delivered tidal volume divided by the preset tidal volume) from 1.2% to 22.2%. Mean volume error was 4.8% for piston-driven ventilator and 6.6%, 10.6%, 13.8%, and 15.2% for the four pneumatically powered

Figure 6.7 Piston-driven ventilator (Tafonius).



ventilators: Large Animal Control Central (Drager), Surgivet LDS 3000 with DHV 1000 large animal ventilator (Smith Medical), Model 2800 large animal anesthesia ventilation system (Mallard Medical), and Model 2800C large animal anesthesia ventilation system (Mallard Medical), respectively. This study demonstrated that pneumatically powered ventilators are less accurate in delivering a preset tidal volume than electrical piston-driven ventilators [96]. Changes in peak inspiratory flow rates, fresh gas flow rates, and preset tidal volume contribute to the volume error. Increased peak inspiratory pressure cause a decrease in delivered tidal volume and an increase in volume error. In addition, increased fresh gas flow rates, increased inspiratory time, and increased preset tidal volume tend to increase the delivered tidal volume and decreased volume error [96]. Other factors that also contribute to volume error include compliance of the breathing circuits (rubber vs. polyvinyl chloride), difference in the bellows attachment location (ascending bellows vs. descending bellows), and leaks in the breathing circuit. The compliance or stretchiness of the breathing circuit, including the bellows and breathing hoses of an anesthesia machine, contributes to the magnitude of volume error delivered to the patients. Rubber breathing hoses and bellows are more compliant, with a greater degree of stretchiness, and consequently reduce the pressure build-up in the breathing circuit, resulting in a decrease in volume delivered from the preset tidal volume and thus greater volume error (Figure 6.8). In contrast, rigid and less compliant polyvinyl chloride breathing hoses allow the pressure within the breathing circuit to build up as needed to deliver the preset tidal volume and thus minimizing the volume error [96, 97] (Figure 6.9). Furthermore, descending (hanging) bellows produced less volume error than ascending (standing) bellows [96]. Descending (hanging) bellows are designed to only fill the bellows to the tidal volume that is preset manually by adjusting a plunger within the hanging bellows cylinder and limiting the descend of the bellows, which minimizes the stretch of the bellows with smaller volume error. Ventilators with ascending (standing) bellows begin the inspiratory phase with the bellows at their maximum



Figure 6.8 Pneumatically powered with electrical control ventilator with rubber breathing system and bellows (SurgiVet).

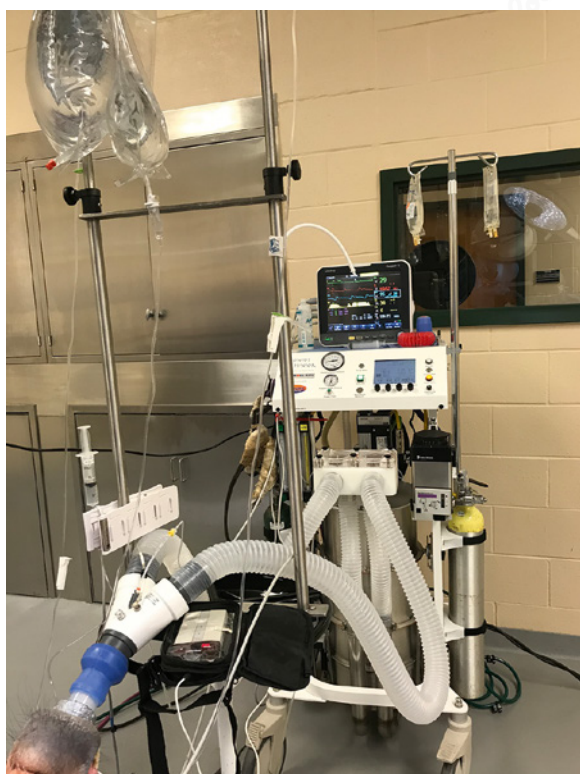


Figure 6.9 Piston-driven ventilator with polyvinyl chloride breathing system (Tafonius).

Table 6.2 Normal respiratory parameters when using control ventilation in cattle, small ruminants, and pigs [95, 99, 100].

Patient	RR (breath/min)	T _v (ml/kg)	PIP (cm of H ₂ O)	I:E ratio	T _i (s)
Adult cattle	10–20	10–20	20–30	1:2–1:4.5	1–1.5
Sheep, goats	15–30	10–20	10–20	1:2–1:3	1–1.5
Alpacas, llamas	10–30	10–20	15–20	1:2–1:3	1–1.5
Pigs	20–30	10–20	10–20	1:2–1:3	1–1.5

RR, respiratory rate; T_v, tidal volume; PIP, peak inspiratory pressure; I:E ratio, inspiratory:expiratory ratio; T_i, inspiratory time.

stretch in the presence of maximum compliance, thus resulting in greater volume error than hanging bellows [96]. Ascending bellows allow for easier detection of system leaks or disconnection. Any leaks within the ventilator or breathing system means the bellows will not be able to rise to the top of the bellow cylinders. On the contrary, it is difficult to detect leaks or disconnection within the descending bellows and the breathing systems. The bellows continue to fill with driving gas and gravity pulls the room air into the bellows with incomplete disconnections, thus decreasing the driving gas, reducing the tidal volume delivered, and, as a result, increasing the volume error [94]. A ventilator with ascending bellows is believed to be safer than descending bellows because the ascending bellows collapse when empty and are easily detected [98]. For more discussion on ventilators, see Lafferty [94] and Mosley [95].

Prior to using a ventilator on an anesthetized patient, the anesthetist needs to have a clear understanding of the setup and operation of the available ventilator and normal respiratory parameters appropriate for each individual patient (Table 6.2).

Checklist for use of nonpiston-driven ventilators:

- 1) Switch machine over to the ventilator, per individual machine.
- 2) Ensure power is available: electrical outlet or source of compressed gas.
- 3) Connect ventilator scavenging hose to a central scavenging system.
- 4) Attach ventilator hose to the rebreathing bag mount, attach rebreathing hoses to the inspiratory and expiratory limb mount. Close the adjustable pressure-limiting valve.
- 5) Anesthesia machines with built-in ventilator that uses a switch, dial or lever to isolate the rebreathing bag and adjustable pressure limiting valve do not require removal of the rebreathing bag and closing the adjustable pressure limiting valve.
- 6) Check leaks by occluding the breathing hoses, filling the bellows with O₂ until full, turning off the O₂ flow, and maintaining the occlusion of the breathing hoses. If the bellows remain full, there are no leaks. The bellows will not stay full if there is a leak.
- 7) Preset the respiratory parameters required for the individual ventilator, e.g. respiratory rate, tidal volume, I:E (inspiratory: expiratory) ratio, inspiratory time, and/or peak inspiratory pressure (Table 6.2).
- 8) Turn on the ventilator.
- 9) Evaluate the peak inspiratory pressure and basic cardiopulmonary parameters, e.g. end tidal CO₂, arterial oxygen saturation, arterial blood pressure, and blood gas analysis, soon after institution of the ventilator and periodically throughout anesthesia.

- 10) Weaning patients from the ventilator. The ventilator can be turned off shortly before completion of the surgery. Reattach the rebreathing bag and allow spontaneous breathing to occur.
- 11) Periodically perform assisted ventilation by squeezing the rebreathing bag to prevent hypoxemia.
- 12) When the patient is disconnected from the anesthesia machine and moved to the recovery area, a demand valve can be used to assist ventilation until the patient resumes normal spontaneous breathing.

Successful general anesthesia with inhalation anesthetics requires experience with successful tracheal intubation and sophisticated anesthetic machines and accessories. A small animal anesthesia machine is usually adequate for newborn calves, small ruminants, potbellied pigs, and young camelids weighing less than 150 kg (Figure 6.10). A large animal machine will be required for adult cattle, camelids, and agricultural commercial pigs (Figure 6.11). Inhalation anesthesia



Figure 6.10 A goat anesthetized with isoflurane using a small-animal anesthesia machine.

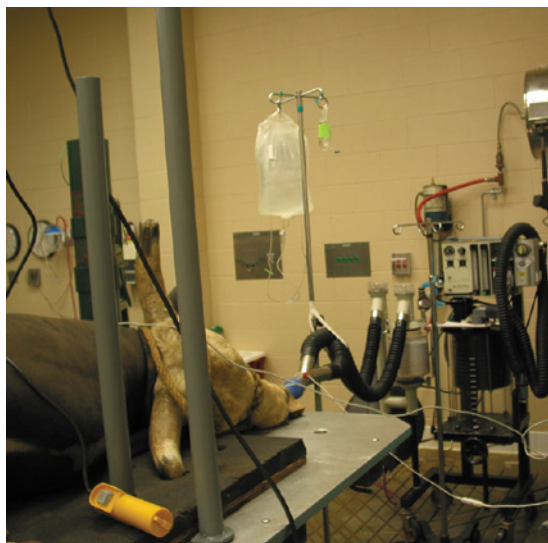


Figure 6.11 A bull anesthetized with isoflurane using a large-animal anesthesia machine.

has the advantage of maintaining steady levels of anesthesia even for lengthy surgical procedures or research experiments. The ease of adjusting the depth of the anesthetic level with inhalation anesthesia greatly improves patient survival and allows longer duration of surgery, which is one of the reasons for the advancement of complicated surgery techniques and research experiments in veterinary medicine in the last two decades.

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7

Perioperative Monitoring and Management of Complications

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7.1 Perioperative Monitoring

Anesthetized animals should be monitored closely and continuously throughout the anesthesia period. Routine variables to be monitored include heart rate and rhythm, pulse strength, respiratory rate and depth, arterial blood pressures, palpebral and corneal reflexes, eyeball rotation, capillary refill time, and mucous membrane color. Accurate assessment of the physical condition of an anesthetized patient and the depth of anesthesia of that patient are best accomplished using a combination of several parameters rather than relying on a single parameter. Presence of palpebral reflex, position of the eyeballs, and change in respiratory rate, heart rate, and arterial blood pressure are the most useful parameters and reliable indicators of the depth of anesthesia. These parameters should be evaluated, and their values recorded periodically throughout the duration of anesthesia. Following induction of anesthesia, peripheral pulse should be palpable, and an electrocardiogram (ECG), if available, should be used at all times. Position of the eyeballs in anesthetized large ruminants correlates well with the depth of anesthesia. During the surgical plane of anesthesia, eyeballs rotate ventromedially, with the cornea partially obscured by the lower eyelids. Palpebral reflex should be sluggish or just absent. As anesthetic depth deepens, eyeballs rotate to the central position with no palpebral reflex, diminished corneal reflex, and dilated cornea (Figure 7.1). Reducing the concentration of injectable or inhalation anesthetic delivered to the patient at this time may be warranted to avoid unnecessarily deepening the plane of anesthesia of the patient. If eyeballs are at the center position with strong palpebral and corneal reflexes, the depth of anesthesia may be inadequate and patients may be too light for surgical manipulation, and an increase in the anesthetic(s) concentration delivered is required. Eyeball rotation or position is not as reliable in small ruminants, camelids, and pigs as an indicator of anesthetic depth as it is in large ruminants. Changes in heart rate, respiratory rate, arterial blood pressures, and palpebral and corneal reflexes can be used to assess the depth of anesthesia in these animals. As a general rule, decrease in heart rate, respiratory rate, and arterial blood pressures, and absence of palpebral and corneal reflexes are more likely indicators of deep anesthesia.

Maintaining normal heart rate and stroke volume is the most important factor in maintaining normal cardiac output (cardiac output = heart rate $\times$ stroke volume) and normal arterial blood pressure (mean arterial blood pressure = cardiac output $\times$ systemic vascular resistance). ECG can

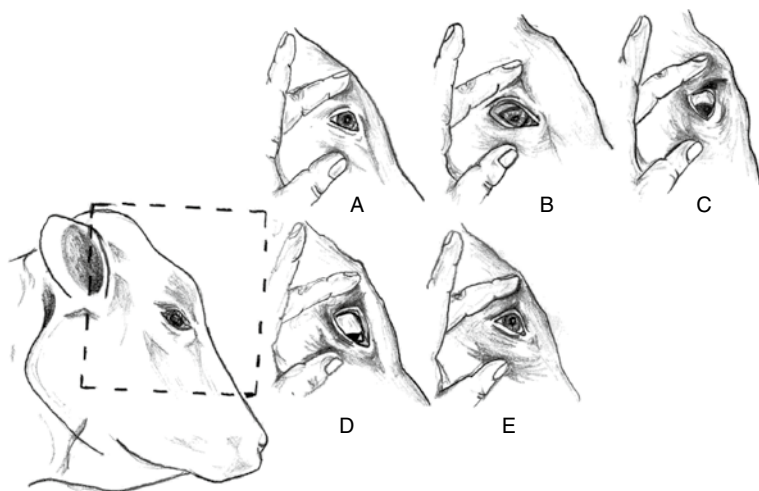


Figure 7.1 Changes in eyeball positions during anesthesia in cattle: A, awake (strong palpebral reflex); B and C, light anesthesia; D, surgical plane of anesthesia; E, deep anesthesia (absence of palpebral reflex). (Source: Illustration by Kim Crosslin.)

be used to monitor heart rate and cardiac rhythm continuously throughout anesthesia. Abnormal cardiac rhythm and significant changes in heart rate have the potential to impact stroke volume, cardiac output, and thus O_2 delivery to the tissues. The most common method for ECG monitoring of ruminant patients requires placement of electrodes at the left forelimb (LA), right forelimb (RA), and left hind limb (LL) of the patient. This simple technique generates three bipolar limb leads for evaluation of the cardiac rhythm. Lead I indicates the voltage difference between the RA and LA electrodes, lead II the voltage difference between the RA and LL electrodes, and lead III the voltage difference between the LA and LL electrodes. These electrodes are attached to a main cable that interfaces with a simple ECG monitor or a multiparameter monitor. The monitor then displays a real-time tracing of cardiac electrical activity using any one of the three leads, most commonly for cardiac rhythm analysis is lead II, but the lead with largest amplitude should be used. The characteristic normal waveform composition includes a distinct P wave, QRS complex, and T wave [1]. Most ECG monitors also display heart rate. Tachycardia, bradycardia, and ventricular dysrhythmias such as premature ventricular contraction and ventricular tachycardia are the most commonly observed cardiac arrhythmias in farm animals undergoing anesthesia. Sinus tachycardia and atrial fibrillation, though rarely, have also been observed in these animals. The ECG only shows the electrical activity of the myocardium; it does not provide information on the arterial blood pressure or pulse strength. Digital palpation of a peripheral artery for pulse strength should always be incorporated with the data from the ECG rhythm.

Arterial blood pressure can be measured by either indirect or direct methods. Indirect arterial blood pressures can be measured using an oscillometric blood pressure machine with an inflatable blood pressure cuff placed on the coccygeal or dorsal metatarsal artery. The cuff is inflated automatically to a suprasystolic pressure, and the air is gradually released until the characteristic arterial oscillation is detected by an electronic sensor. The computer then interprets the oscillation and displays measured values of systolic, mean, and diastolic blood pressures. For accurate measurement, the width of the cuff should be approximately 40% of the circumference of the extremity around which the cuff is placed. Too small a cuff tends to overestimate the blood pressure, whereas too big a cuff tends to underestimate it. Direct arterial blood pressure measurement is achieved

using a catheter placed in a superficial artery such as auricular artery or metatarsal artery. The catheter is connected to an electronic resistance-type transducer via a semirigid saline-filled arterial blood pressure tubing. The transducer is then connected to a cable that interfaces with a simple sphygmomanometer or a multiparameter monitor. A sphygmomanometer provides mean arterial blood pressure, whereas a multiparameter monitor displays systolic, mean, and diastolic arterial blood pressures as well as heart rate. Both indirect and direct methods provide continuous monitoring and reading of the arterial blood pressures. Changes in arterial blood pressures can be detected immediately and treatment can be instituted if needed [1, 2]. Sophisticated multiparameter monitor may not be practical in field settings; simple auscultation of the heart and lung, continuous recording of the heart rate and respiratory rate, digital palpation of the pulse strength, and close monitoring of the eye reflexes should be sufficient for routine patient monitoring during field anesthesia. Significant changes in heart rate, cardiac rhythm, respiratory rate, and breathing pattern should provide sufficient information regarding the depth of anesthesia and the condition of the patient.

The use of capnogram and pulse oximetry to evaluate end-tidal partial pressure of carbon dioxide (ETCO_2) and arterial O_2 saturation via a pulse oximeter (SpO_2), respectively, has become part of the routine monitoring accessories to ensure adequate ventilation, efficient gas exchange, and appropriate oxygenation of an anesthetized patient (Figure 7.2). The alveolar ventilation (V_A) to eliminate overall systemically produced CO_2 determines the arterial partial pressure of CO_2 (PaCO_2). While CO_2 production remains stable under normal conditions, PaCO_2 varies inversely with the changes in V_A . The ability of the lung to remove PaCO_2 indicates the effectiveness of ventilation. When an anesthetized patient is healthy and has no preexisting diffusion disturbance in the pulmonary tissues, ETCO_2 is usually closely related to alveolar CO_2 and PaCO_2 . Therefore, ETCO_2 can be used to estimate PaCO_2 and to assess the adequacy of ventilation. Capnography allows continuous monitoring of the adequacy of ventilation during anesthesia. The amount of alveolar CO_2 and thus ETCO_2 measured in the exhaled gas at the end of expiration is determined by infrared absorption. Samples for measurement of ETCO_2 are collected directly at the connecting



Figure 7.2 Placement of the ETCO_2 sample collection line and SpO_2 probe on adult cattle.

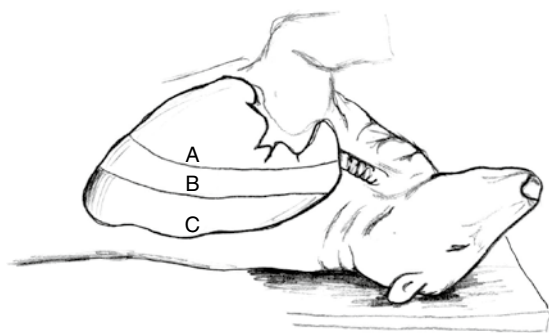


Figure 7.3 V/Q mismatch during dorsal recumbency in adult cattle: (a) $V/Q > 1$, (b) $V/Q \approx 1$, and (c) $V/Q < 1$. Source: Illustration by Kim Crosslin..

point between the Y piece of the breathing system of an anesthesia machine and the end of an endotracheal tube (Figure 7.2). In awake, unsedated cattle, normal PaCO_2 is reported to be between 38 and 43 mmHg [3]. ETCO_2 is usually lower than PaCO_2 by 10–15 mmHg in large animal species due to a slight degree of ventilation/perfusion (V/Q) mismatch even in the awake state [4]. Most anesthetics depress respiratory function, resulting in hypoventilation and a significant increase in PaCO_2 with subsequent respiratory acidosis [5–12]. Severe hypoventilation with PaCO_2 greater than 60 mmHg is common in anesthetized, recumbent farm animals, particularly in adult cattle. Furthermore, a greater difference between ETCO_2 and PaCO_2 is also expected because of the increased V/Q mismatch in anesthetized, recumbent large animals, with the greatest difference occurring during dorsal recumbency (Figure 7.3) [13]. In halothane-anesthetized horses, a significantly greater difference between ETCO_2 and PaCO_2 occurred when they were anesthetized longer than 90 minutes as compared to that recorded at 60 minutes or less. But this increased difference with time between ETCO_2 and PaCO_2 did not occur in isoflurane-anesthetized horses [14]. Though there is no similar study reported in farm animals, increase in the difference between ETCO_2 and PaCO_2 as a result of prolonged duration of isoflurane anesthesia has not been observed in anesthetized adult cattle. The measurement of ETCO_2 does not reflect the true value of PaCO_2 ; clinical experience shows that monitoring of ETCO_2 can be used as an indicator to predict the direction of the change of PaCO_2 during anesthesia. However, it is important to remember that the difference between ETCO_2 and PaCO_2 is affected by the efficiency of the ventilation during anesthesia and the position of the patient required for surgery [4].

Adequate tissue oxygenation is essential for patient survival following anesthesia. Tissue O_2 delivery is determined by the blood flow and arterial blood O_2 content (CaO_2) in that tissue. When O_2 diffuses into the blood, 98% of that is bound to hemoglobin and only 1–2% is dissolved in the plasma. The O_2 -bound hemoglobin is represented by the measurement of O_2 saturation (SaO_2), and the amount dissolved in the plasma is represented as the partial pressure of arterial O_2 (PaO_2). Although PaO_2 only constitutes a small fraction of total CaO_2 , its well-defined relationship with SaO_2 in the arterial blood is demonstrated by the O_2 dissociation curve. Therefore, SaO_2 can be used to estimate PaO_2 . A pulse oximeter uses the difference in the ability to absorb infrared light of saturated and desaturated hemoglobin to calculate the amount of O_2 bound to the hemoglobin (SpO_2) [15]. This technique is noninvasive with the sensor clip or probe placed on a superficial pulsating artery on the lingual artery in the tongue, on the auricular artery in light-colored ears, or occasionally on the mucous membrane of the rectum of the animal (Figure 7.2). In normal, healthy patients, SpO_2 readings are reliable estimates of SaO_2 , ranging from 80% to 100% [16]. Normal hemoglobin SaO_2 should always be near 98–100%, which correlates to a PaO_2 of 95–100 mmHg

when breathing room air with 21% O₂. During anesthesia, when a patient is breathing 100% O₂, PaO₂ can range from 60 to 500 mmHg. Using the O₂ dissociation curve, PaO₂ can be estimated by subtracting 30 from the SpO₂ value when the SpO₂ is in the range of 60–90%. For example, PaO₂ is estimated to be 60 mmHg when the SpO₂ reading is 90% [17]. Factors that alter the pulse strength of a peripheral artery, such as hypotension, hypothermia, and vasoconstriction, affect the ability of a pulse oximeter to accurately estimate the SpO₂ [1, 4]. Increased ETCO₂ and decreased SpO₂ imply inadequate ventilation and severe V/Q mismatch, which are often the result of abnormal positioning of the animal and deep anesthesia. Decrease delivery of anesthetics and assisted or controlled ventilation should be instituted immediately to improve ventilation. Measurements of ETCO₂ and SpO₂ require appropriate pulmonary perfusion and pulsating peripheral arterial blood flow from adequate myocardial contractility and cardiac output. A sudden dramatic decrease in ETCO₂ and SpO₂ is the first indication of impending cardiac arrest. Gradual and persistent increase in ETCO₂ may indicate the beginning of a malignant hyperthermia episode.

Tables 7.1–7.6 provide normal values of commonly monitored physiological parameters (body temperature, heart rate, respiratory rate, and systolic, mean, and diastolic arterial blood pressures), hematology, and blood chemistry for cattle, goats, sheep, camelids, and pigs.

Table 7.1 The body temperature, heart rate, respiratory rate, and arterial blood pressures for farm animals.

Species	Temperature (°F)	Heart rate (beats/minute)	Respiratory rate (breaths/minute)	Arterial blood pressure (mmHg)
Cattle [18]	101–103	70–90	20–30	SAP: 120–150 MAP: 90–120 DAP: 80–110
Camelids [19]	100–102	60–80	10–30	SAP: 60–135 MAP: 70–100 DAP: 45–95
Goats [20]	102–104	70–95	15–30	SAP: 80–120 MAP: 75–100 DAP: 60–80
Sheep [20]	102–104	70–80	20–30	SAP: 80–120 MAP: 75–100 DAP: 60–80
Pigs [21] (adult)	101–104	70–110	20–30	SAP: 95–126 MAP: 68–83 DAP: 44–77
Pigs [21] (weaning)	102	80–100	25–30	SAP: 83–114 ^a MAP: 58–76 ^a DAP: 40–51 ^a

SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure.

^a Lin, H.C. Clinical observation.

Table 7.2 Normal values for hematology and blood chemistry of cattle.

Hematology ^a		Blood chemistry ^a	
Hematocrit (%)	24–46	Blood urea nitrogen (mg/dl)	7–17
Hemoglobin (g/dl)	8–15	Creatinine (mg/dl)	1–3
Red blood cells (10 ⁶ /μl)	5–10	Total protein (g/dl)	5.8–8.5
Mean corpuscular hemoglobin (pg)	14–19	Albumin (g/dl)	3–4.8
Mean corpuscular hemoglobin concentration (g/dl)	30–36	Bilirubin(mg/dl)	0.2–4
Mean corpuscular volume (fl)	40–65	Glucose (mg/dl)	48–70
White blood cells (10 ³ /μl)	5–17	Calcium (mg/dl)	8.5–10.3
Segmental neutrophils (10 ³ /μl)	0.6–4	Phosphorus (mg/dl)	2.4–7.9
Band neutrophils (10 ³ /μl)	0–0.1	Sodium (mEq/l)	137–151
Lymphocytes (10 ³ /μl)	2.5–7.5	Potassium (mEq/l)	2.5–5.9
Basophils (10 ³ /μl)	0–0.1	Chloride (mEq/l)	98–107
Monocytes (10 ³ /μl)	0.025–0.85	Magnesium (mg/dl)	1.9–2.7
Eosinophil (10 ³ /μl)	0–1.6	Bicarbonate (mmol/l)	16–40
Reticulocytes (10 ³ /μl)	0.001–0.008	Anion gap (mmol/l)	10–27
Platelets (10 ³ /μl)	0.1–0.8	Osmolality (mmol/kg)	270–350
Fibrinogen (mg/dl)	100–600	Creatine kinase (U/l)	40–264
		Aspartate aminotransferase (U/l)	69–112
		γ-Glutamyl transferase (U/l)	3.7–31
		Sorbitol dehydrogenase (U/l)	4.5–18

^a Reference data from Clinical Pathology Laboratory, Auburn University.

Table 7.3 Normal values for hematology and blood chemistry of goats.

Hematology ^a		Blood chemistry ^a	
Hematocrit (%)	22–38	Blood urea nitrogen (mg/dl)	10–20
Hemoglobin (g/dl)	8–12	Creatinine (mg/dl)	1–1.82
Red blood cells (10 ⁶ /μl)	8–18	Total protein (g/dl)	6.4–7
Mean corpuscular hemoglobin (pg)	5.2–8	Albumin (g/dl)	2.7–3.9
Mean corpuscular hemoglobin concentration (g/dl)	30–36	Bilirubin (mg/dl)	0.10–1.71
Mean corpuscular volume (fl)	16–25	Glucose (mg/dl)	50–75
White blood cells (10 ³ /μl)	4–13	Calcium (mg/dl)	8.9–11.7
Seg. neutrophils (10 ³ /μl)	1.2–7.2	Phosphorus (mg/dl)	4.2–9.1
Band neutrophils (10 ³ /μl)	0	Sodium (mEq/l)	142–155
Lymphocytes (10 ³ /μl)	2–9	Potassium (mEq/l)	3.5–6.7

(Continued)

Table 7.3 (Continued)

Hematology^a		Blood chemistry^a	
Basophils ($10^3/\mu\text{l}$)	0–0.3	Chloride (mEq/l)	99–110.3
Monocytes ($10^3/\mu\text{l}$)	0–0.05	Magnesium (mg/dl)	2.8–3.6
Eosinophil ($10^3/\mu\text{l}$)	0.05–0.65	Bicarbonate (mmol/l)	N/A
Platelets ($10^3/\mu\text{l}$)	0.3–0.6	Anion gap (mmol/l)	N/A
Fibrinogen (g/l)	100–400	Creatine kinase (U/l)	0.8–9
		Aspartate aminotransferase (U/l)	167–513
		γ -Glutamyl transferase (U/l)	20–56
		Sorbitol dehydrogenase (U/l)	14–23.6

^a Adapted from Ref. [22].**Table 7.4** Normal values of hematology and blood chemistry of sheep.

Hematology^a		Blood chemistry^a	
Hematocrit (%)	27–45	Blood urea nitrogen (mg/dl)	8–20
Hemoglobin (g/dl)	9–15	Creatinine (mg/dl)	1.2–1.9
Red blood cells ($10^6/\mu\text{l}$) ⁶	9–15	Total protein (g/dl)	6–7.5
Mean corpuscular hemoglobin (pg)	8–12	Albumin (g/dl)	2.4–3
Mean corpuscular hemoglobin concentration (g/dl)	31–34	Bilirubin (mg/dl)	0.1–0.5
Mean corpuscular volume (fl)	28–40	Glucose (mg/dl)	50–80
White blood cells ($10^3/\mu\text{l}$)	4–12	Calcium (mg/dl)	11.5–12.8
Seg. neutrophils ($10^3/\mu\text{l}$)	0.7–6	Phosphorus (mg/dl)	5–7.3
Band neutrophils ($10^3/\mu\text{l}$)	0	Sodium (mEq/l)	139–152
Lymphocytes ($10^3/\mu\text{l}$)	2–9	Potassium (mEq/l)	3.9–5.4
Basophils ($10^3/\mu\text{l}$)	0–0.3	Chloride (mEq/l)	95–103
Monocytes ($10^3/\mu\text{l}$)	0–0.75	Magnesium (mg/dl)	2.2–2.8
Eosinophil ($10^3/\mu\text{l}$)	0–1	Bicarbonate (mmol/l)	20–25
Platelets ($10^3/\mu\text{l}$)	0.21–0.71	Creatine kinase (U/l)	8–13
Fibrinogen (mg/dl)	100–500	Aspartate aminotransferase (U/l)	60–280
		γ -Glutamyl transferase (U/l)	20–52
		Sorbitol dehydrogenase (U/l)	5.8–27.9

^a Adapted from Ref. [22].

Table 7.5 Normal values for hematology and blood chemistry of camelids.

Hematology ^a		Blood chemistry ^a	
Hematocrit (%)	34 ± 4.0 25–46	Blood urea nitrogen (mg/dl)	29.0 ± 6.1 9–34
Hemoglobin (g/dl)	15.3 ± 1.7 11.5–19.5	Creatinine (mg/dl)	2.5 ± 0.5 1.4–3.2
Red blood cell (10 ⁶ /μl)	10.88 ± 1.1 9.9–17.7	Total protein (g/dl)	5.9 ± 0.5 5.1–7.8
Mean corpuscular hemoglobin (pg)	11.2 9.8–12.7	Albumin (g/dl)	3.6 ± 0.6 3.1–5.2
Mean corpuscular hemoglobin concentration (g/dl)	43.3 37.7–49	Bilirubin (mg/dl)	0.2 ± 0.2 0–0.2
Mean corpuscular volume (fl)	26 22–30.1	Glucose (mg/dl)	134.2 ± 36.0 74–154
White blood cell (10 ³ /μl)	8.0–23.3 7.5–20.0	Calcium (mg/dl)	9.0 ± 0.7 7.4–10.4
Seg. neutrophils (10 ³ /μl)	4.18–14.87	Phosphorus (mg/dl)	5.8 ± 2.2 2.6–7.3
Band neutrophils (10 ³ /μl)	0–0.13 0–169	Sodium (mEq/l)	149.4 ± 5.4 148–158
Lymphocytes (10 ³ /μl)	0.96–7.64 0.7–4.9	Potassium (mEq/l)	3.8 ± 0.9 3.7–6.1
Basophils (10 ³ /μl)	0–0.3	Chloride (mEq/l)	115.9 ± 4.8 102–120
Monocytes (10 ³ /μl)	0.0–1.34 0.0–1.0	Magnesium (mg/dl)	1.9 ± 0.3
Eosinophil (10 ³ /μl)	0.07–5.83 0.16–4.5	Bicarbonate (mmol/l)	N/A
		Total CO ₂ (mm/l)	13–31
Reticulocytes (10 ³ /μl)	12–79	Creatine kinase (U/l)	81.8 ± 110 8–77
Platelets (10 ³ /μl)	200–600	Aspartate aminotransferase (U/l)	216–378 166–447
Fibrinogen (g/l)	300 ± 114 100–500	γ-Glutamyl transferase (U/l)	7–29 9–27
		Sorbitol dehydrogenase (U/l)	1–17 1–5

^a Adapted from (a) Oregon State University Veterinary Diagnostic Laboratory; (b) Ref. [23]; (c) Ref. [24].

Table 7.6 Normal values for hematology and blood chemistry of pet pigs.

Hematology^{a,b}		Blood chemistry^{a,b}	
Hematocrit (%)	32–50 (30–50)	Blood urea nitrogen (mg/dl)	10–25 (9.2–29.2)
Hemoglobin (g/dl)	10–16	Creatinine (mg/dl)	0.5–1.7 (1.2–2)
Red blood cells (10 ⁶ /μl)	5–8	Total protein (g/dl)	6.2–9.3 (6.1–8.9)
Mean corpuscular hemoglobin (pg)	17–21	Albumin (g/dl)	3.1–4.3 (3.9–5.6)
Mean corpuscular hemoglobin concentration (g/dl)	30–34	Bilirubin (mg/dl)	0.5–1 (0–0.3)
Mean corpuscular volume (fl)	50–56	Glucose (mg/dl)	31–77 (36.4–123.2)
White blood cells (10 ³ /μl)	11–22 (6.6–18.6)	Calcium (mg/dl)	8.3–10.4 (9.6–11.6)
Seg. neutrophils (10 ³ /μl)	3.2–10	Phosphorus (mg/dl)	4.9–9.1 (5.1–8.1)
Band neutrophils (10 ³ /μl)	0–0.8	Sodium (mEq/l)	135–153 (144–152.6)
Band neutrophils (%)	(0.0–1.2)	Potassium (mEq/l)	3.9–6 (4–5.2)
Lymphocytes (10 ³ /μl)	4.5–13	Chloride (mmol/l)	92–117 (94.4–114)
Lymphocytes (%)	(19.2–72)	Magnesium (mg/dl)	2.7–3.7
Basophils (10 ³ /μl)	0–2	Bicarbonate (mmol/l)	21–31
Basophils (%)	(0–2.5)	Anion gap (mmol/l)	14–23
Monocytes (10 ³ /μl)	0.25–2	Creatine kinase (U/l)	77–256 (48–288)
Monocytes (%)	(1.1–13.9)	Aspartate aminotransferase (U/l)	53–162 (10.4–56)
Eosinophil (10 ³ /μl)	0.05–2	Sorbitol dehydrogenase (U/l)	1–5.8
Eosinophil (%)	(0–10)	γ-Glutamyl transferase (U/l)	11–39
Platelets (10 ³ /μl)	130–950 (201–679)		
Fibrinogen (mg/dl)	100–500		

^aValues in parenthesis for Yucatan miniature pigs.^bAdapted from (a) Ref. [25]; (b) Ref. [26].

7.2 Supportive Fluid Therapy

Supportive fluid therapy during anesthesia is not absolutely necessary in healthy animals undergoing short-term surgery. However, if the animal is fasted and water is withheld for 24 hours or longer prior to anesthesia, a balanced electrolyte solution should be administered. In large ruminants, a 12- or 14-gauge needle or 5/4-inch Teflon indwelling catheter can be placed in the jugular vein for fluid administration and, if needed, for administration of emergency drugs. A 14- or 16-gauge, 3–5/4-inch indwelling catheter is usually used for small ruminants and camelids. Normal maintenance fluid therapy in healthy patients during anesthesia is 4–8 ml/kg/hour, but 10–25 ml/kg/hour may be required to correct hypotension in compromised patients. Ruminants salivate copiously during anesthesia, but administration of balanced electrolyte solution for replacement of fluid loss through salivation usually is not required [27, 28]. Camelids do not handle the administration of large amount of fluid in a short period of time well. Hypoproteinemia and subsequent pulmonary edema may develop and thus impair gas exchange within the alveoli. As a result, respiratory distress and death may occur [29].

Intravenous (IV) catheterization for perioperative fluid therapy in pigs is difficult and often impossible, particularly in potbellied pigs, because of the lack of visible superficial veins. An ear vein can be used for placement of an IV catheter if the pig cooperates. This may be easier to accomplish in a large farm (agricultural) pig, while it can be quite difficult in an awake potbellied pig but easier when done during anesthesia. Ear veins, especially lateral auricular veins, are common sites because they are superficial and easily accessible. An 18- or 20-gauge, 1–1½-inch hypodermic needle, indwelling catheter, or butterfly catheter can be used for large adult pigs, while 21- or 23-gauge is suitable for smaller-sized pigs and pigs with small ears. Intramedullary cannulation has been used for fluid and drug administration when no other vascular access can be established. An 18-gauge cannula can be placed into the greater tubercle of the humerus or the trochanteric fossa of the femur for intramedullary administration. This technique can be performed in immature pigs, but the administration rate of drug solution or fluid may be limited in older pigs due to the presence of fat and fibrosis of the medullary canal [30]. In debilitated pigs, a 14-, 16-, or 18-gauge, 20-cm central venous catheter can be placed using Large Animal Long Term Venous Catheterization with Seldinger Technique: Guidewire Introducer (Mila International, Inc) as described by Maxwell and Kennedy (2020) [31]. The tip of the catheter should be located at the anterior vena cava if the catheter is of appropriate length. The catheter can be used for long-term fluid therapy, multiple administration of antibiotics, and frequent blood sampling. General anesthesia will be required for the placement of the catheter (Figure 7.4). Please refer to Chapter 11 for a detailed discussion on fluid therapy in farm animals.

7.3 Positioning

Improper positioning of the patient can result in postanesthetic neuromyopathy in cattle and camelids, similar to that seen in horses. Uneven distribution of the body weight of the animal and inadequate surface padding such as would occur on gravel, concrete, or a metal table surface without foam padding where the animal was placed during anesthesia are examples of improper positioning. Myopathy does not occur as readily in large ruminants, but nerve paralysis due to improper positioning has occurred in adult cattle and camelids following anesthesia. Adult cattle should be placed on a 10-cm-thick high-density foam pad, whereas a 5-cm-thick foam pad is sufficient for calves, small ruminants, camelids, and pigs. When placed in dorsal recumbency, the veterinarian



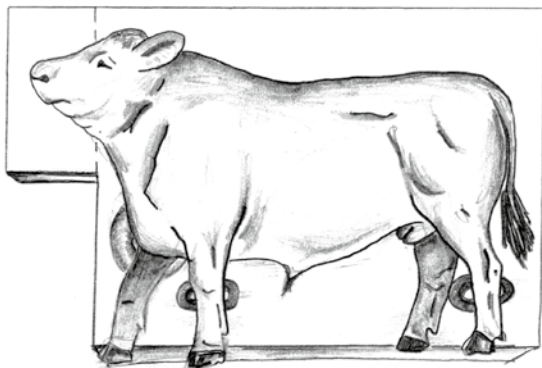
Figure 7.4 Placement of a jugular catheter for collection of blood samples and drug and fluid administration in pigs.

should make sure that the animal is balanced squarely on its back with gluteal areas bearing equal weight. All limbs should be flexed and relaxed. While in lateral recumbency, an automotive inner tube (valve stem pointed down) can be placed under the elbow of the dependent forelimb. The inner tube can be placed directly under the shoulder (Figure 7.5a) or through the dependent forelimb and under the shoulder (Figure 7.5b). Duct tape or other nonelastic tape can be placed on the part of the inner tube that is not under the shoulder (opposite of valve stem) (Figure 7.5c), which prevents collapsing of the inner tube under the animal and, at the same time, limits the expansion of the inner tube that is not under the animal. Once the inner tube is in place, pulling the dependent forelimb anteriorly will help to distribute the weight of the thorax on the triceps rather than on the humerus. The upper forelimb and hind limb should be positioned perpendicularly to the table surface, with both uppermost limbs elevated and parallel to the table surface (Figure 7.6). These techniques minimize the pressure on the radial or femoral/peroneal nerve of the dependent limb and prevent nerve paralysis [28]. The head and neck should be at a slightly extended position. If possible, the head should be slightly lower than the neck, which will allow draining of the saliva and ruminal contents if regurgitation occurs. Apply ophthalmic ointment in the eyes and make sure the dependent eye is closed to minimize the risk of a corneal ulcer [2, 28].

7.4 Recovery

Ruminants and camelids usually recover from anesthesia smoothly but gradually. Emergence delirium and premature attempts to stand seldom occur in these animals. They should be placed in sternal recumbency with support during the recovery period. If regurgitation occurred during anesthesia, the oral cavity and pharynx should be lavaged to prevent aspiration of ruminal materials and subsequent aspiration pneumonia. The endotracheal tube with the cuff still inflated should be left in place until the animal regains its chewing and coughing reflexes. The tube should be

(a)



(b)

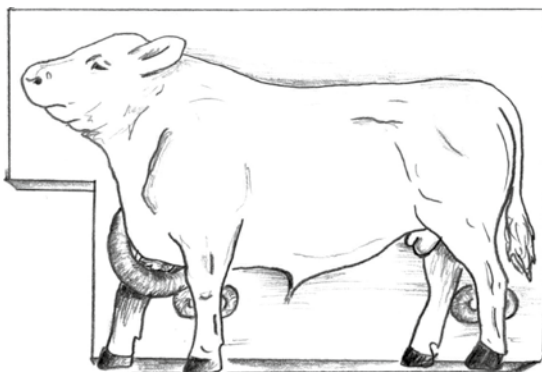


Figure 7.5 (a) Placement of an inner tube under the shoulder during lateral recumbency in adult cattle. (b) Placement of an inner tube through the dependent forelimb under the shoulder during lateral recumbency in adult cattle. (c) Taped inner tube. Source: Illustration by Kim Crosslin.

(c)

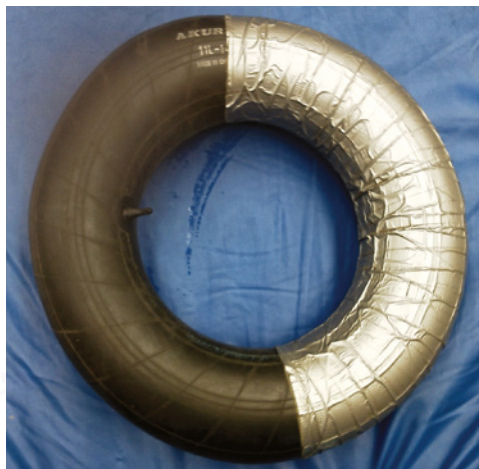


Figure 7.6 Anesthetized adult cattle in the lateral recumbency position.

removed with the cuff inflated. Pigs can be placed in either lateral or sternal recumbency for recovery as long as adequate ventilation is ensured. Deflate the cuff of the endotracheal tube after the pigs are disconnected from the anesthesia machine and remove the tube when swallowing and coughing reflexes return.

7.5 Perioperative Complications

7.5.1 Regurgitation and Aspiration Pneumonia

Regurgitation can occur during light (active regurgitation) and deep (passive regurgitation) anesthesia in ruminants in spite of preoperative fasting and withholding of water. Active regurgitation is a reflexive, protective mechanism of the body, intent on rejecting unwanted materials from the pharynx, upper airway, and upper digestive tract. Active regurgitation is characterized by explosive discharge of large quantities of ruminal materials. Passive regurgitation occurs when the esophageal muscles and transluminal pressure gradients relax as a result of the anesthetic effect. Aspiration pneumonia or, in most severe cases, death can occur if the airway is not protected, and a large amount of ruminal materials can be aspirated into the airway and reach small airways. Please refer to Chapter 1 for detailed discussion on aspiration pneumonia. Preanesthetic feed and water withholding and endotracheal intubation with the cuff adequately inflated are recommended in all anesthetized ruminants and camelids for prevention of aspiration pneumonia [32]. Preventive measurements such as elevation of the neck using a sandbag or a rolled towel as well as avoiding vigorous manipulation of the rumen and other internal abdominal organs during surgery help to minimize the occurrence of regurgitation. If regurgitation occurs prior to intubation and protection of the trachea, the veterinarian should either quickly lower the animal's head or place the endotracheal tube in the esophagus and inflate the cuff to allow ruminal contents to flow out of the mouth while another endotracheal tube is placed in the trachea [2]. IV aminophylline (2–4 mg/kg over a period of 5 minutes or 11 mg/kg over a period of 20 minutes) or other bronchodilators along with 100% O₂ can be administered to relieve bronchospasm at the time of aspiration. If the animal survives the initial insult, corticosteroids and broad-spectrum antibiotics are indicated for the treatment of pneumonia. If regurgitation occurs after the endotracheal tube is in place, make sure the cuff is properly inflated and then lavage the mouth, nares, and pharynx with water to minimize the risk of aspiration of the regurgitated materials on extubation. Always pull the endotracheal tube with the cuff inflated, so the remainder of the ruminal materials accumulated around the trachea cephalad to the cuff can be removed along with the endotracheal tube. Other methods that can be used to decrease the risk of perioperative regurgitation include positioning the animal in left lateral or sternal recumbency if possible to reduce pressure on the rumen and avoiding vigorous manipulation of the rumen and intestinal tracts during surgery [2, 28].

7.5.2 Airway Obstruction

Airway obstruction can occur in ruminants from aspiration of ruminal contents during induction (active regurgitation) or during maintenance (passive regurgitation) of anesthesia. Ruminal contents contain more solid materials than gastric contents of monogastric animals. Liquid ruminal content tends to drain out from the mouth, while solid materials are easily lodged at the larynx and can be aspirated into the airway and result in airway obstruction. If the cause of the obstruction is from active regurgitation, treatment should include rapidly increasing the depth of anesthesia and

placement of an endotracheal tube. For an animal with an endotracheal tube already in place, removal of regurgitated materials from the buccal cavity either manually or by lavaging the buccal cavity with water or irrigation saline should be performed prior to the removal of the endotracheal tube as the animal recovers from anesthesia [2]. Improper positioning of the head and malposition of an anesthetic machine during anesthesia can result in kinking of the endotracheal tube and, subsequently, airway obstruction. Airway obstruction can also result from inflation of the cuff on an esophageal placement of the endotracheal tube and overinflation of the cuff on a correctly placed endotracheal tube; either cause may lead to collapsing of the tube. Observe the movement of the chest wall and/or the movement of the rebreathing bag of an anesthesia machine or the presence of the ET CO_2 waveforms on the multiparameter monitor to confirm correct placement of the endotracheal tube to prevent dyspnea and apnea due to accidental airway obstruction.

Dorsal displacement of the soft palate following extubation of an endotracheal tube in camelids results in the soft palate being situated dorsally to the epiglottis and thereby subsequently hindering the airflow into the larynx. This is a serious condition because camelids are obligate nasal breathers and the obstruction, if not corrected immediately, can lead to dyspnea and eventually cardiac arrest. If the animal is awake enough at the time of extubation and the swallowing reflex has returned, then the problem can be corrected by initiating a swallowing reflex to allow the soft palate to return to its normal position and thus remove the source of airway obstruction. However, if the swallowing reflex has not yet returned, then the animal needs to be reintubated until it does [32]. Prolonged duration of dorsal recumbency in camelids often results in severe nasal edema and congestion. Upper airway obstruction sometimes occurs following extubation during recovery. Placing the animal in sternal recumbency, keeping the head high, administering nasal spray containing phenylephrine, and insufflation of 100% O_2 should be instituted until the nasal edema diminishes and adequate airflow in and out of the nasal cavity resumes.

Pigs are more difficult to intubate and several attempts are sometimes required to place the endotracheal tube successfully. Repeated attempts at intubation may provoke laryngeal edema and laryngospasm, which may result in airway obstruction in lightly anesthetized pigs. Application of topical lidocaine to the larynx and an adequate plane of anesthesia aid in a smooth and successful intubation and minimize trauma to the larynx. Because of the long soft palate of pigs engaging the larynx, dorsal displacement of the soft palate may result in airway obstruction, and suffocation has been reported in swine [33]. This complication can occur following extubation and also in pigs that are not intubated during anesthesia. In sows receiving spinal anesthesia and placed in lateral recumbency for cesarean section, restraining the head with rope may be necessary to prevent head movement. Care should be taken not to place the head in extension to avoid dorsal displacement of the soft palate. Noisy respiration after extubation indicates possible laryngeal spasm or upper airway obstruction and should be investigated immediately [34].

7.5.3 Ruminal Tympany/Bloat

Ruminal tympany or bloating can occur during anesthesia as a result of anesthetic-induced decreased gastrointestinal motility, accumulation of gas produced by fermentation of ingesta, and the animal's inability to eructate. Consequently, intra-abdominal pressure increases, which pushes the diaphragm cranially and ventrally. Therefore, the functional residual capacity of the lungs decreases, resulting in severe hypoventilation accompanied by hypercapnia and hypoxemia. Placing the animal in sternal recumbency immediately after anesthesia helps to eliminate the accumulated gas in the rumen. However, decompression of the rumen may need to be performed while the surgery is in progress and the animal is still anesthetized. Passage of a stomach tube or,

alternatively, insertion of a 12-gauge needle through the abdominal wall allows an outflow for the accumulated gas and reduces the pressure in the abdomen and on the diaphragm, thereby improving the ventilation of the patient. Trocarization to relieve bloating should only be performed as a last resort due to the potential for peritoneal cavity contamination and peritonitis. Preanesthetic fasting may reduce gas production, but it does not prevent continuous fermentation of the ingesta during anesthesia. In addition, most anesthetics, particularly α_2 agonists (e.g. xylazine) and opioid agonists (e.g. morphine), decrease gastrointestinal motility. Fortunately, there are antagonists available to reverse the gastrointestinal effect of an α_2 agonist or an opioid agonist to treat the ruminal tympany if necessary. Preoperative fasting is strongly recommended in ruminants and camelids to reduce the amount of gas produced from fermentable food materials and thereby decrease the chance of developing perioperative ruminal tympany and bloating [32].

7.5.4 Salivation

A ruminant normally produces copious quantities of saliva (i.e. 50 l/day for cattle, 6–16 l/day for sheep) [35, 36] that continue to flow even after the induction of anesthesia and loss of swallowing reflex. Older inhalation anesthetics such as halothane have been reported to decrease salivation in dogs and humans [37, 38]. Compared to ether and chloroform, salivation in cattle was reduced from 78 and 33.9 ml/minute, respectively, to 24 ml/minute during halothane anesthesia [39]. It is reasonable to expect that isoflurane and sevoflurane, like halothane, are capable of reducing salivation to some extent in ruminants. In the past, atropine had been administered routinely to ruminants prior to induction of anesthesia to reduce salivation. However, atropine does not completely inhibit salivation. More importantly, atropine decreases the water content of the saliva, which causes the saliva to be more viscous and more difficult to clean out of the trachea, particular in neonates [40]. Today, atropine is only administered for treatment of bradycardia and for emergency situations when needed. Positioning of an anesthetized ruminant and camelid to elevate the neck to avoid pooling of saliva and regurgitated materials [2, 28] has been described in section 7.3.

7.5.5 Hypoventilation

Placing an anesthetized animal in lateral or dorsal recumbency is required for most surgical procedures requiring general anesthesia. This alteration of the animal's normal position often results in cranial shift of the abdominal organs and the diaphragm and, as a result, decreases the functional residual lung capacity of the animal. Awake animals may respond to decreased functional residual capacity by increasing respiratory rate and tidal volume. However, this response may be obtunded by the anesthetics administered, and respiratory depression develops. Severe hypercapnia and hypoxemia characterized by a significant increase in PaCO_2 and decrease in PaO_2 resulting from significant V/Q mismatch and eventually right-to-left shunting due to the abnormal body position required by surgery and anesthetic-induced respiratory depression are common complications during anesthesia. In conscious sheep, lateral recumbency alone induces significant hypoxemia [41]. When cows were placed in dorsal recumbency either in an awake state or sedated with intramuscular (IM) xylazine (0.22 mg/kg) while breathing room air, PaO_2 decreased to a dangerous level of 45–60 mmHg. Returning these cows into sternal recumbency greatly improved PaO_2 values [28, 42]. Assisted or controlled ventilation by simply squeezing the rebreathing bag or using a mechanical ventilator with positive pressure set at 20–25 cm of H_2O for small ruminants and camelids and 25–30 cm of H_2O for large ruminants can be used to minimize hypercapnia and/or

hypoxemia during inhalation anesthesia. Supplemental O₂ without an anesthesia machine can be provided to sedated animals through an orotracheal or endotracheal tube by using an O₂ demand valve during recumbency, particularly if xylazine is part of the anesthetic regimen. Occasionally, apnea may occur and persist throughout anesthesia. Veterinarians should always make sure the animal is under an adequate plane of anesthesia, not deeply anesthetized, before instituting any drug treatment. Doxapram, a respiratory stimulant, can be administered at 0.1–0.5 mg/kg IV to initiate respiration. If the apnea persists, doxapram can be administered as a continuous IV infusion (5–10 µg/kg/minute) [43]. Doxapram is not effective in stimulating respiration if the cause of apnea is deep anesthesia. Doxapram does not just stimulate the respiratory center in the medulla; it is in fact a generalized central nervous system stimulator. Therefore, administration of doxapram may result in movement and awakening of the animal during the surgery.

7.5.6 Cardiac Arrhythmias

Severe cardiac arrhythmias rarely occur in anesthetized farm animals. However, premature ventricular contractions have been observed in animals with preexisting electrolyte imbalance and severe hypercapnia or during light anesthesia. Bigeminal premature ventricular contractions have been associated with the administration of xylazine in adult cattle, especially in more excitable ones. Xylazine is known to sensitize myocardium to circulating catecholamines and lower the arrhythmogenic threshold for cardiac arrhythmias. Isoflurane and sevoflurane do not sensitize the myocardium to circulating catecholamines. Anesthetic-induced cardiac arrhythmias caused by xylazine have not been a major concern in anesthetized farm animals. However, in case of severe premature ventricular contraction, especially when cardiac output and arterial blood pressures are affected, lidocaine is the drug of choice for treatment. A single dose of lidocaine (1–2 mg/kg IV) is effective for treatment of premature ventricular contractions. Premature ventricular contractions may return, and continuous infusion of lidocaine (40–60 µg/kg/minute) may be instituted for longer-lasting effect [28]. Atrial fibrillation, a consequence of gastrointestinal disease or obstruction, and the resultant metabolic disturbances in cattle, is often resolved when the primary cause is surgically corrected. Physical restraint combined with local anesthesia provides adequate analgesia and is often used to perform standing abdominal surgery in these animals [2]. In goats with experimentally induced urethral obstruction, hyperkalemia often with profound increases in serum potassium concentration has been associated with sinus arrhythmias with occasional premature ventricular contraction. Though in most cases no drug treatments are necessary except administration of IV 0.9% sodium chloride, goats should be closely monitored to ensure they are under a light plane of anesthesia throughout the surgical period.

Traction or pressure on the eyeball causes bradycardia as a result of oculocardiac reflex mediated through the trigeminal and vagal nerves. Enucleation-induced bradycardia is frequently observed in horses. Similarly, manipulation and traction of the abdominal organs such as the ovary also induce vagal stimulation and bradycardia. Relieving the traction or pressure on the eyeball or ovary usually returns the heart rate back to within baseline range. Atropine (0.06–0.12 mg/kg IV) can be administered if bradycardia persists and cardiac output and arterial blood pressure are affected [28]. Camelids tend to be more sensitive to vagal stimulation caused by tracheal intubation or painful surgical stimulation, and atropine (0.02 mg/kg IV or 0.04 mg/kg IM) has been administered for treatment of bradycardia [2].

Preanesthetic fasting for 48 hours has been reported to cause bradycardia in cattle [44]. It is believed that increased vagal tone and/or decreased sympathetic tone is responsible for the bradycardia since there are vagal afferent nerve fibers located throughout the gastrointestinal tract with

receptors that can be activated by changes in pH (gastric chemoreceptors), stretch (gastric mechanoreceptors), or other chemical mediators associated with food withdrawal [45, 46]. The clinical experience of the author suggests that there are no significant hemodynamic changes or detrimental effects associated with preanesthetic withholding of feed and water for 48 and 24 hours, respectively, in cattle. Nevertheless, one should be aware that pain-induced sympathetic stimulation when an animal is under light plane of anesthesia and the subsequent increase in heart rate may be masked by the bradycardia resulting from deprivation of feed so that the heart rate of the animal may appear to be lower than normal or within normal ranges [45].

7.5.7 Hypotension

In horses, hypotension with a mean arterial blood pressure below 60 mmHg persisting for long periods during anesthesia has been associated with increased incidence of postanesthetic neuromyopathy. However, hypotension is rarely observed in anesthetized adult cattle unless these animals are under excessive deep anesthesia [47]. Thus, adult cattle may not be as prone to develop postanesthetic neuromyopathy as horses. On occasion, postanesthetic neuromyopathy does occur, particularly nerve paralysis, due to inappropriate positioning and anesthetic-induced severe cardiovascular depression and hypotension. Xylazine-induced cardiovascular depression has been shown to result in hypotension [48]. Lateral and dorsal recumbencies in adult cattle have been associated with hypotension as a result of the compression of the vena cava caused by the pressure from the abdominal cavity, which in turn decreases venous return, cardiac output, and arterial blood pressures. The primary goals of anesthetic management for anesthetized animals are to maintain reasonable depth of anesthesia and normal cardiovascular function. For mild hypotension during anesthesia, reducing anesthetic concentration administered and initiating IV infusion of a balanced electrolyte solution and calcium borogluconate (23% solution) may be sufficient to return arterial blood pressure back to acceptable ranges. Calcium is an essential electrolyte for adequate muscle contraction including skeletal muscles, vascular smooth muscles, and myocardial muscles. The administration of calcium borogluconate enhances myocardial contractility and thus indirectly increases cardiac output and arterial blood pressure. However, ruminants tend to be more sensitive to calcium and bradycardia, and further decreases in cardiac output and arterial blood pressure may negate the usefulness of calcium borogluconate [2]. If decreasing anesthetic concentration in hypotensive patients does not return blood pressure back to within the normal range without the patient awakening from anesthesia, then treatment with a sympathomimetic drug, such as dobutamine, dopamine, phenylephrine, or ephedrine, should be instituted. Dobutamine is a β_1 agonist. When administered at a low dosage (1–5 $\mu\text{g}/\text{kg}/\text{minute}$), dobutamine increases cardiac output and arterial blood pressure by increasing myocardial contractility. Dobutamine seldom increases heart rate except in animals suffering hypovolemia or when the drug is administered at high doses [49]. Dopamine is a dose-dependent dopaminergic, α and β agonist. When administered at a low infusion rate of 1–2 $\mu\text{g}/\text{kg}/\text{minute}$, dopamine increases renal perfusion by stimulating renal dopaminergic receptors. Increasing the infusion rate to 2–10 $\mu\text{g}/\text{kg}/\text{minute}$ results in stimulation of β_1 receptors and subsequently increases heart rate. Vasoconstriction and an increase in arterial blood pressure mediated by stimulation of α_1 receptors are not evident until a high infusion rate of greater than 10 $\mu\text{g}/\text{kg}/\text{minute}$ is administered [50]. Phenylephrine is a pure α_1 agonist, and it increases arterial blood pressure by its effect on peripheral vasoconstriction. Phenylephrine can be administered as a bolus at 2–4 mg/kg IV, or it can be administered as a continuous infusion at 0.2–0.4 $\mu\text{g}/\text{kg}/\text{minute}$ for a longer-lasting effect. Ephedrine is a mixed α_1 and β_1 agonist (22–66 $\mu\text{g}/\text{kg}$ IV), and it increases arterial blood pressure by improving cardiovascular

functions with only a small increase in heart rate but without significant vasoconstriction [51]. Though any one of the four aforementioned drugs is useful in the treatment of hypotension, the most effective treatment for hypotension during anesthesia is maintaining an adequate plane of anesthesia.

7.5.8 Hypothermia

Decreased heat production and increased heat loss are the primary causes for the significant decrease in body temperature observed during anesthesia and surgery [52]. Hypothermia is a common anesthetic complication in small companion animals, but it is rarely an issue for adult cattle and camelids because of their large body mass to surface area ratio and, in camelids, thick hair coat. The body temperature of adult cattle and camelids seldom drops more than 0.5°C unless a major body cavity is opened during anesthesia. However, hypothermia can be a significant problem for small ruminants and pigs, especially in pediatric patients. Hypothermia can result in a significant reduction in anesthetic requirement and prolonged recovery [53]. Although often obese, pigs lack an insulating hair coat, thus are prone to hypothermia, and must be protected from extreme temperature and insensible heat loss during anesthesia [21]. An average decrease of $2.8 \pm 0.6^\circ\text{C}$ ($5.04 \pm 1.08^\circ\text{F}$) in body temperature was reported in pigs weighing 46–109 kg (101.2–239.8 lb) that underwent experimental magnetic resonance imaging guided convection enhanced drug delivery. These pigs were premedicated with azaperone (2 mg/kg IM) and ketamine (10 mg/kg IM), and anesthesia was induced with propofol (1.87 ± 0.6 mg/kg IV, to effect) and maintained with isoflurane. The average duration of anesthesia (from injection of propofol to the time of extubation) was 304 ± 55 minutes. Peripheral vasodilation, depression of thermoregulatory center, cool ambient temperature, and long duration of anesthesia were most likely the contributing factors of hypothermia in the pigs of this study [54]. In a pediatric potbellied pig, a long duration of anesthesia (4 hours) even with supplemental heat still resulted in significant hypothermia with a body temperature of 33.3°C (92°F) and a prolonged recovery (personal observation). Therefore, supplemental heat with circulating warm air or a warm water blanket, heating pad, or, at the very least, latex gloves or plastic bottles filled with warm water can be placed around the animal to minimize the decrease in body temperature and prevent severe hypothermia during anesthesia.

7.5.9 Malignant Hyperthermia

Malignant hyperthermia, also referred to as “porcine stress syndrome,” is a genetic disorder with mutation on the ryanodine receptors (ryr-1 locus) of the calcium channels in the skeletal muscles [55–57]. Detailed descriptions of the mechanism and causes of malignant hyperthermia have been discussed in Chapters 1 and 6. The clinical signs of malignant hyperthermia syndrome are manifested as sudden and dramatic increases in body temperature and ETCO_2 followed by excessive muscle fasciculation, muscle rigidity, tachypnea, tachycardia, arrhythmias, myoglobinuria, metabolic acidosis, renal failure, and, often times, death. Sudden increases in ETCO_2 and muscle rigidity are the early indication of an imminent malignant hyperthermia episode. If recognized very early and treatments instituted immediately, survival rates improve and the prognosis is more favorable than if treatment is delayed. However, prognosis is often poor once the episode is initiated in spite of aggressive treatments. Halogenated inhalation anesthetics are known triggers for malignant hyperthermia, and halothane seems to be the most potent trigger and has been most frequently reported in pigs [58]. The newer inhalation anesthetics, isoflurane, sevoflurane, and

desflurane, have also been reported to trigger malignant hyperthermia in Pietrain, Pietrain-mixed, Poland China, and Large White pigs [59–61]. Compared to halothane-induced malignant hyperthermia, the malignant hyperthermia episodes induced by desflurane and isoflurane were reported to have a slower onset than halothane [59]. Only one incidence of isoflurane-induced malignant hyperthermia has been reported in a potbellied pig [62]. In recent years, the development of a DNA test for malignant hyperthermia has allowed accurate identification of the malignant hyperthermia mutation genotypes from carriers to noncarriers, resulting in the elimination of the malignant hyperthermia mutation from breeding stock [63–65]. As a result, there have been fewer malignant hyperthermia cases reported in pigs in recent years.

A case of malignant hyperthermia in cattle was reported in an isoflurane-anesthetized Angus bull [66]. The bull was sedation with xylazine (0.1 mg/kg IV) and anesthesia was induced in 5 minutes with 5% guaifenesin (34 mg/kg IV) and ketamine (3 mg/kg IV). Controlled ventilation (7 breaths/minute) with isoflurane in O₂ was used to maintain anesthesia. The result of arterial blood gas taken at 30 minutes after induction was within normal ranges. However, at 75 minutes after induction, progressive increase in heart rate (from 55 to 70 beats/minute) and ET_{CO}₂ (from 38 to 60 mmHg) with respiratory acidosis (pH 7.268) and a moderate increase in Pa_{CO}₂ (from 29.7 to 66.4 mmHg) were observed. At this time, isoflurane was discontinued and replaced with a different anesthesia machine. Heart rate (from 70 to 155 beats/minute) and ET_{CO}₂ (from 60 to 218 mmHg) continued to increase at 140 minutes postinduction. Body temperatures recorded from a nasopharyngeal probe increased from 39.5 °C (103.1 °F) at 75 minutes and 43.5 °C (110.3 °F) at 140 minutes. Unfortunately, the bull developed ventricular fibrillation which progressed to asystole and the cardiopulmonary resuscitation effort was unsuccessful [66]. This is believed to be the first reported malignant hyperthermia case in cattle. Unlike malignant hyperthermia in pigs [67, 68], muscle rigidity, one of the typical clinical signs of malignant hyperthermia, was not observed in this bull. In addition, clinical signs of malignant hyperthermia in pigs usually develop within minutes following exposure to a triggering agent, whereas progression of the clinical signs in this bull did not occur until 75 minutes after initiation of isoflurane [66].

Treatments for malignant hyperthermia are primarily symptomatic. Early recognition of symptoms, such as muscle rigidity, sudden rise in body temperature, and ET_{CO}₂, and aggressive treatments, such as immediate discontinuation of inhalation anesthetic and institution of ice packs and alcohol baths, are the keys to a more favorable prognosis. Controlled ventilation should also be instituted at an early stage to remove excessive CO₂ and maintain normal blood pH and acid–base status. Dantrolene sodium has been shown to be effective for treatment (1–3 mg/kg IV) and prophylaxis (5 mg/kg PO) of malignant hyperthermia episodes [30]. In 1981, McGrath et al. [69] reported that acepromazine at 1.1 and 1.65 mg/kg IM reduced the incidence of malignant hyperthermia by 40% and 73%, respectively. A lower dose of 0.55 mg/kg IM was only able to delay the onset but did not prevent the episode. Azaperone at doses of 0.5–2.0 mg/kg IM has been shown to offer 100% protection against malignant hyperthermia in susceptible Pietrain pigs [70].

7.5.10 Postanesthetic Neuromyopathy

Ruminants are not as susceptible to postanesthetic myositis or nerve paralysis as are horses. Fortunately, postanesthetic localized or generalized myositis like that observed in horses has not been reported in adult cattle and camelids. However, inadequate padding and/or positioning combined with severe hypotension during anesthesia has resulted in temporary radial nerve paralysis in adult cattle and llamas when placed in lateral recumbency. Affected animals stood but were not able to bear weight on the affected limb. The condition improved within 24 hours and recovery

with full motor function returned in 2 to 3 days. Affected animals should be treated symptomatically, which may include maintaining circulating blood volume by infusion of balanced electrolyte solutions, administration of anti-inflammatory drugs to relieve inflammation, analgesics to relieve pain, diazepam to reduce anxiety and provide muscle relaxation, and sodium bicarbonate (350–500 mEq/450 kg [990 lb] IV) for correction of metabolic acidosis. During anesthesia, preventive measures should include the following: maintaining light anesthesia, reducing the dose of anesthetics that produce profound cardiovascular depression, close monitoring, maintaining cardiovascular function with infusion of balanced electrolytes and vasoactive and inotropic drugs (dobutamine, dopamine, ephedrine), ensuring adequate padding of the surgical table, even distribution of the body weight of the anesthetized animal, proper means to protect radial and femoral nerves, support of the upper front and hind legs, and minimizing the duration of anesthesia [43].

7.5.11 Cardiovascular Collapse

During anesthesia, significant and prolonged decrease in pulse pressure, hypotension, increased capillary refill time, pale mucous membranes, bradycardia, and/or tachycardia can lead to cardiovascular collapse. Causes of perioperative collapse include significant endotoxin-induced peripheral vasodilation, severe systemic disease, extreme hypovolemia due to dehydration and/or blood loss, and excessive deep anesthesia resulting in profound myocardial depression. Treatment of impending cardiovascular failure should begin with correction of the causative disease status, rapid administration of supportive fluid (90 ml/kg), and reduction or even cessation of anesthesia. Additional symptomatic treatments include vasoactive drugs (e.g. dopamine, phenylephrine, ephedrine) for hypotension, inotropic drugs (e.g. dobutamine) for myocardial depression, chronotropic drugs (e.g. atropine, glycopyrrolate) for bradycardia, and antiarrhythmic drugs (e.g. lidocaine) for ventricular arrhythmias such as ventricular tachycardia or premature ventricular contractions [43].

Prolonged untreated cardiovascular collapse may result in cardiac arrest and death. Cardiopulmonary resuscitation (CPR) should follow the general *ABC technique*. *A* is opening of the airway by endotracheal intubation, *B* is the initiation of controlled breathing by squeezing an Ambu bag or using the rebreathing bag of an anesthesia machine (12–20 breaths/minute), and *C* is the establishment of artificial circulation by cardiac compression (80–100 compressions/minute). After CPR has been instituted, an IV catheter should be placed if one is not already in place. If the attempts at IV catheterization are unsuccessful, emergency drugs may be administered intratracheally through the endotracheal tube at 2–2.5 times the IV dose after dilution with sterile water or saline to a volume of 5–10 ml. Absorption of the drugs from the lung is sometimes significant enough to be more effective than IV administration through a peripheral vein [43]. Emergency drugs and products frequently used during CPR include 100% O₂, balanced electrolyte solutions, atropine, lidocaine, and epinephrine. Depending on the animal's condition, the vasoactive drugs mentioned previously can be administered in conjunction with emergency drugs. Electrical defibrillation is the most effective treatment for conversion of ventricular fibrillation, but it is not practical in field situations or effective in large animals. Epinephrine (10 µg/kg IV) is usually the drug of choice for treatment of ventricular fibrillation. Epinephrine induces peripheral vasoconstriction and increases arterial diastolic blood pressure, intracranial and coronary blood flow, coarseness of ventricular fibrillation, and positive inotropic effect by stimulating α and β adrenoceptors. Potential side effects of epinephrine include increased myocardial and cerebral O₂ demand, postresuscitation arrhythmia, and tachycardia. A bolus injection of lidocaine (0.5–2 mg/kg IV) may be used to treat postresuscitation ventricular arrhythmia. Chemical defibrillation with IV potassium chloride (1 mg/kg) and

acetylcholine (6 mg/kg) followed by administration of 10% calcium chloride (1 ml/10 kg [22 lb]) has been recommended for treatment of ventricular fibrillation. Although it is ineffective in defibrillation, this technique usually converts fibrillation to asystole [43]. A normal sinus rhythm is actually easier to initiate from asystole than from fibrillation.

In general, the best treatment for perioperative complications is prevention, which requires a devoted and vigilant anesthetist. Careful preanesthetic evaluation and preparation, proper use of anesthetic regimens, and adjustment of the dosages of the anesthetics used can prevent most anesthetic-related complications. Close monitoring and attention to detail allow the anesthetist to recognize potentially dangerous situations quickly and institute corrective measures at an early stage. Always keep in mind that “there are no safe anesthetics; there are no safe anesthetic techniques; there are only safe anesthetists.”

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8

Local and Regional Anesthesia in Food Animals

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Local and regional anesthesia provide many benefits in food animal medicine. General anesthesia in ruminants has inherent risks such as bloat or cardiopulmonary depression. Local and regional nerve blocks can provide a safe, effective, and humane alternative to perform surgical procedures. Additionally, general anesthesia requires more physical labor and equipment compared to local and regional anesthesia. Most local and regional anesthetic techniques are not difficult to perform and require only minimal expense and equipment. When used in conjunction with sedation and physical restraint, local anesthesia can improve the efficacy and efficiency of a procedure while increasing the safety for the surgeon and the animal. When local or regional nerve blocks are used in conjunction with general anesthesia, the dose requirement of anesthetic drugs can be reduced, enhancing animal safety and ensuring a smoother recovery. Furthermore, anesthetizing pain receptors helps to prevent post-surgical pain until other analgesics can be administered.

Local and regional anesthesia should be performed with the animal in proper physical restraint and under aseptic technique. The area should have the hair removed and surgical preparation should be performed.

8.1 Local Anesthetic Agents

Numerous anesthetic agents are available to produce local and regional anesthesia. Differences in cost, toxicity, potency, and tissue drug residues must be considered during the selection process (see Chapter 12). The most commonly used agents in food animal medicine are 2% lidocaine hydrochloride and 2% mepivacaine hydrochloride, which are less expensive and have lower potential for toxicity than other options. Lidocaine induces more swelling and local irritation than mepivacaine [1].

It is important to keep in mind the potential for lidocaine toxicity. The maximal safe dose for cattle is 10 mg/kg of body weight. Small ruminants are more sensitive to lidocaine, with a maximal safe dose of 6 mg/kg of body weight used conservatively [2]. A pharmacokinetic study determined that a greater dose of 7 mg/kg was not only tolerated but considered safe for small ruminants [3]. When anesthetizing larger body surfaces or using lidocaine in smaller animals, the 2% lidocaine can be diluted with sterile saline at a 1 : 1 dilution to decrease the amount of lidocaine administered [4].

Adding sodium bicarbonate or epinephrine to injectable lidocaine solution can enhance the ease of administration and efficacy of lidocaine. Sodium bicarbonate (8.4% solution) can be added to decrease the initial discomfort associated with lidocaine administration. Mixing 2% lidocaine with 8.4% sodium bicarbonate at a 9:1 ratio decreases the discomfort of lidocaine administration [5, 6]. Lidocaine has vasodilatory properties, causing the undesirable effect of increased blood flow and hemorrhage when tissues are incised at the site of lidocaine administration. The addition of epinephrine to lidocaine at a ratio of 1:200 000 decreases the vasodilatory effect, reduces systemic absorption, and, as a result, prolongs the duration of the local anesthetic effect of lidocaine [7]. It is important to note that epinephrine should not be used in close proximity to wound edges or in the subarachnoid space due to the risks of tissue necrosis or spinal cord ischemia [8].

Local anesthetic agents prevent the initiation of the neuronal cell membrane action potential of the nerve fibers by blocking the voltage-gated sodium channels. It is important to consider the condition of the tissue when administering local anesthetics. Inflamed and infected tissues are more acidic and do not respond to anesthetic agents as normal healthy tissues do. The efficacy and duration of anesthesia is decreased in these tissues due to greater ionization of the local anesthetic. Neonates and pregnant females are at a greater risk of anesthetic toxicity because of decreased cholinesterase activity [9, 10]. Additionally, pregnant females have greater cardiac output and higher plasma concentrations of α -1-acid glycoprotein, which increases the uptake of local anesthetics, reaching levels potentially high enough to be harmful to the neonate [11, 12]. Accidental intravenous administration of a local anesthetic agent is the most common reason for overdosing and development of toxicity. In severe cases, cardiac arrest occurs. Other signs of overdose include twitching, collapse, convulsions, coma, and methemoglobinemia [11, 13–15].

8.2 Anesthesia for Dehorning

Dehorning or disbudding of large ruminants is commonly performed with local anesthesia of the horns along with physical restraint in a squeeze chute and head restraint. A cornual nerve block provides anesthesia to the horn and surrounding skin. This area is innervated by the cornual branch of the lacrimal nerve (also known as the zygomaticotemporal nerve). The lacrimal nerve originates from the ophthalmic branch of the trigeminal nerve. The cornual nerve runs dorsally through the periorbital tissues continuing along the frontal crest until it reaches the horn base. In cattle, a small amount (5–10 ml) of 2% lidocaine is deposited superficially along the zygomatic arch, halfway between the horn base and the lateral canthus of the eye (Figures 8.1 and 8.2). A depression can be palpated in this area. It is important to remember that full local anesthetic effect does not occur until 10–15 minutes after administration. Depth of administration varies from 1.0 to 2.5 cm, depending on the size of the animal [16]. A similar technique is used to block the cornual nerve in small ruminants, except that the palpable depression below the zygomatic arch is much smaller (Figure 8.3). Additional lidocaine can be administered at the caudal aspect of the horn base in a ring block. This is necessary in ruminants with a larger horn base, as superficial branches of the second cervical nerves need to be desensitized for a complete local anesthesia for dehorning [17–19].

Blocking the cornual branch of the infratrochlear nerve enhances the local anesthesia during dehorning of small ruminants and cattle. The nerve branches are located halfway between the medial canthus of the eye and the middle of the horn base (Figures 8.3–8.5) [16]. Lidocaine (2%) is

Figure 8.1 Lateral view of cow head. Cornual nerve (white arrow) for dehorning. *Source:* Courtesy of Dr. Ray Wilhite.

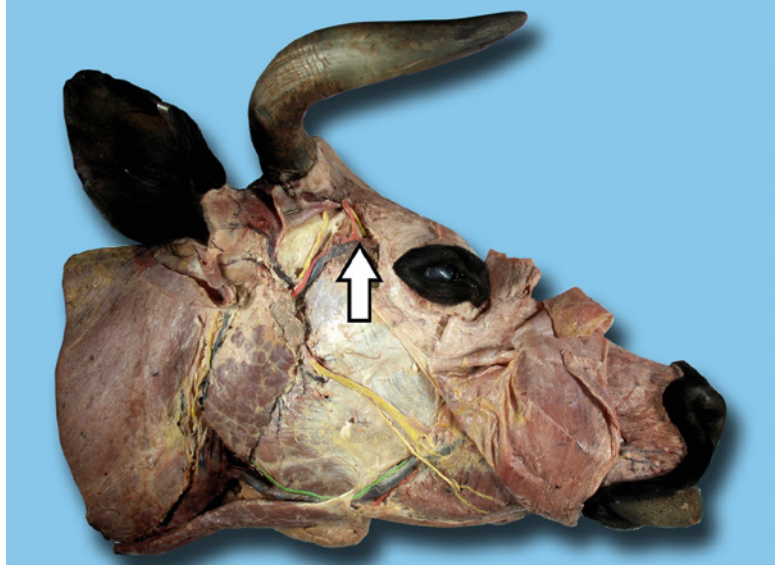
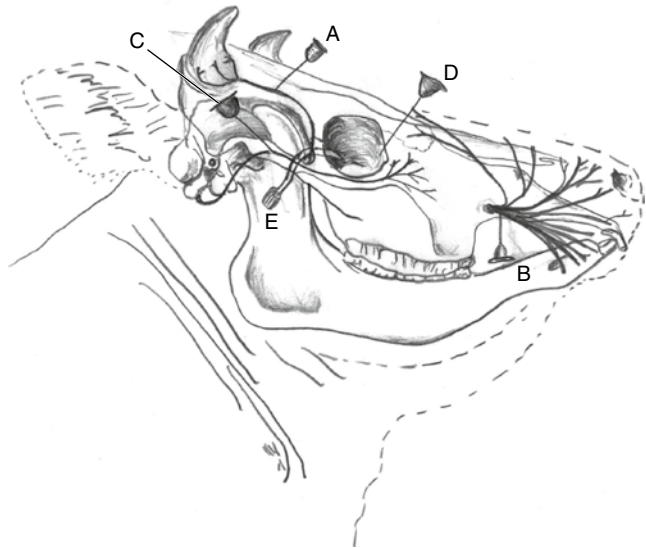


Figure 8.2 Facial nerve blocks in cattle: (A) cornual nerve block for dehorning, (B) infraorbital nerve block, (C) auriculopalpebral nerve block, (D) local infiltration of the eyelids, and (E) injection site for Peterson eye block. *Source:* Illustration by Kim Crosslin.



administered along the dorsomedial aspect of the orbit, parallel to the surface of the skin (Figures 8.4 and 8.5, Video 8.1). It is best to distribute lidocaine using a fanning technique or as a line as this nerve often has many branches. A 20- or 22-gauge needle is used to perform this block in small ruminants, as a larger gauge needle makes it difficult to administer lidocaine solution. Compared to cattle, the volume of lidocaine used in small ruminants is much lower, and approximately 2–3 ml of 2% lidocaine should be used for each site [16].

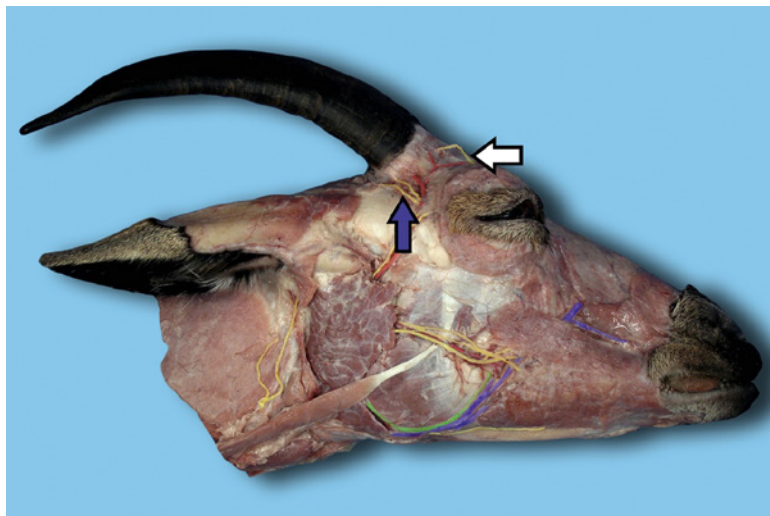


Figure 8.3 Lateral view of goat head. Cornual branch of the infratrochlear nerve (white arrow) and cornual nerve (blue arrow) for dehorning. *Source:* Courtesy of Dr. Ray Wilhite.



Figure 8.4 Cornual block for dehorning in a small ruminant (dorsal view). Cornual branch of the infratrochlear nerve (A) and the cornual nerve (B).



Figure 8.5 Cornual block for dehorning in a small ruminant (lateral view). Cornual branch of the infratrochlear nerve (A) and cornual nerve (B).

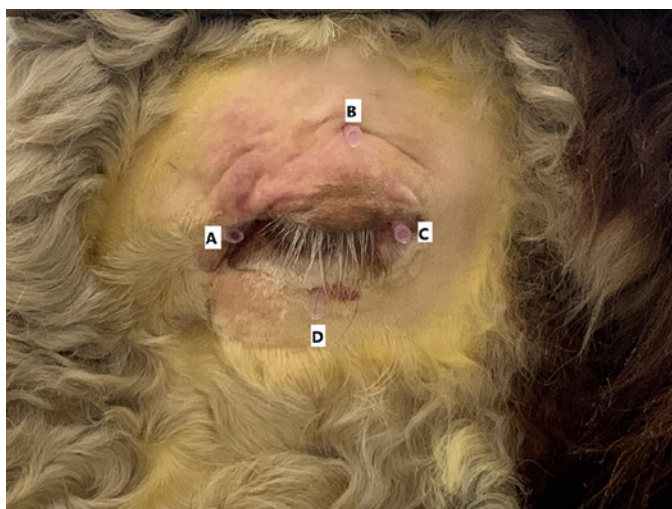
8.3 Anesthesia for the Eye and Eyelids

Multiple nerves control the sensory and motor function of the structures within and around the orbit. Sensory fibers of the ophthalmic branch of the trigeminal nerve provide sensory innervation of the globe, third eyelid, conjunctiva, and eyelids. The motor function of the extraocular muscles is supplied and innervated by different cranial nerves. The trochlear nerve innervates the dorsal oblique muscle. The abducens nerve supplies the lateral rectus and retractor oculi muscles. The oculomotor nerve supplies the remaining ocular muscles (inferior oblique, superior rectus, medial rectus, inferior rectus, levator palpebrae superioris, ciliary muscle, and sphincter muscles). The eyelids are innervated by the auriculopalpebral nerve [16, 20].

Blocking the auriculopalpebral nerve, a branch of the facial nerve, abolishes the motor function of the eyelids [21]. The nerve can be palpated as it passes over the zygomatic arch. In cattle, 5–10 ml of 2% lidocaine is administered subcutaneously along the zygomatic arch (Figure 8.2) [16]. The purpose of this block is to allow for manipulation of the eyelids and examination of the cornea, and it can be used in conjunction with a topical anesthetic if painful corneal disease exists [21]. A ring block using a 20- to 25-gauge needle with 10–20 ml of 2% lidocaine is used for surgical procedures on the eyelid such as eyelid laceration repair or mass removal.

Anesthesia for surgical procedures on the eye, including enucleation or exenteration, is provided by administration of a retrobulbar or Peterson eye block. Appropriate physical restraint and sedation aid in administration of these blocks. Commonly preferred sites of administration of retrobulbar injections include injections through the upper and lower eyelids or medial and lateral canthus (Figure 8.6). To reach the necessary depth for efficient block, a 7.5–12-cm, 18-gauge needle is needed for cattle and a 3.75-cm, 22- to 20-gauge needle is adequate for small ruminants. The globe must be shielded by the surgeon's finger to prevent accidental puncture of the globe. When administering at the medial canthus, the needle must be advanced through the conjunctiva of the medial canthus rostrally to the third eyelid and dorsomedially to the globe (Video 8.2). The bony orbit can be felt as the needle is passed caudally. Injection of the anesthetic can be

Figure 8.6 Four point retrobulbar eye block. Needles are placed at the four injection sites. The medial (A) and lateral (C) locations are at each canthus. The needle is inserted through the eyelids for the dorsal (B) and ventral (D) site.



performed as the needle is advanced caudally or the entire volume can be administered once the needle is fully seated in the orbit. The process is repeated dorsally, ventrally, and laterally to the globe. For the dorsal and ventral locations, it is common to insert the needle through the eyelids. In cattle, 20–25 ml of 2% lidocaine is administered to facilitate proptosis of the globe indicating proper retrobulbar administration. Possible detrimental effects of the retrobulbar injections include optic hemorrhage, optic nerve damage, increased globe pressure, and accidental administration of lidocaine into the optic nerve meninges [22].

While perceived to be less reliable due to decreased distribution of a local anesthetic than the retrobulbar nerve block [23], the Peterson eye block offers some advantages for ocular surgical procedures and is often combined with an auriculopalpebral block. The anatomic landmarks for the Peterson eye block are identified as the deviation created by the supraorbital process cranially, coronoid process of the mandible caudally, and zygomatic arch ventrally (Figures 8.2 and 8.7) [8, 24]. The skin is desensitized with 5 ml of 2% lidocaine. A 2.5-cm, 14-gauge needle can be placed into the deviation to serve as a guide cannula. A 10–12-cm, 18-gauge needle with a slight curve (Figure 8.8) is advanced through the cannula horizontally and posteriorly until the needle connects with the coronoid process of the mandible (Video 8.3) [25]. The authors prefer not to use a guide needle for this technique but advance the needle as described. The needle is walked off the front of the process and advanced to the pterygopalatine fossa. The typical depth is approximately 7.5–10 cm in most cattle [25]. Care must be taken not to rotate the curved needle out of the horizontal plane as this could result in detrimental effects on the patient. Once the needle encounters bone a second time, the needle is withdrawn by several millimeters, the syringe is aspirated, and 10–30 ml of 2% lidocaine is deposited. Aspiration and needle withdrawal ensure that injection of lidocaine into the optic nerve and ophthalmic artery



Figure 8.7 Peterson's eye block. Landmarks are supraorbital process (black rectangle), zygomatic arch (blue rectangle), and coronoid process of the mandible (red rectangle). Location of needle insertion (star).

Figure 8.8 Curved needle used for Peterson's eye block.



does not occur [24]. When administered successfully, the Peterson technique blocks the oculomotor, abducens, and trochlear nerves as well as the ophthalmic, maxillary, and mandibular branches of the trigeminal nerve.

Successful retrobulbar and Peterson's eye blocks inhibit the ability of the eye to blink for several hours. Sterile saline should be used to irrigate the globe to prevent damage to the cornea during the procedure. Ocular ointment should be applied to prevent detrimental effects associated with dry eye following the completion of the surgery. These protective measures must be taken until the return of motor function of the eye to prevent idiopathic keratoconjunctivitis. Exposure to direct sunlight, dust, or wind should be minimized. If the eye proptoses during the post-surgical phase, gentle traction on the eyelids can replace the globe back into the bony orbit.

Anesthetic technique for enucleation, exenteration, and proptosis in small ruminants and camelids is similar to the technique used in cattle. The use of 5-cm, 20- or 22-gauge needles is more appropriate in these species. The authors strongly recommend that small ruminants and camelids are sedated to ensure compliance of the animal during these procedures. Please refer to Chapter 3 for options of standing sedation and chemical restraint protocol.

8.4 Nasal Anesthesia

The infraorbital nerve provides sensory input to the nose. It originates from the maxillary branch of cranial nerve 5 (trigeminal nerve). This nerve is relatively flat as it passes through the infraorbital canal and is then covered by the levator nasolabialis muscle [17].

Nasal anesthesia is used for placement of nose rings in cattle or the repair of nasal lacerations. This can be accomplished by injecting 20–30 ml of 2% lidocaine bilaterally at the infraorbital canal (Figures 8.2 and 8.9) where the infraorbital nerve exits. The canal can be challenging to locate but lies in front of the facial tuberosity between the second maxillary premolar and the nasomaxillary notch [16].



Figure 8.9 Bovine skull. Infraorbital foramen (blue arrow) and facial tuberosity (orange line).

8.5 Anesthesia for Reproductive Procedures and for Cessation of Straining

Caudal epidural, continuous caudal epidural, and pudendal nerve blocks are routinely performed to provide anesthesia to the perineal area. All of these techniques provide relief of rectal tenesmus and they are cost-effective and require only minimal training to perform them successfully [16]. The sacral paravertebral nerve block is another option can be used to relieve tenesmus while maintaining the motor function of the tail.

8.5.1 Caudal Epidural Anesthesia

Caudal epidural anesthesia is easily performed in ruminants with a small amount of local anesthetic, which can be administered in the epidural space of either the sacrococcygeal space or the first and second intercoccygeal space (Figure 8.10). A caudal epidural anesthesia at the sacrococcygeal space desensitizes sacral nerves 2 through 5, whereas when performed at the first and second intercoccygeal space, the block desensitizes sacral nerves 3 through 5. Increasing the volume of anesthetic administered enhances the cranial distribution of the anesthetic, and nerves cranial to sacral nerve 2 may become affected. The space used for injection is palpated by moving the tail up and down, and palpating a depression between the movable vertebrae. The cranial space most used for injection may be ossified in older cows [18], and both spaces may be affected by ossification or fibrosis in embryo donor animals due to repeated caudal epidural administration.

The space used for injection is easily located when standing directly behind the animal. The injection site should be aseptically prepared prior to needle placement to prevent the risk of ascending infection. The recommended dose of 2% lidocaine is 0.5 ml per 45 kg (99 lb) of body weight for cattle [24]. A 3.75–5-cm, 18-gauge needle is advanced perpendicularly through the skin on the midline [16]. A small amount of lidocaine is placed in the hub of the needle until a meniscus is

Figure 8.10 Locations for needle placement for caudal epidural anesthesia at sacrococcygeal space (blue arrow) and first intercoccygeal space (orange arrow).



formed (known as the hanging drop technique). The needle is then advanced into the epidural space. When negative pressure in the epidural canal pulls the lidocaine solution from the needle hub, this confirms proper needle placement [24]. Occasionally, this suction by the negative pressure in the epidural space can result in an audible sound. When the block is successful, the tail becomes flaccid and straining stops. Uterine motility is unaffected by caudal epidural injection of lidocaine, thus administration of a tocolytic agent, such as epinephrine, is necessary if uterine relaxation is desired. Recumbency can be achieved by using high-volume caudal epidural anesthesia if the lumbosacral space is not easily palpable or administration is not feasible. High-volume caudal epidural anesthesia is performed as described above, but instead uses 1 ml of 2% lidocaine per 45 kg (99 lb) of body weight [26]. High-volume caudal epidural anesthesia produces anesthesia reaching the ventral flank area just behind the umbilicus. This technique can be used for abdominal surgeries such as umbilical resection, ventral-midline cesarean sections, or abdominal exploratory surgeries. Cranial distribution of lidocaine in the epidural canal can be affected by arthritis or fat deposition in older or obese animals, respectively [8, 27–29]. Abdominal analgesia can be enhanced by using local or regional anesthetic techniques (see section 8.6).

Analogous to cattle, the caudal epidural anesthesia technique can be used for surgery of the caudal reproductive tract, reproductive emergencies, or surgery of the gastrointestinal tract in small ruminants and camelids [30]. In sheep with docked tails, the caudal epidural injection may be impossible to administer, leaving lumbosacral epidural anesthesia as the only option available. In goats and camelids, a 3.8-cm, 20-gauge needle is inserted at a 45° angle to the vertebrae at the most cranial movable space. The hanging drop technique, described above, is used to ensure correct placement of the needle. The recommended dose range of lidocaine is 1 ml/15–50 kg (33–110 lb) of body weight [30]. The authors commonly use 1 ml/10–20 kg (22–44 lb) of body weight. Bupivacaine (0.5%) has been used at a dosage of 1 ml/4 kg (8.8 lb) of body weight [31]. Complications associated with prolonged recumbency are more commonly encountered when using bupivacaine, and this drug should be used with caution [30, 31].

In animals that require tail docking or amputation, either for cosmetic purposes or as a result of trauma, different anesthetic techniques are more appropriate for different species. In sheep, a ring block is more efficacious than a caudal epidural anesthesia for tail-docking procedures [30]. The

ring block should be placed proximally to the site of amputation using lidocaine at a dose of 6 mg/kg of body weight. In cattle and goats that have incurred tail trauma, a caudal epidural anesthesia effectively allows amputation. In the authors' experience, if amputation is required in an adult small ruminant, sedation is helpful to complete the procedure.

In cases in which long-term desensitization is required, an alcohol epidural injection can be performed with anesthesia resulting from demyelination of the nerve roots. A mixture of 70–95% ethyl or isopropyl alcohol with equal part of lidocaine is administered at similar volumes as described for lidocaine epidural anesthesia technique. This alcohol epidural anesthesia results in desensitization of the pelvic and perineal area as well as paralysis of the tail for weeks to months. Return of sensation depends on the rate of remyelination of the nerve roots. Common complications of this technique are associated with chronic paralysis of the tail such as inflammation and fly strike of the perineal area. Overdose of alcohol results in longer duration or permanent pelvic limb paralysis [8].

8.5.2 Continuous Caudal Epidural Anesthesia

A continuous caudal epidural anesthesia can be utilized to facilitate pain management or to provide relief in animals with chronic vaginal or rectal prolapse that have continuous tenesmus after the administration of a traditional caudal epidural anesthesia. A catheter is placed and maintained in the epidural space for repeated administration of local anesthetics or analgesics. This procedure requires a Tuohy needle (available from various manufactures in different sizes, e.g. B. Braun Medical, Bethlehem, PA, USA), which is a specialized epidural needle with a slightly curved tip and a stylet (Figure 8.11). The needle is advanced cranially into the space between the first and second coccygeal vertebrae at a 45° angle (Figure 8.12). The stylet is removed, and 2 ml of anesthetic is administered to ensure the needle is in the epidural space. A closed-tip nylon catheter is placed in the needle and advanced 2–4 cm cranially to the end of the needle. The Tuohy needle is removed

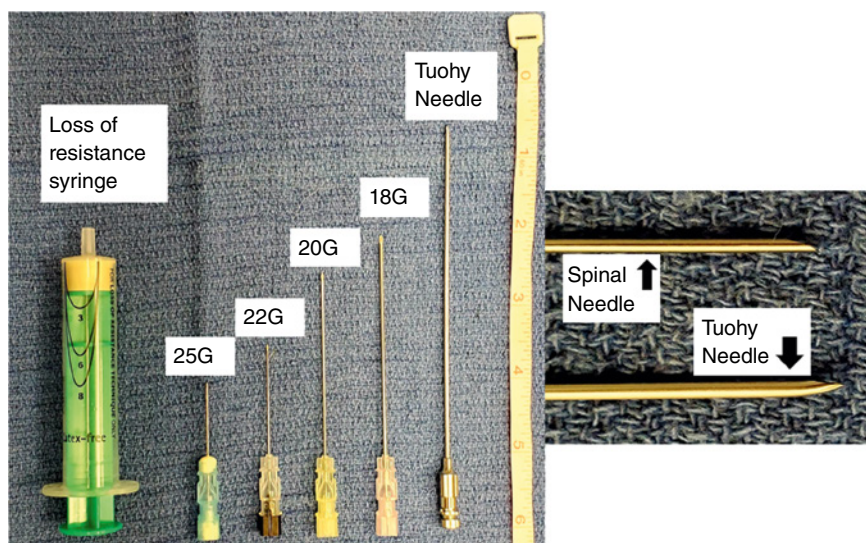


Figure 8.11 Tuohy needle. Left, the difference in length of a Tuohy needle and common hypodermic needles. Right, the curved tip end of a Tuohy needle in comparison to a spinal needle. *Source:* Courtesy of Dr. Stuart Clark-Price.



Figure 8.12 Lumbosacral epidural catheterization in laterally recumbent cattle. This procedure can also be performed with the animal in the standing position or in sternal recumbency. The same technique can be used for placement of epidural catheter in the caudal epidural space. *Source:* Courtesy of Dr. Stuart Clark-Price.

and the catheter is maintained in place. An adapter is connected to the catheter and sutured to the skin of the tail head to stabilize the catheter. Anesthetic drugs or analgesics may then be administered as needed via the catheter [16, 24].

Lidocaine, xylazine, procaine, morphine, and ketamine have all been used for epidural anesthesia [19, 32–35]. Lidocaine doses ranging from 0.1 to 0.25 mg/kg alone or in combination with other drugs can be used. Ketamine alone or in combination can also be used at dosages of 0.25–0.7 mg/kg. The use of lidocaine and ketamine in combination provides epidural anesthesia twice as long as that obtained using either drug alone and has been used successfully for surgery of the paralumbar fossa [33, 36]. Xylazine at a dose of 0.1 mg/kg of body weight diluted with lidocaine to a final volume of 0.5–0.6 ml/kg was used for an umbilical surgery with success [34]. Alpha-2 agonists and opioids can be used for epidural administration in ruminants. Xylazine dosed at 0.05 mg/kg diluted to 5–12 ml with sterile saline or at 0.3 mg/kg in combination with 5 ml of 2% lidocaine has been used. While similar in effect to lidocaine alone, using xylazine as described prolongs the duration of epidural anesthesia for up to 3–4 hours. Systemic effect of xylazine can occur and includes sedation, salivation, and ataxia [8]. Xylazine was reported to have potential to cause spinal cord demyelination [19]. Morphine dosed at 0.1 mg/kg diluted in 20 ml of sterile saline provides analgesia for up to 12 hours. At this dose, morphine was used by the authors for pain management in a calf with a septic stifle. Treatment resulted in ataxia; however, as indicated by the calf's behavior, treatment appeared to provide analgesia to the affected limb. Limitations of a morphine epidural include lower potency as compared to lidocaine and delay onset of the maximal effect by 2–3 hours.

Complications associated with long-term epidural catheter are documented and include spinal hematoma, meningitis, abscessation, pruritus, and demyelination [2, 19, 37].

8.5.3 Internal Pudendal Nerve Block

The internal pudendal nerve block was first used in bulls to provide penile relaxation without inducing ataxia, as is possible with caudal epidural anesthesia. The block allows for relaxation and examination of the penis, as anesthesia is provided distal to the sigmoid flexure. In cows, this block can be administered to alleviate straining due to chronic vaginal or uterine prolapse. Other uses include removal of rectal and vaginal masses, as well as surgical intervention due to urethral calculi [38].



Figure 8.13 Pudendal nerve block. Caudal view of a bull. Needles 1 and 2 show the locations for placement of guide needles.

With the animal standing in the chute, a 1.9-cm, 14-, or 16-gauge needle is used as a guide to prevent the spinal needle from bending or dulling when penetrating the skin (Figure 8.13). The lesser sciatic foramen is palpated rectally, which has been described as a depression in the sacrosacral ligament. Although this is the described landmark, one author (JR) finds the internal pudendal vein and artery to be more easily palpable and therefore a better landmark for deposition of anesthetic. An 8.25-cm, 18-gauge needle is passed through the guide needle and advanced 4–5 cm, in most cattle, to the internal pudendal nerve (Video 8.4). The needle tip should be medial to the sacrosacral ligament, and 20–25 ml of 2% lidocaine is deposited at this location. The needle is then withdrawn, redirected 2–3 cm dorsocaudally, and 10 ml of lidocaine is deposited at this location to the branches of the middle hemorrhoidal nerve. This technique is performed bilaterally. Onset of anesthesia occurs in 10–20 minutes with a duration of 2–4 hours. When this technique is performed in bulls, the penis should be replaced into the preputial cavity with a bandage to prevent damage until the anesthetic is metabolized [16].

A lateral approach has been described in sheep by passing the needle through the gluteal region. The surgeon places a finger into the rectum locating the sciatic foramen. A 3.75-cm, 18-gauge needle is advanced through the skin to the level of the foramen and 2–3 ml of lidocaine is deposited. The procedure is performed bilaterally [16, 38].

Caution should be exercised if moving large bulls immediately after the procedure as splaying of the hind limbs can occur if a large volume of lidocaine is administered. Hobbles can be placed, and the animal can be left standing for 4 hours after completion of the surgical procedure.

8.5.4 Dorsal Penile Nerve Block

Following desensitization of the dorsal penile nerve proximal to the surgical site, many penile surgeries can be performed with the bull standing in a chute or restrained on a tilt table. The penis should be manually extended and held either with a towel clamp placed under the dorsal apical ligament or with a gauze tourniquet around the free portion of the penis distal to the surgical site. With the penis extended, 2–4 ml of 2% lidocaine is administered along the dorsal aspect of the penis proximal to the area of interest (Figure 8.14) [39]. Catheterization of the urethra should be performed if removing many soft tissue masses to aid in visualization and prevent incision into the urethra.

Figure 8.14 Dorsal penile nerve block. The arrow indicates the location for local anesthetic administration. Catheterization of the urethra is important when performing simple surgical techniques on the prepuce and penis.



Alternatively, the dorsal penile nerve can be desensitized where it crosses over the ischial arch. Desensitization at this site causes both penile anesthesia and relaxation. A 4-cm, 20-gauge needle is inserted 10 cm ventrally to the anus and 2.5 cm laterally to the midline through the skin and advanced approximately 5–7 cm until the pelvic floor is reached. Aspiration is necessary to ensure that the needle has not been placed into the dorsal penile artery. If blood is aspirated, the needle is withdrawn about 1 cm prior to administration of 20–30 ml of 2% lidocaine. The procedure is repeated on the contralateral side. If performed correctly, penile analgesia, relaxation, and protrusion occur within 20 minutes and last 1–2 hours [9].

8.5.5 Sacral Paravertebral Nerve Block

The sacral paravertebral nerve block is a lesser utilized nerve block, but it allows for anesthesia of the anus, vulva, and vagina of the cow as it desensitizes the pudendal nerve, medial hemorrhoidal nerve, and caudal hemorrhoidal nerve by blocking sacral nerves 3, 4, and 5 as they exit the sacrum [16]. In bulls, penile relaxation occurs as the retractor penile muscles are innervated by sacral nerve 3. This block provides the added benefit of maintaining the animal's ability to move the tail and decreased risk of recumbency as the sciatic nerve is not blocked. For animals with chronic vaginal or rectal prolapse, the sacral paravertebral block eliminates tenesmus associated with these conditions. There is a decreased chance of the animal wanting to lie down and it allows for the animal to urinate and defecate normally [8].

Sacral foramina S3, S4, and S5 are located on either side of the spine approximately 1.5 cm from the midline bilaterally (Figure 8.15). The S5 foramen is located at the level of the S5 and Cd1 vertebrae. The S4 and S3 foramen are 3 and 6 cm cranial to the S5 foramen, respectively. Approximately 5–10 ml of anesthetic is deposited using a 7.5-cm, 18-gauge spinal needle at each foramen opening. The anesthetic desensitizes the anus, vulva, and vagina within 10–15 minutes, and the block lasts approximately 2 hours. This block provides decreased motor function to the anus while urinary bladder sphincter tone and clitoral sensation remain normal [16]. In severe chronic cases when extended relief is necessary, the procedure may be performed with 70–95 ml of isopropyl or ethyl alcohol, providing up to 5 weeks of relief. However, caution should be used in bulls as a sacral paravertebral block performed with alcohol could cause paraphimosis. While technically more

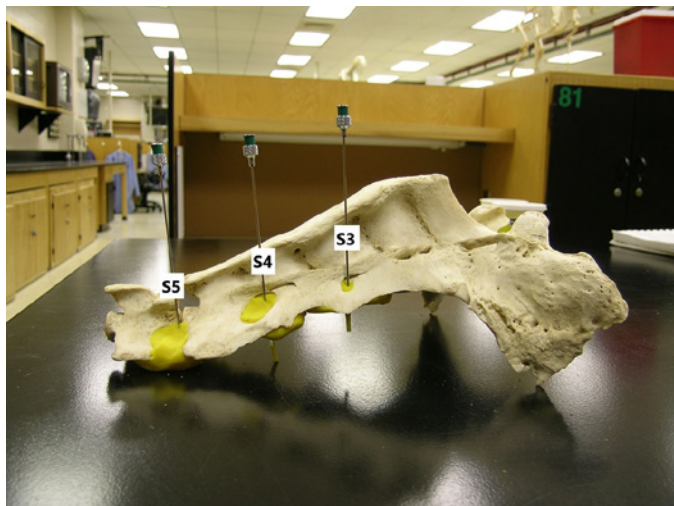


Figure 8.15 Sacral paravertebral nerve block. Lateral sacrum. Needles in sacral foramen 3 (S3), 4 (S4), and 5 (S5). *Source:* Permission of Dr. Richard Hopper, Bovine Reproduction.

challenging, the sacral paravertebral nerve block does not have the undesired effects of a caudal epidural anesthesia with alcohol, such as prolonged ataxia and potential paralysis [35, 40].

8.5.6 Lumbosacral Epidural Anesthesia

A lumbosacral epidural anesthesia is commonly used to achieve recumbency without sedation and allows for abdominal surgery, including cesarean section in small ruminants or ventral midline cesarean section in cows. The achieved pelvic limb paralysis and recumbency enhance safety for the animal and the surgeon. In large cattle, this block requires more technical help and sufficient padding for the recumbent cow to ensure that paralysis of peripheral nerves does not occur. Prior to administering the epidural, the animal should be in a location where it can safely recover and stand once the anesthetic effects have worn off. In cattle, a 9–16-cm, 18–20-gauge needle is advanced perpendicularly to the skin into the lumbosacral epidural space. Needle placement is on the midline, immediately caudal to the L6 vertebra (Figure 8.16a). The location is immediately caudal to a transverse line drawn between the wings of the ilium. A palpable depression is present. A palpable “pop” can be felt when the ligamentum flavum is penetrated. The hanging drop technique, as described in caudal epidural anesthesia, is also used with this technique (Video 8.5). The dose of lidocaine administered depends on the procedure being performed. The dose recommended for umbilical surgery in calves is 0.4–0.6 ml/kg of 2% lidocaine [38]. The most common dose used by the authors is 1 ml of 2% lidocaine per 10 kg (22 lb) of body weight, but greater doses have also been recommended at 1 ml/4.5 kg (9.9 lb) of body weight [9, 25]. An effective block causes pelvic limb paralysis, analgesia to the paralumbar fossa and ventrum, and tail paralysis within 2–10 minutes following lidocaine administration. While the hanging drop technique normally identifies the epidural space successfully, accidental advancement of the needle into the subarachnoid space is possible. In this case, cerebrospinal fluid becomes visible in the needle, and only half of the planned anesthetic dose should be administered. When penetrating the subarachnoid space, the anesthetic should be administered more slowly. Adverse effects of administering large volumes of local anesthetic into the subarachnoid space include unconsciousness, flexor spasms, respiratory depression due to paralysis of intercostal muscles and diaphragm, and hypotension [16]. The authors have used the lumbosacral epidural anesthesia in conjunction with sedation for ventral

(a)



(b)



(c)



Figure 8.16 (a) Needle placement for lumbosacral epidural anesthesia in cattle. (b) Needle placement with hanging drop technique for lumbosacral epidural anesthesia in a small ruminant. (c) Catheterization for continuous lumbosacral epidural anesthesia in a small ruminant.

midline cesarean sections, orthopedic procedures on the hind limbs, and umbilical resection surgery in young calves.

The lumbosacral epidural anesthesia is also very valuable for small ruminants, camelids, and swine. Hind limb amputation, cesarean section, resolution of dystocia, vaginal and uterine prolapse, and castration are examples of procedures in which the lumbosacral epidural anesthesia can be utilized. In small ruminants, a 3.8-cm, 18- or 20-gauge spinal needle is most commonly used to perform this block (Figure 8.16b,c). In heavier muscled breeds and obese animals, an 8.9-cm, 18- or 20-gauge spinal needle may be necessary. Most camelids require an 8.9-cm, 18- or 20-gauge spinal needle for this purpose, unless they are very thin [9, 38]. The location for spinal needle placement is the depression palpated on the midline from a transverse line drawn with the wings of the ilium. The hanging drop technique, as described above, is used with small ruminants and camelids. Recommended dosages of 1 ml/4.5 kg (9.9 lb) of body weight have been reported [41]. Recommended dosages in camelids range from 1 to 2, 2 to 4, and 2 to 4 mg/kg for bupivacaine, lidocaine, and mepivacaine, respectively [41]. A dose of 1 ml/10 kg (22 lb) of body weight of 2% lidocaine is commonly used by the authors. Caution should be exercised in animals with thin body condition and those with respiratory disease, as paralysis of the diaphragm can occur if large volumes of local anesthetics are used. As described above, half of the planned dose should be administered if the subarachnoid space is penetrated. The authors have frequently penetrated the subarachnoid space while performing lumbosacral epidural technique and have not observed complications following administration of half of the planned dose.

Lumbosacral epidural anesthesia can be used for various procedures in swine, such as repair of uterine, vaginal, or rectal prolapse, castration, surgical repair of hernias, surgery of the penis or prepuce, and surgery or immobilization of the rear limbs [25]. Swine have six or seven lumbar vertebrae, and the location for needle placement for lumbosacral epidural technique can be identified as described above for ruminants. The depression formed by the lumbosacral space may be farther caudal (0.5–2.5 cm). A 14-gauge needle is passed through the skin to use as a guide cannula to prevent the spinal needle from bending when the thick skin is penetrated. The needle is placed into the lumbosacral space at a 20° angle to the spine [25]. While the body weight of swine largely determines the size of needle used, 3.5–15-cm, 18- or 20-gauge spinal needles are commonly used [42, 43]. The recommended dose of lidocaine is 1 ml/4.5 kg (9.9 lb) of body weight. Hind limb paralysis and recumbency usually occur within 10 minutes and last 2 hours [25]. An alternative dosage of 1 ml/7.5 kg (16.5 lb) of body weight in swine up to 50 kg (110 lb) with an additional 1 ml for every 10 kg (22 lb) increase in body weight has been recommended [9, 43].

8.6 Anesthesia for Laparotomy

While the lumbosacral epidural anesthesia technique described above results in anesthesia of the paralumbar fossa and recumbency, anesthetizing the paralumbar fossa can be successfully performed in standing animals using the line block, inverted L block, proximal paravertebral block, or distal paravertebral block. These blocks can be used for a variety of standing abdominal procedures, such as those of the digestive tract, cesarean section, ovariectomy, and abdominal exploratory.

8.6.1 Line Block

The line block is the most basic of the techniques for anesthetizing the paralumbar fossa. The anesthetic agent is administered at the planned incision site. Multiple small injections of 5–10 ml are administered in a line formation using a 3.8-cm, 18- or 20-gauge needle (Figure 8.17). The local



Figure 8.17 Line block for laparotomy (blue line) or cesarean section (yellow line) in cattle.

anesthetic is deposited into the subcutaneous space and abdominal musculature. The pain of administration can be decreased by starting dorsally and moving ventrally while inserting the needle into the ventral aspect of the previous administration site [16]. A longer needle, 7.5 cm, may be necessary to extend through the extra fat or thicker muscle layers when performing this block in overconditioned or heavily muscled animals [25]. The volume of anesthetic agent varies depending on the surgery location and animal species. At 10 mg/kg of body weight using 2% lidocaine in a 450 kg (990 lb) cow, 225 ml would be a safe dose. In small ruminants, the authors use up to 6 mg/kg of body weight of 2% lidocaine as the maximal safe dose. Therefore, a 20 kg (44 lb) goat or sheep should receive no more than 6 ml of 2% lidocaine. In small ruminants with low body weight, the authors often dilute the 2% lidocaine to a 1% solution, thus allowing for a greater injection volume. This is performed with a 1:1 dilution of sterile saline and 2% lidocaine solution. When combining a lumbosacral epidural anesthesia with a local block, the total volume of anesthetics used for each block must be within the safe dosage range. The toxic dose of lidocaine in camelids is recommended to be greater than 5 mg/kg. However, it has been reported that camelids are more susceptible to lidocaine toxicity [41]. Disadvantages of the line block include increased hemorrhage due to lidocaine-induced vasodilation, distortion of the tissues resulting from deposition of the local anesthetic solution at the site of surgery, and delayed healing of the incision site.

8.6.2 Inverted L Block

The inverted L block, also known as the reversed seven block, desensitizes all nerves within the area of the paralumbar fossa. Anesthetic is deposited in two lines extending caudally from the last rib, parallel to the transverse processes of the lumbar spine and ventrally from the first or second transverse process of the lumbar vertebrae, parallel to the last rib, respectively (Figure 8.18). In the interest of reducing discomfort during administration, the block should be administered starting cranially progressing caudally and dorsally progressing ventrally as the nerves in the paralumbar fossa run caudoventrally from the spine. Dosages of lidocaine can be administered depending on the size of the animal and the toxic dose for each species. For adult large ruminants, the



Figure 8.18 Inverted L block (blue lines) with incision site (yellow line) in cattle.

recommended volume of 2% lidocaine administered is 5–10 ml per injection site. When performing this block in small ruminants, consider diluting the 2% lidocaine solution with sterile saline to a 1% solution to reduce the risk of toxicity.

In swine, both line block and inverted L block can be used to produce effective local anesthesia when performing field surgery. A dose of up to 4 mg/kg of lidocaine was reportedly used for the line block and inverted L block in swine [42, 43]. Doses of 15 and 42 mg/kg have been demonstrated to induce seizures in piglets [42, 44]. It is important to remember that many studies on local anesthetic toxicity evaluate these drugs following intravenous use. Certainly, the susceptibility to local anesthetic toxicity of an animal depends on the volume used, systemic absorption from the injection site, interaction with other drugs, health of the patient, and individual variation [38].

8.6.3 Proximal Paravertebral Block

The proximal paravertebral block provides anesthesia to the paralumbar fossa by blocking the dorsal and ventral branches of thoracic 13 (T13), lumbar one (L1), and lumbar two (L2) spinal nerves at the site of emergence from the intervertebral foramen of the respective vertebrae. A guide needle is often used to aid the insertion of a long spinal needle. A 3.8-cm, 14-gauge needle is placed at the level of the transverse processes, which is 4–5 cm from the midline in most cattle (Figures 8.19 and 8.20). A 7.6–15.2-cm, 18-gauge spinal needle is advanced through the guide needle until it contacts the transverse process of the T13 vertebra. The needle is walked caudally off the transverse process and advanced 1–2 cm through the fascia, then 5–10 ml of 2% lidocaine is deposited. The needle is then withdrawn approximately 1–2 cm and an additional 5–10 ml of 2% lidocaine is deposited dorsally to the transverse process. A total of approximately 20 ml can be administered at each site. For the L2 and L3 spinal nerves, the process is repeated and the needle is walked off the caudal aspect of the transverse process of L1 and L2 vertebrae (Video 8.6). A successful block causes the paralumbar musculature to become desensitized and relaxed, scoliosis occurs, and the spine curves toward the side of the block. The skin is warm to the touch in the desensitized area

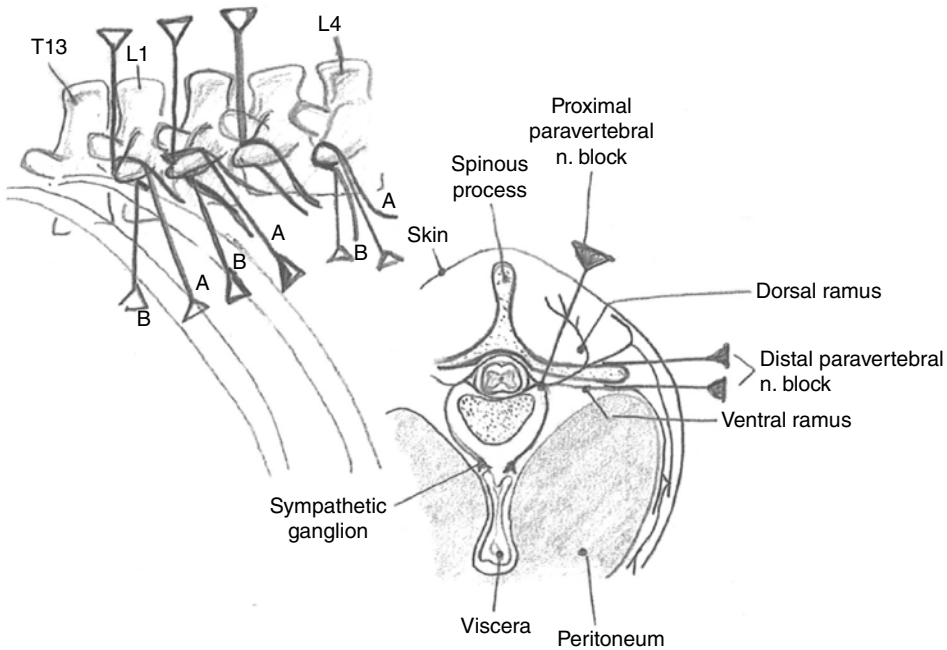


Figure 8.19 Proximal and distal paravertebral blocks. *Source:* Illustration by Kim Crosslin.

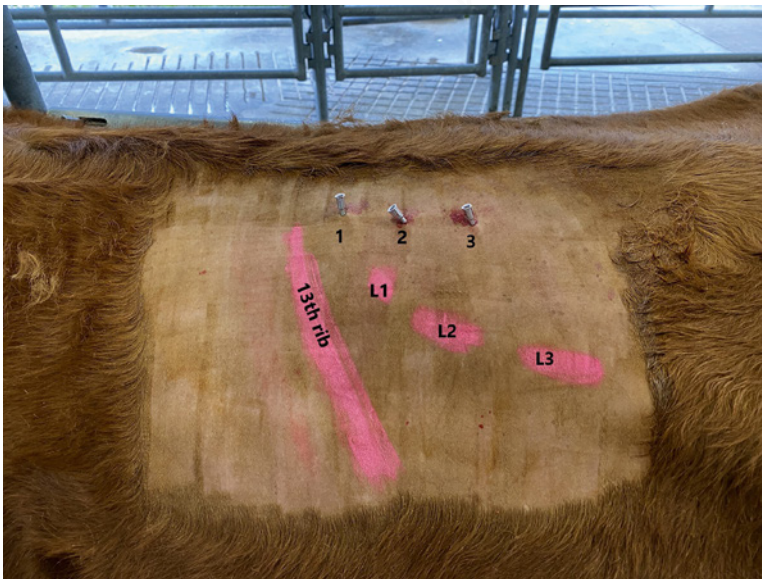


Figure 8.20 Proximal paravertebral block in cattle. Left lateral view of a cow with the head to the left of the image. The transverse process of lumbar vertebrae 1 (L1), 2 (L2), and 3 (L3). The guide needles indicate the locations for placement of spinal needles for proximal paravertebral block, which are cranial to the transverse processes of the lumbar vertebrae. The needles (1, 2, and 3) are at the locations to block spinal nerves thoracic 13, lumbar 1, and lumbar 2, respectively.

due to vasodilation and increased blood flow to the area. The area may also appear pinker in non-pigmented cattle. Anesthetic effect occurs within 10 minutes and lasts approximately 90 minutes. The advantages of this block include provision of a large, uniform area of local anesthesia with muscle relaxation, minimal intra-abdominal pressure, and lower volume of anesthetic as compared to other blocks [16]. A disadvantage of this block is that it can be more technically challenging to perform in overconditioned animals.

The proximal paravertebral nerve block can also be performed in small ruminants, calves, and camelids. It is important to remember that there can be a variable number of vertebrae in sheep, complicating identification of needle placement sites if counting from the tuber coxae. The use of a 2.5–3.8-cm, 20-gauge needle with volumes of 2% lidocaine not exceeding the toxic dose of 6 mg/kg are commonly used in small ruminants [38]. Sedation can ease the administration of the block in these species. Please refer to Chapter 3 for options of sedation protocol.

8.6.4 Distal Paravertebral Block

Similar to the proximal paravertebral block, the distal paravertebral block desensitizes the T13, L1, and L2 spinal nerves. However, the location of local anesthetic administration is different. A 3.8–7.5-cm, 18-gauge needle is advanced through the skin of the distal ends of the L1, L2, and L4 transverse processes (Figures 8.19 and 8.21). Fifteen milliliters of 2% lidocaine is deposited in a fan shape pattern (5 ml cranially, 5 ml medially, and 5 ml caudally) dorsally and ventrally to each transverse process. It is best to walk the needle off the dorsal and ventral aspect of the transverse process to ensure that the anesthetic is deposited in close proximity to the nerve (Video 8.7). The advantages of this block are lack of scoliosis as seen with the proximal paravertebral block, decreased



Figure 8.21 Distal paravertebral block. Left lateral view of a cow with the head to the left of the image. The transverse processes of lumbar vertebrae 1–4 (L1, L2, L3, and L4) with the three involved in the block (L1, L2, and L4) being marked with pink paint. Needles indicate the locations, both dorsal and ventral to the transverse processes of lumbar 1 (L1), lumbar 2 (L2), and lumbar 4 (L4) vertebrae for local anesthetic administration for the block.

risk of puncturing vasculature, and minimal ataxia [16]. Disadvantages of this block include the need for larger volume of the local anesthetic as compared to the proximal paravertebral block and difficulty of administration in overconditioned animals, resulting in lower effectiveness compared to inverted L or line blocks [16].

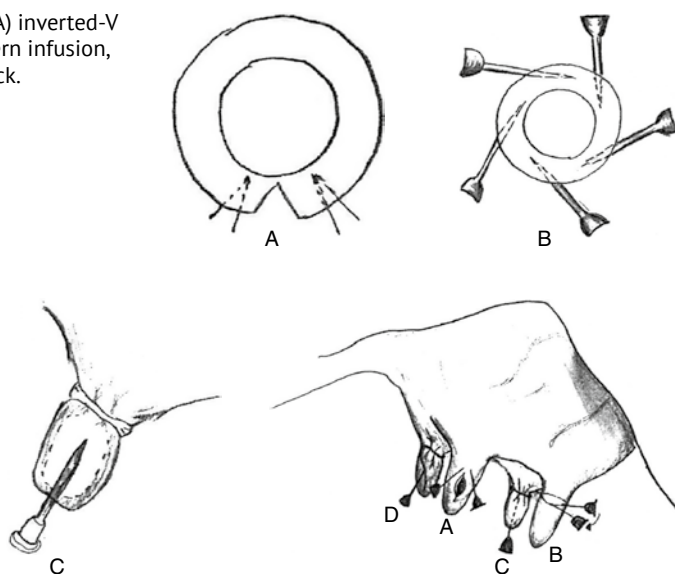
8.7 Anesthesia for Udder and Teats

Teat lacerations, udder injury, complication from mastitis, presence of supranummery teats, and teat amputation are common reasons for anesthesia of the udder and teats. Physical restraint and mild sedation are often useful when performing local anesthesia to provide safety to the veterinarian.

The udder is innervated by multiple nerves. The cranial udder is supplied by the lumbar spinal nerves 1–4. To perform surgery on the cranial half of the udder, a proximal or distal paravertebral block can be performed as described in section 8.6. The caudal half of the udder is supplied by the pudendal and caudal branch of the genitofemoral nerve [38]. Caudal epidural anesthesia does not desensitize the caudal half of the udder. Administration of high-volume caudal epidural anesthesia or lumbosacral epidural anesthesia, as described in section 8.5, causes recumbency and allows surgical procedures on the udder to be performed [34]. Recumbency is induced within 8–20 minutes and the duration of anesthetic effect is 60–80 minutes [16].

Local infiltration of anesthetic to the udder is the most commonly used method of providing local anesthesia to the teat for surgical procedures. A ring block or inverted V block can be administered for teat lacerations and teat amputations (Figure 8.22). A ring block is performed by injecting 4–6 ml of anesthetic using a 1.6-cm, 22–25-gauge needle into the skin and muscularis at the teat base. The anesthetic takes effect in 10 minutes and lasts for 2 hours, which allows for minor procedures in a standing animal. Similarly, 4–6 ml of 2% lidocaine can be administered into the skin and muscularis of the teat as an inverted V shape proximally to the surgical site to perform teat laceration repair or wart removal [16].

Figure 8.22 Teat blocks for cattle: (A) inverted-V block, (B) teat ring block, (C) teat cistern infusion, and (D) intravenous regional teat block. *Source:* Illustration by Kim Crosslin.



Udder amputation or complex udder surgeries require general anesthesia due to the extensive vasculature, which requires extended surgery times. Indications for udder amputation include gangrenous mastitis, inappropriate lactation syndrome, suspensory ligament breakdown, and trauma.

8.8 Anesthesia of the Limbs

Anesthesia of the limbs is used for surgical procedures, intensive hoof trimming, or lameness localization. Blockade is achieved by using a ring block, local infiltration of the nerves, or, more commonly, intravenous regional anesthesia. In adult cattle, the skin distal to the tarsus and carpus can make local infiltration of an anesthetic difficult because of its thickness and the tight adherence of subcutaneous tissues [38].

Innervation of the forelimb is supplied by the median, ulnar, and radial nerves. Once these nerves course over the carpal region, extensive branching occurs and innervation to the distal limb and foot is provided. Ring block or nerve blockade is performed by using a 3.8-cm, 18- or 20-gauge needle with 10–20 ml of 2% lidocaine. Aspiration after needle puncture is necessary to ensure that inadvertent vascular administration does not occur.

The saphenous, peroneal, and tibial nerves supply innervation of the hindlimbs. Due to the ease of use of intravenous regional anesthesia, the need for nerve blocks is uncommon. Local nerve blockade in the hindlimbs is often used when there is such significant swelling that the vessels cannot be located. The peroneal nerve can be palpated as it courses caudally over the lateral condyle of the tibia. The tibial nerve branches at the tibia and divides into plantar common digital nerves II and III [38]. These nerves become the axial and abaxial plantar digital nerves that supply some innervation to the digits. Ring blocks applied near the metacarpus/metatarsus can be performed. Injection of a local anesthetic is performed on either side of the extensor tendons. A 2.5–3.8-cm, 18–22-gauge needle with 15–25 ml of 2% lidocaine is used for this block. Multiple needle punctures are necessary, which increases the risk of infection and the likelihood of edema formation.

Intravenous regional anesthesia (Bier block) is commonly administered and is the preferred technique for lower limb surgery in ruminants. A tourniquet is placed proximally to the site of administration of the Bier block and surgery. Once the tourniquet is placed the needle or butterfly catheter should be inserted within 10–20 seconds to avoid vessel collapse. The area of administration is clipped and aseptically prepared. The veins used for injection on the thoracic limb include the common dorsal metacarpal, palmar metacarpal vein, and radial vein (Figure 8.23). For the pelvic limb, the lateral plantar digital vein and lateral saphenous veins are options for injection (Figure 8.24). The veins may not be visible even with maximal distention due to the thick skin of the cattle and the degree of pathology in the distal limb. A 3.3-cm, 20-gauge needle or a 19–21-gauge butterfly catheter is commonly used to administer the anesthetic. A dose of 20 ml of 2% lidocaine is the standard dosage used for lower limb procedures in cattle, including claw amputation, interdigital fibroma removal, arthrodesis/ankylosis of the distal interphalangeal joint, and other painful procedures of the lower limb. The authors prefer using butterfly catheters over a hypodermic needle. When using a butterfly catheter, the hub end must be kept in close proximity to the limb to prevent inadvertent removal of the needle on limb movement. Two locations are available for administration of a local anesthetic. The first is directly on the midline approximately 3–4 cm proximal to the interdigital space (Figure 8.25 and Video 8.8). The second is on the lateral aspect of the limb, about a thumb's width from the dewclaw (Figure 8.26 and Video 8.9). Once

Figure 8.23 Bovine thoracic limb. Radial vein (orange arrow) and abaxial palmar vein (blue arrow). *Source:* Courtesy of Dr. Ray Wilhite.



Figure 8.24 Bovine pelvic limb. Lateral saphenous vein (black arrow) and dorsal common digital vein (white arrow). *Source:* Courtesy of Dr. Ray Wilhite.

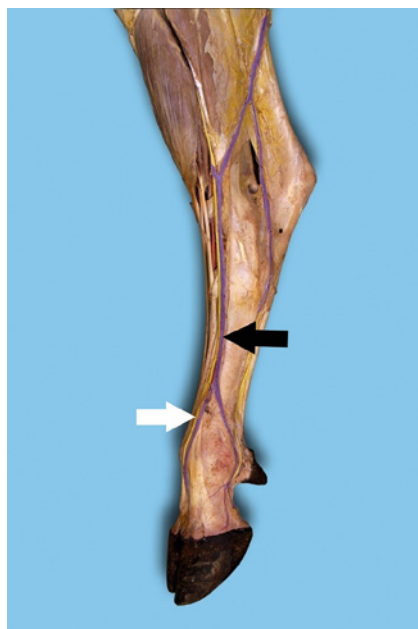




Figure 8.25 Bier block performed at the medial approach of the front limb with the butterfly catheter (A) in the dorsal digital vein in cattle.



Figure 8.26 Bier block performed at the lateral approach of the front limb with the butterfly catheter (A) placed in the abaxial palmar vein in cattle.

venipuncture has been achieved, care should be taken not to aspirate the syringe as this may disrupt the vein integrity. Anesthesia is achieved within 5–10 minutes of the administration of 2% lidocaine solution. The tourniquet should be removed as soon as the surgery is complete, and the surgery time should not exceed 30–60 minutes [8, 16].

Administration of the Bier block and nerve blockade can also be performed in small ruminants, calves, camelids, and pigs. The location and the vessels utilized for local anesthetic administration vary depending on the procedure being performed. A 21-gauge butterfly catheter or small gauge needle is most appropriate for these procedures. Toxic doses of the anesthetic need to be avoided, especially in smaller ruminants and pigs. Most pigs and small ruminants require sedation for these procedures to be performed. In the authors' experience, the vasculature is more easily identified in small ruminants, camelids, and pigs than in cattle. The authors have successfully used Bier blocks for limb amputation, arthrocentesis, joint flush, and interdigital fibroma removal.

The brachial plexus block can be used for surgeries of the forelimb. This block has been described in cattle and sheep [38, 45]. The ventral roots of C6-T2 are desensitized when this block is used [38]. The brachial plexus block has been used in combination with sedation in small ruminants for limb amputation when general anesthesia was not an option. The location of the needle insertion is 12–14 cm (cattle) or 6–10 cm (small ruminants) cranial to the palpable acromion of the scapula [9]. The needle is advanced caudally while staying in parallel with the animal's ribs and neck. A 7.6–15.24-cm, 18-gauge spinal needle is used in adult cattle. Once the needle is completely advanced, aspiration is crucial to ensure that no vasculature structures have been inadvertently punctured. An 8.2-cm, 20–22-gauge spinal needle is used in small ruminants and calves. A total of 20–25 ml of 2% lidocaine should be administered in adult cattle [38]. Dosages for small ruminants are based on the animal's body weight and the toxic dose of the anesthetic for individual species, and 2% lidocaine is commonly used for this procedure. Bupivacaine has been used for the brachial plexus block in sheep. The dosages ranged from 0.5 to 4.3 mg/kg and no evidence of cardiac or central nervous system toxicity was observed [46]. A dose of 30 ml of bupivacaine was reported to be adequate, with evidence of optimal distribution [46]. The brachial plexus block should not be administered bilaterally due to the risk of decreasing motor function of the diaphragm [38].

8.9 Castration

Administration of an anesthetic locally or systemically while castrating young bulls or piglets has become common practice and improves animal welfare, feed consumption, and growth rate. Similarly, when castrating small ruminants or camelids, local anesthesia (best with sedation) should be performed to alleviate pain and discomfort. The technique for local blockade is quite simple and easy to perform. In all ruminants and swine, the scrotal skin and spermatic cord or testicle are blocked. This can be performed with the animal standing in a chute with a tail-jack in place or under sedation. Adult ruminants pose a concern because of the extensive size of the testicles and large vascular beds that are present. Proper technique must be performed to avoid overt hemorrhage and potential death.

Once the needle is placed in the spermatic cord or testis, aspiration prior to administration ensures that the anesthetic is not inadvertently injected intravascularly. The scrotal skin can be desensitized by injecting 5–10 ml of 2% lidocaine, depending on the size of the animal. A 3.8–7.5-cm, 18–20-gauge needle is inserted into the center of each testicle (Figure 8.27 and Video 8.10). Ten to 15 ml of 2% lidocaine per 200 kg (440 lb) can be administered into the testis in bulls. Lidocaine is quickly absorbed by the lymphatics to provide anesthesia. In younger, smaller calves,



Figure 8.27 Intratesticular anesthesia. The bull is in left lateral recumbency with the head to the right of the image. The testicles are pushed down within the scrotum. The right testicle (A) is injected with an anesthetic solution. *Source:* Courtesy of Dr. Ray Wilhite.



Figure 8.28 Spermatic cord block. The bull is in left lateral recumbency with the head to the right of the image. The spermatic cord (A) is isolated and anesthetic is injected into the spermatic cord.

2–10 ml of 2% lidocaine is sufficient to provide local anesthesia for the castration [17]. The spermatic cord may be blocked by manually isolating the cord in the neck of the scrotum and advancing a 3.8-cm, 18-gauge needle through the skin and into the spermatic cord. A volume of 3–10 ml of 2% lidocaine is administered depending on the size of the cattle (Figure 8.28).

When castrating small ruminants, sedation is produced by using an intramuscular or intravenous combination of xylazine (0.05–0.2 mg/kg) and midazolam (0.2–0.4 mg/kg), midazolam (0.2–0.4 mg/kg) and ketamine (1–2 mg/kg), or xylazine (0.05–0.2 mg/kg) and ketamine (1–5 mg/kg) before removal of the testicles. Castration of small ruminants prior to puberty is discouraged due to the increased risk of urolithiasis in those animals in which the urinary tract has not fully developed in the absence of testosterone. The scrotal skin is clipped and surgically prepared. An intratesticular or spermatic cord block (Video 8.11) following a block of the scrotal skin is performed using 2% lidocaine at a dosage of 6 mg/kg. A 50 kg (110 lb) goat could receive a maximum of 15 ml for blocking of the spermatic cord, testes, and scrotal skin. Maximal anesthetic effect occurs within 2–5 minutes and the castration can be performed.

Intratesticular sedation can also be used by injecting 0.1–0.2 mg/kg of xylazine and 0.1–0.2 mg/kg of midazolam into one testicle [47]. The time to effect is approximately 5–10 minutes with this combination. Although it has been recommended to divide the dose between the two testes, the full dose can be administered into one testicle. The testicle in which the drugs were injected should be removed last.

Castration of camelids should never be performed in the first year of life, as is common in other ruminant species. Alpacas and llamas should be castrated when they are at least 12 months or 18–24 months old, respectively [48]. Prescrotal and scrotal castration techniques can be performed successfully for camelids [48–51]. The authors have used intravenous “Llama Lullaby” at a dose of 1 ml/45 kg (99 lb) of body weight to produce anesthesia, which was followed by a local skin block at the incision site. The intramuscular dose for “Llama Lullaby” is 1 ml/18.2 kg (40 lb) of body weight in alpacas and 1 ml/22.7 kg (50 lb) of body weight in llamas. The intramuscular route allows for a longer duration of anesthesia and surgery time than the intravenous route. The authors prefer a prescrotal technique for camelid castration. Intratesticular block is commonly performed in camelids and provides adequate anesthesia for the procedure. The spermatic cords are difficult to isolate in camelids, thus making the intratesticular approach more suitable. The skin of the testicles is clipped and aseptically prepared. The testicles are isolated and a 3.5-cm, 20-gauge needle is used to inject 2 ml of lidocaine into each testicle. As described above, a lumbosacral epidural anesthesia can be used to perform castration in camelids.

The authors recommend that castration of older commercial boars or those kept as pets be performed under sedation and with local anesthesia. Proper restraint and handling are imperative for castration of swine and sedation protocols can be found in Chapter 3. Depending on the age of the animal, the authors have used prescrotal and scrotal castration techniques to castrate pigs. When performing castration on pet pigs, the prescrotal technique allows for visualization and closure of the inguinal rings and is preferred by the authors. Once sedated, the scrotal hair is clipped and aseptically prepared. Intratesticular lidocaine is commonly used at a dosage of 6 mg/kg of body weight because localization of the spermatic cord is difficult. The total volume of lidocaine is split between the testicles and the scrotal skin. The authors have used this dose and no adverse effects have been observed. Boars can be castrated using a lumbosacral epidural anesthesia with proper restraint or sedation as described in previous section. Intratesticular anesthesia has also been performed using drug combinations including xylazine, midazolam, ketamine, or Telazol. Please refer to Chapter 3 for information on standing sedation and chemical restraint and Chapter 4 for information on injectable anesthesia.

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9

Anesthetic Management of Specific Procedures

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Selection and implementation of anesthetic protocols in farm animals are largely influenced by the species of animal, the particular procedure to be performed, individual knowledge and experience of the veterinarian with respect to inhalation or injectable anesthesia agents, economics, and the facilities and personnel available for support. The purpose of this chapter is not to present an in-depth discussion of surgical procedures, as details on the surgical approaches and procedures are well documented in other texts [1–3]. Rather, this section presents anesthetic techniques utilized routinely for the procedures described. The authors recognize that many alternatives and personal preferences exist for anesthetic management of various conditions in farm animals and ultimate selection of the anesthetic protocol will be dictated by many factors, including clinician preference, logistical constraints, and animal welfare considerations.

Because of the docile nature of ruminant patients and the capability for physical restraint in a chute, most standing surgical procedures in field settings can be performed in cattle using local anesthetics alone or utilizing combinations of chemical restraint with local or regional anesthesia. Chemical restraint can also be utilized for procedures where recumbency is preferred. Although the term “balanced” anesthesia is not often associated with field anesthesia in farm animals, the reality is that most surgical procedures involving ruminants can be accomplished using this method, where combinations of two or more classes of drugs, including sedatives, tranquilizers, analgesics, and local anesthetics, are utilized to provide sedation, analgesia, and muscle relaxation. The advantage of utilizing multiple classes of drugs in an anesthetic plan is safety, as smaller doses of two or more agents are considered safer than the usual large dose of a single agent. Swine, including pot-bellied pigs, are less tolerant of physical restraint, therefore deep sedation or general anesthesia is often necessary to perform even minor surgical procedures.

For surgical procedures where recumbency is preferred or where a procedure requires an extended period of immobility or high level of analgesia, general anesthesia offers optimal restraint, ability for aseptic surgical conditions, proper handling of tissues, and hemostasis. Location for performing the general anesthesia, positioning of the patient, and preparing for regurgitation, rumen tympany, and salivation are important considerations prior to induction (Chapter 1). The choice of injectable or inhalation maintenance general anesthesia often depends on the availability of gas anesthetic equipment and personal experience. Since depth of anesthesia can be easily and rapidly adjusted with inhalation anesthetics (e.g. isoflurane, sevoflurane, and desflurane)

(Chapter 6), inhalation anesthesia is preferred over injectable anesthesia for lengthy procedures or for patients considered higher anesthetic risk because of systemic illness. If general anesthesia is utilized, anesthetic protocols should be individually designed, especially with respect to critically ill patients, neonates, and other animals where anesthetic risk is considered high. Prior to anesthesia, patients should be evaluated by physical examination with or without clinical pathologic examination to assess their risk associated with anesthesia and surgery. Heart defects and pulmonary dysfunction can be identified during careful auscultation of the thorax, and evidence of cardiovascular compromise can be subjectively assessed by mucous membrane color and capillary refill time. Complete blood counts and biochemistry panels should be evaluated in cases where inflammatory disease, electrolyte derangements, or vital organ dysfunction is suspected. Classification of animals by physical status 1–5 has been proposed to aid in determining anesthetic risk, with higher physical status having greater risk of complications associated with anesthesia [4]. Apparently healthy animals undergoing an elective surgical procedure can be classified as physical status 1. For simple elective surgical procedures in young, apparently healthy animals, preoperative laboratory evaluation is not usually necessary. An animal with a slight to moderate systemic disturbance that does not interfere with function is physical status 2, and examples include mild dehydration, obesity, umbilical hernias, poor body condition, and simple fractures. Physical status 3 animals are those with slight to moderate systemic disturbances that do interfere with normal function, and examples include heart defects, severe electrolyte imbalances, oxygen exchange problems such as pneumonia, moderate to severe dehydration, and compound fractures. Physical status 4 animals are those with uncompensated systemic disturbances or life-threatening conditions where surgical intervention is deemed lifesaving. Finally, physical status 5 animals are those in moribund condition. If at all possible, assessing clinical pathology and stabilizing body systems by provision of fluid and electrolyte therapy are important in physical status 3–5 animals. Packed cell volume and total protein measurements are screening tests which are easily performed and can provide information that can influence preparation for anesthesia and surgery. For physical status 4 and 5 animals, anesthesia and surgery are often performed without the luxury of time and presurgical stabilization. Monitoring of high-risk patients during anesthesia is important and should continue throughout the recovery phase. Anesthetic deaths can occur during the recovery phase.

9.1 Urogenital Surgery in the Male

9.1.1 Castration

Castration represents one of the most frequent surgical procedures performed in farm animal species. The methodology and anesthesia of castration to minimize associated stress and pain is currently the focus of heavy research. The acute distress of castration is effectively eliminated by the administration of local anesthetics, which is the most commonly used anesthesia protocol for castrating food animals. However, the integrated cortisol response is less efficiently controlled with local anesthesia alone, and a multimodal approach to anesthesia should be considered, particularly when castration is performed in older animals [5]. There are currently no drugs labeled for the control of surgical pain in farm animals in the USA other than local anesthetics. Nonsteroidal anti-inflammatory drugs (NSAIDs) in conjunction with local anesthetics effectively minimize the acute and prolonged pain response associated with castration. Labeled for the control of inflammation or as an antipyretic, flunixin meglumine (1.1–2.2 mg/kg) is the sole NSAID labeled for use for

farm animals in the USA and must be given intravenously at least daily for efficacy. Longer-acting NSAIDs, such as meloxicam, may be used more effectively to control pain associated with castration when used in accordance with extralabel drug use regulations [5].

Young ruminants: Castration in young ruminants can be done with the animal standing or in lateral recumbency; adequate physical restraint in either case is required. Infusion of 2% lidocaine in the skin and/or spermatic cord can then be performed, although many procedures are done with only physical restraint to minimize the time of the procedure and the stress of being separated from the dam. A small-gauge needle is used to infiltrate 1–3 ml of 2% lidocaine in the scrotal skin along the proposed line of the incision. An additional 1–2 ml may be injected into each spermatic cord. Vasodilation associated with lidocaine increases the risk of hemorrhage but, in the experience of the author, has not resulted in clinically significant blood loss. Dilution of lidocaine with sterile saline to a final concentration of 0.5–1% should be considered in lambs and kids due to their sensitivity to local anesthetics. General anesthesia or heavy sedation is sometimes used in pet animals; injectable anesthesia is usually sufficient to provide ample time for the procedure. Intravenous (IV) administration of ketamine (2–3 mg/kg) and xylazine (0.1–0.2 mg/kg) will usually provide 20–30 minutes of anesthesia. Other drugs can also be used successfully (Chapter 4), and the choice of agents will depend on the anesthetist's or surgeon's preference.

Adult ruminants: Several local blocks have been described for the castration of older, or mature, ruminants. In addition to the aforementioned techniques, anesthesia can be provided by injecting 10–15 ml of 2% lidocaine subcutaneously in a ring block of the scrotal neck, followed by the administration of 5 ml of 2% lidocaine into each spermatic cord. When castration of several patients is to be performed, the animal can be released and the block performed on other patients to allow a 10-minute period for the onset of anesthesia. Alternatively, intratesticular administration of a local anesthetic can be performed in addition to subcutaneous (SC) infiltration of the scrotal skin. In mature animals, a 3.75–7.5-cm, 16- to 18-gauge needle is used; for smaller animals, a 2.5–3.75-cm, 20-gauge is preferred. With the testicle grasped firmly, the needle is inserted just ventral to the tail of the epididymis and advanced toward the center of the testicle at approximately a 30° angle from perpendicular. Depending on the size of the animal, 2–15 ml of 2% lidocaine is deposited at the center of the testicle. Sedation is more commonly used when performing castration on older ruminants. General anesthesia using either injectable or inhalation anesthetics should be considered for mature animals or when physical restraint is inadequate.

Camelids: Castration of New World camelids is best performed with some degree of sedation or general anesthesia although the procedure can be performed with adequate physical restraint and local anesthesia. Camelids are less sensitive to the effects of xylazine than small ruminants, thus a higher dose of the drug is usually required to achieve a comparable state of sedation. Mild sedation with xylazine (0.3 mg/kg IV) with local infiltration of the skin of the surgical site is adequate. If heavier sedation is desired, xylazine can be administered in conjunction with ketamine. Xylazine (0.6 mg/kg intramuscular [IM]) and ketamine (6 mg/kg IM) provide satisfactory sedation for castration of llamas. In alpacas, the doses are increased slightly to 0.7 mg/kg IM of xylazine and 7 mg/kg IM of ketamine. *Llama Lullaby* produces short-term anesthesia in llamas and alpacas for completion of short surgical procedures, including castration, and is favored by the author for field procedures. The solution is made by combining 1 ml (100 mg) of xylazine, 1 ml (10 mg) of butorphanol, and 10 ml (1000 mg) of ketamine. The resulting combination is administered intramuscularly at a dose of 1 ml/23 kg (50.6 lb) for llamas or 1 ml/18 kg (39.6 lb) for alpacas to provide approximately 20–30 minutes of anesthesia. General anesthesia using inhalation anesthetics is a viable option; addition of a local infiltration of 2% lidocaine to the incision site is recommended for additional pain management [6].

Swine: In swine, castration is ideally performed before 2 weeks of age to minimize stress and behavioral changes associated with castration. Piglets are best castrated by suspending them by the hind limbs in vertical restraint. Anesthesia is provided by injecting 0.5–1.0 ml of 2% lidocaine into the scrotal skin over each testicle and 0.5 ml into each spermatic cord in the inguinal canal. Heavy sedation or general anesthesia is preferred for the castration of older pigs. A combination of tiletamine, zolazepam, ketamine, and xylazine (TKX-P) for pigs is favored by many clinicians. The combination is formed by reconstituting one 500 mg vial of Telazol with 250 mg (2.5 ml) of ketamine and 250 mg of xylazine (2.5 ml). The resulting combination is dosed at 1 ml/35–75 kg (77–165 lb) in commercial pigs or 1 ml/75–140 kg (165–308 lb) in potbellied pigs. Alternatively, IM induction of general anesthesia using ketamine (5 mg/kg), midazolam (0.2 mg/kg), and detomidine (0.1 mg/kg) followed by inhalation anesthesia has been described for urogenital surgeries in pot-bellied pigs [7]. A combination of xylazine and ketamine (2 and 11 mg/kg IM, respectively) provides deep sedation, but pigs may still respond to surgical stimulation. The same combination of drugs, albeit at lower doses (1–2 and 3–5 mg/kg, respectively), can be administered by intratesticular injection to induce immobilization and anesthesia for castration of mature boars. Half the total dose is injected into each testicle; removal of the testicle removes unabsorbed drug residue and hastens recovery.

9.1.2 Penile Papilloma

Penile papillomata represent the most common penile tumor of the bovid, and anesthesia for surgical removal is adequately provided by local or regional techniques. The bull should be restrained in a standing chute or on a tilt table. Mild sedation can be used as needed for fractious animals. The dorsal penile nerve is desensitized by infusion of 2–4 ml of 2% lidocaine subcutaneously across the dorsum of the penis using a 22- or 24-gauge needle. Alternatively, local infiltration of 2% lidocaine around the base of the tumor, particularly for well-pedunculated papillomata, provides adequate analgesia. A pudendal nerve block will also successfully desensitize the surgical site but is less commonly employed due to a higher degree of technical difficulty of administration.

9.1.3 Persistent Frenulum

Correction of persistent frenula occurs with the bull in standing restraint or lateral recumbency; general anesthesia is not usually warranted. Mild sedation may be employed, but tranquilization is contraindicated as it is desirable that the bull retract the penis into the sheath postoperatively for protection against trauma and as an aid in hemostasis. Analgesia is most easily and commonly provided by local injection of the frenulum attachments with 1–2 ml of 2% lidocaine using a small-gauge needle. Local anesthesia can also be supplied by inserting a small-gauge needle through the lamina interna at the dorsal aspect of the preputial orifice. Injection of 2% lidocaine in a semicircle over the dorsal aspect of the penis will successfully desensitize the dorsal penile nerve. Alternatively, regional anesthesia can be provided by the administration of a pudendal nerve block.

9.1.4 Penile Translocation

Penile translocation surgery is performed with the patient in dorsolateral recumbency to allow access to the ventral midline and one flank. General anesthesia is preferred for the procedure, although heavy sedation and local anesthesia are also acceptable. Specific agents to be used will

depend on the surgeon's preference, but a combination of xylazine (0.1 mg/kg IV) and ketamine (2.0 mg/kg IV) or the use of *Bovine Triple Drip* (1 ml/kg IV for induction, 2 ml/kg/hour for maintenance) works well when injectable anesthesia is indicated. Local anesthesia is provided by infusing 2% lidocaine subcutaneously in a modified ring block approximately 10 cm around the periphery of the preputial orifice and prepuce to within approximately 5 cm of the scrotal neck. A second SC ring block can be performed at the translocation site in the flank.

9.1.5 Epididymectomy

Epididymectomy can be performed in all farm animal species for the process of sterilization or the preparation of teaser animals, often in conjunction with other procedures. General anesthesia is indicated in mature boars and can also be used in small ruminants and camelids but is not required. The choice of injectable or inhalation anesthesia is dictated by surgical conditions, surgeon's preference, and additional procedures to be performed, if any. When local anesthetic techniques will be solely used, the choice of standing or lateral restraint is at the discretion of the surgeon. The surgical site is desensitized by local infiltration of 2% lidocaine with a small-gauge needle in the scrotal skin directly over the epididymis. Deposition of 2% lidocaine directly into the epididymis can be considered for additional analgesia but is not commonly performed.

9.1.6 Vasectomy

Like epididymectomies, vasectomies in ruminants are usually performed under local anesthesia; general anesthesia can be considered in small ruminants but is not often practical, and local anesthetic techniques provide adequate analgesia. After the application of standing or lateral restraint, with or without the use of sedation, 2–4 ml of 2% lidocaine is infused into the posterior scrotal skin just proximal to each testicle using a 20- or 22-gauge needle. Infusion of local anesthetic directly into each spermatic cord with a fine needle at the surgery site provides additional analgesia but is believed by some clinicians to hinder identification of the vas deferens. In swine, general anesthesia is recommended. Injectable anesthetic protocols in conjunction with local infusion of lidocaine provide adequate analgesia for the procedure. General anesthesia is also recommended when performing the procedure in New World camelids.

9.2 Urogenital Surgery in the Female

9.2.1 Cesarean Section

Cattle: Patient positioning and surgical approach for the bovine cesarean section will be influenced by multiple factors, including fetal viability, patient's temperament, available facilities, and clinician experience and preference. Discussion of the benefits and drawbacks of the various approaches is beyond the scope of this text; the standing flank and ventral midline approaches are used most commonly. Both approaches are performed successfully under regional and local anesthesia. Epidural anesthesia is provided at the discretion of the surgeon. A caudal epidural anesthesia using 2% lidocaine will not provide analgesia to the surgery site but will decrease straining. In recumbent animals, this may also decrease the resultant hind limb movement and assist in restraint. In standing procedures, caution is warranted when administering epidurals as excessive anesthesia can result in recumbency. The dose of local anesthetic is 0.5 ml per 45 kg (99 lb) of body weight.

The use of sedatives or tranquilizers is optional for bovine cesarean section and is dictated by the attitude of the patient and available facilities. When a standing approach is preferred, care must be taken not to induce recumbency. Sedation with acepromazine (0.01 mg/kg IV, 0.1 mg/kg IM) is preferred by the authors when performing standing cesarean sections on nervous or fractious patients. Xylazine is a commonly used sedative in bovine medicine and may aid in restraint of recumbent animals. However, the ecbolic activity of xylazine may hinder uterine manipulation and thus is not favored for cesarean sections. Cattle in dorsal or dorsolateral recumbency experience cardiovascular and respiratory compromise, and this must be accounted for when choosing whether to use sedation and, if so, which drug to employ. While sedation or tranquilization is acceptable, and even beneficial in selected cases, local anesthesia and physical restraint are sufficient for most cesarean sections in the bovine patient.

Local blocks providing anesthesia to the paralumbar fossa include the proximal and distal paravertebral nerve blocks, inverted-L block, and line block; these are discussed in detail in Chapter 8. Selection of a particular block is influenced by the condition of the patient and surgeon's preference. For ventral midline celiotomies, local anesthesia is provided by the infusion of a field block of 2% lidocaine along the intended incision line. An 18-gauge, 3.8-cm needle is used to infuse multiple, small injections of 10 ml of local anesthetic solution subcutaneously and into the deep layers and peritoneum. High-volume caudal epidural anesthesia (1 ml of 2% lidocaine per 5 kg [11 lb] of body weight) has also been used to facilitate the procedure from the ventral midline approach [8].

Small ruminants: Anesthetic protocols for cesarean sections in small ruminants are similar to those used in cattle and primarily depend on the surgical approach to be used. Local anesthetic techniques are performed as in cattle. However, it must be remembered that small ruminants are much more sensitive to lidocaine than their larger counterparts with the recommended maximum dose not to exceed 6 mg/kg. Regional anesthesia using a lumbosacral epidural is a viable alternative for cesarean sections in sheep and goats; the recommended dose is 2 ml of 2% lidocaine per 10 kg (22 lb) of body weight. An 18- or 20-gauge, 3.8-cm needle is sufficient in most animals. Onset of anesthesia occurs within 5–15 minutes and generally lasts 60–120 minutes. General anesthesia is also suitable for the procedure in small ruminants. Maintenance with an inhalation anesthetic, such as isoflurane, is preferred.

Camelids: Cesarean sections are less commonly performed in New World camelids than in ruminant species. When indicated, the left lateral abdominal approach is used most commonly. General anesthesia is preferred and either injectable or inhalation anesthetic protocols are suitable; the final anesthetic choice will depend on the drug availability and clinician preference. *Llama Lullaby*, described above, can be used for injectable anesthesia. However, initial dosing will generally provide only 20–30 minutes of anesthesia and so it is likely that additional doses may be needed depending on the length of the procedure. A similar duration of anesthesia can be achieved using propofol (4.0 mg/kg), a combination of ketamine (2.0 mg/kg) and propofol (2.0 mg/kg), or a combination of ketamine (4.0 mg/kg) and diazepam (0.1 mg/kg) [9]. Additional use of local anesthetic infusions and/or regional anesthetic blocks for enhanced pain management is encouraged.

Swine: In swine, cesarean sections are indicated when transcervical extraction of pigs from the uterus is not feasible or are performed electively to obtain gnotobiotic or specific pathogen-free pigs. General anesthesia is desirable for cesarean sections in swine. Anesthetics with minimal depressive effects on the piglets are favored when live births are anticipated. If the piglets will remain with the sow, it is desirable that anesthesia is chosen which allows the sow to nurse the pigs immediately after surgery. The most viable piglets are obtained when inhalation anesthetics are used to induce and maintain anesthesia of the sow.

Where labeled for use, azaperone (2.2 mg/kg IM) produces a predictable and consistent sedative effect in pigs. However, the drug will cross the placental barrier and result in respiratory depression and sedation in piglets, although the pigs will usually survive with appropriate postnatal care. When general anesthesia is not possible due to available facilities or the state of the patient, local anesthesia can be used in conjunction with sedation and physical restraint. A combination of ketamine and xylazine, either intravenously or intramuscularly, often yields satisfactory results when combined with a field block of 2% lidocaine. Selection of specific injectable anesthetic(s) is left to the discretion of the clinician; specific protocols are provided in Chapter 4. Alternatively, a lumbosacral epidural anesthesia (1 ml of 2% lidocaine per 4.5 kg [9.9 lb] of body weight) results in recumbency and desensitization of the ventral midline surgical site. Similar results are seen at a dose of 1 ml per 7.5 kg (16.5 lb) for pigs up to 50 kg (110 lb); for larger pigs, 1.0 ml of lidocaine is added for every additional 10 kg (22 lb) of body weight. A maximum total volume of 20 ml is suggested (Chapter 8).

9.2.2 Ovariectomy

In cattle, ovariectomy is most commonly performed in feedlot heifers through either a paralumbar or vaginal approach. Both approaches are done with the animal in standing restraint; sedation can be employed at the discretion of the operator but is not often necessary. When the flank approach is preferred, any of the commonly employed local or regional techniques for anesthesia of the paralumbar fossa (Chapter 8) may be satisfactorily employed. A distal paravertebral nerve block is preferred by some clinicians for its quickness and ease of administration. Original descriptions of procedures utilizing the vaginal approach did not suggest anesthesia; however, a caudal epidural can be applied easily to desensitize the pelvic and perineal regions. Occasionally, unilateral ovariectomy is indicated in mature cows with ovarian pathology. When pathology is extensive and the surgical procedure is expected to involve extensive tissue dissection, general anesthesia may be warranted. If additional local analgesia is desired in such cases, a sterile gauze soaked in 2% lidocaine can be wrapped briefly around the ovarian attachment before surgical transection. Pet animals represent the most common populations of swine and small ruminants that present to the clinician for ovariectomy. In both groups, the procedure is most commonly performed with the animal in dorsal recumbency; general anesthesia with inhalation anesthesia maintenance is preferred in both cases.

9.2.3 Vaginal Prolapse

A variety of procedures have been described for the correction of vaginal prolapse in cattle and swine. Caudal epidural administration is indicated for the manual manipulation of the prolapse and placement of the retention sutures. In swine, local infiltration of the vestibular area provides effective analgesia when administration of a caudal epidural is difficult or ineffective. Cervicopexy by the modified Winkler method is a relatively permanent repair of cervicovaginal prolapse. Sedation is employed based on the temperament of the patient. Successful anesthesia is achieved by administration of a distal paravertebral nerve block or other technique to desensitize the paralumbar fossa. A caudal epidural is also recommended for the procedure.

9.2.4 Perineal Laceration

Perineal lacerations are classified according to location and tissues involved; surgical repair is usually attempted after secondary healing has occurred. Standing restraint is required, and sedation

can be achieved with acepromazine (0.01 mg/kg IV, 0.1 mg/kg IM) or other sedatives according to the surgeon's preference. A caudal epidural is indicated to provide anesthesia to the perineum and rectovestibular shelf. Some clinicians advocate the use of xylazine in the caudal epidural for this procedure, but this may not be advantageous in all cases. The dose for xylazine given via caudal epidural is 0.05 mg/kg diluted to 5 ml in 0.9% saline. When given by epidural, xylazine will provide approximately 2–3 hours of anesthesia beginning 20–40 minutes after administration.

9.3 Surgical Disorders of the Abdomen

9.3.1 Laparotomy

Abdominal surgery (laparotomy, celiotomy) is the most common major surgical procedure performed by farm animal veterinarians. Laparotomy is used to access the abdominal cavity during diagnostic exploration, cesarean section, ovariectomy, rumenotomy, urolithiasis with or without ruptured urinary bladder, intestinal accidents, abomasal displacements and volvulus, biopsy of abdominal organs, large intestinal disorders, and renal disease. Surgical exploration of the abdomen should not be considered only for therapy but is also a cost- and time-efficient diagnostic tool. Many surgical approaches exist for entering the abdominal cavity. Because of the large size of the cattle abdomen, it is advantageous to enter the abdomen as close to the lesion or target as possible, which necessitates a thorough physical examination to determine the optimal approach for success. The main approaches for a laparotomy in cattle are the right paralumbar fossa, the left paralumbar fossa, the ventral midline, and paramedian. The standing approaches are preferred for exploratory laparotomy because the internal organs are in their normal position as compared to the approaches utilizing lateral or dorsal recumbency. The standing right paralumbar fossa laparotomy using local/regional anesthesia with or without sedation is a very common approach in adult cattle and can be utilized for exploration of the abdomen and therapy for conditions which include cecal dilatation and dislocation, enterotomies, displaced abomasum, small intestinal accidents, surgery of the colon, nephrectomy, and physiologic mastectomy.

In general, most cattle, especially dairy cattle, are docile and calm enough that most abdominal surgeries can be performed in the standing animal under local or regional anesthesia alone. Anesthesia of the paralumbar fossa and abdominal wall for standing laparotomies can be achieved by local infiltration of anesthetic or several different regional anesthetic techniques described in Chapter 8. The standing laparotomy is preferred for many conditions and reduces problems associated with bloat, regurgitation, and nerve or muscle damage. In fractious and aggressive cattle, mild sedation with xylazine (0.015–0.025 mg/kg IV or IM) can be utilized to assist with performing the regional anesthetic technique. In this use, xylazine will provide sedation but should not be relied on for significant analgesia when injections of local or regional anesthetics are made. The onset of IV administration is rapid and the duration of sedation is dose dependent. Quiet cattle require less of a dose for standing sedation than anxious or unruly cattle [9]. Using the IV dose (0.01 mg/kg) in an IM or SC route xylazine can produce mild sedation with a lower risk of recumbency. For extremely agitated or aggressive cattle, xylazine sedation can also be utilized, but higher doses are necessary for sedation (0.02–0.05 mg/kg IV), and the potential for recumbency increases. For this reason, many clinicians have utilized a *ketamine stun* technique, which is the addition of a small dose of ketamine to an injectable chemical restraint technique [10]. The ketamine stun can be given IV, IM, or SC, but the SC route is preferred for a standing paralumbar fossa laparotomy. A combination of butorphanol (0.01 mg/kg), xylazine (0.02 mg/kg), and ketamine (0.04 mg/kg) is

given SC, with onset of activity occurring in 5–10 minutes. This protocol has been referred to as the 5–10–20 technique because for a 500-kg (1100-lb) cow, 5 mg of butorphanol, 10 mg of xylazine, and 20 mg of ketamine are used. Morphine can be substituted for butorphanol at a dose of 0.05–0.06 mg/kg, thus converting the 5–10–20 technique to a 25–10–20 technique (25 mg of morphine for a 500-kg (1100-lb) cow). The purpose of the ketamine stun for a standing laparotomy is to calm the patient; local or regional anesthetic techniques are still necessary to perform the laparotomy. Duration of activity is approximately 60–90 minutes. If the duration of the procedure dictates extending the ketamine stun, xylazine and ketamine can be administered subcutaneously at 25–50% of the initial doses. Including butorphanol in the redosing regimen has been associated with a greater likelihood of recumbency.

Although laparotomy is performed at a greater frequency in adult cattle, camelids, small ruminants, calves, and swine occasionally require a laparotomy. Laparotomy is often performed in the recumbent small ruminant or calf patient because most will lie down during the procedure if a standing procedure is attempted. Sheep, goats, and calves should be heavily sedated combined with local/regional anesthesia or preferably placed under general anesthesia. Llamas and alpacas that require a laparotomy are best placed under general anesthesia. While combinations of xylazine at 0.25 mg/kg and ketamine at 2–5 mg/kg can be used for minor dental procedures, wound care, etc. their duration of activity and depth of anesthesia are often unsatisfactory for laparotomy in camelids. For pigs, the most common indication for a laparotomy is cesarean section, which is described in section 9.2.1.

9.3.2 Disorders of the Forestomachs

Disorders of the forestomach in ruminants can result from a variety of causes, including those that are dietary, inflammatory, and/or mechanical. Acute lactic acidosis (grain overload, acute carbohydrate engorgement) is an example of a dietary forestomach disease resulting from consumption of large amounts of rapidly fermentable concentrate feeds. If in the acute stage of the disease, a rumenotomy can be performed to remove as much of the offending feedstuff as possible. This procedure can also be performed for lead toxicity or other conditions where removal of feed material from the reticulorumen is warranted. The rumen is apposed against the left body wall, which makes this location an ideal portal to access the rumen, reticulum, and reticulo-omasal canal. The surgical procedure is ideally performed in the standing patient with the approach being the left paralumbar fossa. Regional anesthesia alone is the preferred method of anesthesia, although mild sedation can be added. Most cases of acute lactic acidosis have some degree of depression and metabolic abnormalities, so choice of sedative and dose is important.

Rumenotomy can also be performed to diagnose ruminal-reticular diseases (rumenitis, parakeratosis), remove foreign material (bags, plastic, placenta), remove impacted ingesta, and as part of the treatment for traumatic reticuloperitonitis (hardware disease). Traumatic reticuloperitonitis is a disease primarily of cattle because of their indiscriminate eating behavior. Metal linear foreign bodies, that is, wire and nails, perforate the cranial aspect of the reticulum, resulting in an inflammatory reaction, forestomach stasis, localized or generalized peritonitis, a perireticular abscess, and adhesions or vagal indigestion. The foreign body can also continue to migrate, resulting in pericarditis or myocarditis. For traumatic reticuloperitonitis, a standing left paralumbar fossa laparotomy and rumenotomy can be utilized for therapeutic and diagnostic purposes. The left paralumbar fossa is anesthetized using local or regional anesthetic techniques with or without sedation as described for laparotomy. In cattle too weak to stand for the lengthy procedure, sedation combined with local/regional anesthesia or general anesthesia can be used with the patient

positioned in right lateral recumbency. Although small ruminants and camelids rarely get hardware disease, a rumenotomy is occasionally necessary for removal of toxic ingesta or foreign bodies. Placement of the animal in right lateral recumbency using general anesthesia is recommended.

9.3.3 Displacements and Volvulus of the Abomasum

Left displaced abomasum is one of the most common digestive tract conditions in dairy cattle and is associated with significant economic losses from both decreased milk production and increased culling rates. Several minimally invasive closed procedures along with several surgical techniques have been described to correct abomasal displacement in dairy cattle [11]. Minimally invasive closed procedures include rolling, blind tack, toggle pin, and laparoscopy-assisted toggle pin. For all but laparoscopy, the procedure is of short duration (<15 minutes) and can be accomplished by casting the animal using ropes or using a rapid-acting, short-duration sedative, with xylazine (0.05–0.1 mg/kg IV) most commonly used since it can be reversed with yohimbine (0.125 mg/kg IM) or tolazoline (2.0 mg/kg IM) after the procedure has been completed.

Laparoscopic correction of abomasal displacements has been described using either a one-step or two-step approach. Laparoscopy is a minimally invasive technique that permits the observation of the abdominal organs. Minimal invasion of the abdominal cavity with this technique is therapeutically beneficial with quick return to normal activity. The one-step approach involves either a left paralumbar fossa incision or ventral paramedian incision, while the two-step approach involves both incisions [12]. Anesthesia for the left paralumbar incision is provided by local or regional anesthesia. For the ventral paramedian incision, xylazine (0.05–0.1 mg/kg IV) sedation combined with local or regional anesthetic techniques is used.

Conventional open surgical procedures for correction of a displaced abomasum include standing right paralumbar fossa omentopexy or pyloropexy, standing left paralumbar fossa abomasopexy, or dorsal recumbent paramedian abomasopexy. For abomasal volvulus, the standing right flank paralumbar fossa approach or dorsal recumbency paramedian approach is used. For the standing procedures, anesthesia is usually accomplished with local/regional anesthetic techniques alone or with mild sedation. For the dorsal recumbent paramedian abomasopexy, the cow is often placed in dorsal recumbency using casting ropes, but for fractious cattle, sedation can be provided to assist with casting and placement in dorsal recumbency. Xylazine (0.05–0.1 mg/kg IV) is the most frequently used sedative for this purpose, but acepromazine (0.025–0.075 mg/kg IV) or butorphanol (0.0025–0.005 mg/kg IV) can also be used.

9.3.4 Small Intestine Disorders (Intussusception, Intestinal Volvulus, Intestinal Obstruction)

The prevalence of surgical conditions requiring anesthesia for small intestinal disorders is much less than for the forestomach or abomasum in cattle. Obstructive lesions of the small intestine are more common in cattle than in small ruminants and swine. In cattle, most obstructive lesions occur in the distal jejunum. Ileus, sequestration of fluid, colic, abdominal distension, and scant or absent fecal production are clinical signs observed. Careful physical examination, along with clinical pathologic examination and abdominocentesis, is important to determine if a surgical disease is present. Intussusception is the invagination of one portion of intestine into the lumen of adjacent bowel, often creating an intestinal obstruction. Laparotomy is indicated for intussusception and intestinal obstruction, and the right paralumbar fossa approach provides the best exposure to

the small and large intestine. A standing right paralumbar fossa laparotomy can be performed using mild sedation and local/regional anesthesia as previously described, but resection and anastomosis of intestine is difficult in the standing patient. Manipulation of the bowel and mesentery often results in pain and recumbency in the patient. In the authors' experience, general inhalation anesthesia with the patient positioned in left lateral recumbency is preferred for resection and anastomosis. The cow with abdominal distension and placement in lateral recumbency is at greater risk for regurgitation of rumen contents, so the head should be tilted downward and a cuffed endotracheal tube should be securely placed during the procedure. Injectable anesthesia protocols are usually for short-duration procedures but can be utilized in surgical correction of intestinal disorders. Surgical time must be considered. Injectable anesthesia protocols usually involve double drip (ketamine added to 5% guaifenesin at 1 mg/ml) or *bovine triple drip* (ketamine at 1 mg/ml and xylazine at 0.1 mg/ml added to 5% guaifenesin) (Chapter 4). The use of xylazine in compromised ruminant patients, which many cases of intestinal accidents are, is risky because of the cardiovascular-depressant effects. Double drip or bovine triple drip is slowly administered to effect to induce anesthesia. Anesthesia can be maintained by constant rate infusion of double drip or bovine triple drip at 2.6 ml/kg/hour.

Intestinal volvulus can involve either segmental volvulus of the jejunoileum or torsion of the mesenteric root. The distal jejunum and ileum have a longer mesentery, often referred to as the distal flange, and this section of intestine is more mobile and prone to volvulus. Cattle affected by the segmental volvulus will present with clinical findings very similar to those with an intussusception. Torsion of the mesenteric root is a very dramatic and painful condition of cattle. Animals with torsion of the mesenteric root have bilateral abdominal distension and are very difficult to examine because of the pain associated with the condition, and epidural administration of xylazine (0.05–0.07 mg/kg) can be used to assist with examination. Both intestinal volvulus conditions require surgical intervention. While performing the surgery standing has the advantage of the bowel being suspended in the abdominal cavity, making manipulation easier, the pain associated with manipulation of distended bowel usually results in recumbency. For this reason, general anesthesia is much preferred, with placement of the animal in left lateral recumbency.

9.3.5 Urolithiasis and Bladder Rupture

Obstructive urolithiasis is the most common urinary tract disease of small ruminants. Males, especially castrated males, are most commonly affected. Urolithiasis is a multifactorial disease process with diet, water intake, and urinary pH all providing contributing roles to the formation of uroliths. Complete physical examination and evaluation of clinical pathology are important to perform prior to anesthesia. Ruminants with a ruptured urinary bladder often have severe hemoconcentration and acid–base and electrolyte abnormalities that can result in cardiac arrhythmias during anesthesia. Numerous surgical techniques are available for treatment of obstructive urolithiasis and involve surgery of either the urethra or the urinary bladder. Surgical procedures involving the urethra include urethral process amputation, penile amputation, perineal or ischial urethrostomy, or urethrotomy. Most of these procedures can be performed in the standing patient under local and/or caudal epidural anesthesia or in the recumbent patient using a lumbosacral epidural (2 ml of 2% lidocaine per 10 kg (22 lb) of body weight) or general anesthesia. Acepromazine (0.05–0.1 mg/kg IV or IM) or diazepam (0.1 mg/kg IV) are preferred by the author when sedation is indicated for urethral relaxation and/or suppression of anxiety. Use of α_2 agonists, including xylazine, increases diuresis and thus, should be used cautiously in animals with complete urethral blockage.

If rupture of the urinary bladder is confirmed by abdominal ultrasound or abdominocentesis, then urinary bladder surgery is often warranted. In addition, when dealing with breeding livestock where surgery of the penile urethra is contraindicated, urinary bladder surgery is performed. Surgical procedures involving the urinary bladder include cystotomy, tube cystostomy, and bladder marsupialization. Bladder surgery is more difficult to perform than urethral surgery under field conditions. General anesthesia is preferred, but combinations of injectable, local, and epidural anesthesia can be used. For all procedures, the patients are placed in dorsal recumbency, so rumen tympany, excess salivation, and regurgitation are important considerations during anesthesia.

9.3.6 Umbilical Hernias

Calves: Umbilical hernias in calves occur with relative frequency and may be hereditary or acquired in origin. General anesthesia is recommended, particularly for large hernias or those with associated abscessation that requires additional dissection and extended surgical times. Surgical success is enhanced when patient movement is minimized throughout the procedure. IV administration of ketamine (2–3 mg/kg) and xylazine (0.1–0.2 mg/kg) is a commonly used induction protocol and will usually provide 20–30 minutes of anesthesia. The duration of anesthesia can be extended by intubation and maintenance with inhalation anesthetics such as isoflurane, or in field situations, by additional dosage of injectable anesthetics. Redosing with a third to half of the induction dose of ketamine and xylazine or ketamine alone (1–2 mg/kg given slowly to effect) will provide an additional 15 minutes of anesthesia in most cases. Induction and maintenance with xylazine alone induce a decrease in heart rate, and for this reason, the addition of ketamine to injectable anesthesia protocols is preferred. In one study, calves undergoing umbilical hernia repair were more likely to experience hypoxemia and had a greater intraoperative response to surgical stimulation when maintained on injectable anesthesia than when maintained on isoflurane after induction [13]. Periumbilical infusions of local anesthetic (described in the following paragraph) are recommended for use in conjunction with general anesthetic protocols.

Heavy sedation in conjunction with local and regional anesthetic techniques has also been used successfully for umbilical hernia repair in calves. A ring block with local anesthetic is performed at the periphery of the surgical site. A SC ring block can be followed by deposition of 2–5 ml of local anesthetic at approximately 1–2-cm intervals deep to the SC block to desensitize the underlying muscle layers. Alternatively, high-volume caudal epidural anesthesia (Chapter 8) has been shown to be an acceptable protocol for umbilical surgery [13]. High-volume caudal epidurals are administered at the standard caudal epidural site but, as the name implies, involve the administration of lidocaine in much larger volumes (1 ml per 5 kg [11 lb] of body weight) than typically given for perineal anesthesia. Some clinicians use the higher dose of 1 ml per 2 kg (4.4 lb) of body weight without ill effect. Recumbency and loss of hind limb motor control last for 4–6 hours following epidural administration, and proper postoperative care must be taken for the safety and welfare of the patient. IM xylazine sedation (0.1 mg/kg) has been used in conjunction with a lumbosacral epidural of 2% lidocaine (0.18–0.24 ml/kg) and xylazine (0.05 mg/kg) for umbilical hernia repair but without perfusion of local anesthetic was insufficient for adequate analgesia [13].

Swine: In swine, general anesthesia, either with inhalation or injectable anesthetics, is commonly used for umbilical hernia repair when surgical correction is pursued. As in calves, periumbilical infusions of local anesthetic are recommended for maximum analgesia. Alternatively, a lumbosacral epidural (Chapter 8) can provide adequate analgesia for umbilical surgery. Desensitization of the

area caudal to the umbilicus is achieved with a dose of 1 ml of 2% lidocaine per 4.5 kg (9.9 lb) of body weight. The anesthetic should be infused at a rate of 1 ml per 2–3 seconds and provides approximately 2 hours of anesthesia. Alternatively, similar results are seen at a dose of 1 ml per 7.5 kg (16.5 lb) for pigs up to 50 kg (110 lb); for larger pigs, 1.0 ml of lidocaine is added for every additional 10 kg (22 lb) of body weight.

9.4 Musculoskeletal Indications

9.4.1 Dehorning

Dehorning of cattle and goats is indicated to prevent tissue bruising of penmates and to enhance the safety of animal handlers; it is one of the oldest and most commonly performed surgical procedures of ruminants. It is preferable to perform the procedure in young animals to minimize the pain and stress associated with the procedure. Local anesthesia effectively eliminates the acute pain and distress of dehorning but may not mitigate the prolonged stress response. Research on analgesia and pain management in cattle undergoing dehorning is abundant and has been reviewed [14, 15]. A multimodal approach is preferable for optimum alleviation of stress associated with dehorning and may include the use of NSAIDs and sedatives with analgesic properties in addition to local anesthetic techniques [16], particularly in older animals in which the procedure is more involved. The cornual process, under the horn bud, connects to the skull at approximately 2 months of age in calves, and at 4–6 months of age the frontal sinus becomes contiguous with the horn. The use of NSAIDs and/or sedation must be done in accordance with established regulations concerning extralabel drug use in food animal species [17].

In calves, a cornual nerve block is performed to provide analgesia of the horn bud and surrounding tissue. The cornual nerve, a branch of the zygomaticotemporal nerve, is desensitized by using a 20-gauge, 2.5- or 3.8-cm needle inserted under the frontal ridge midway between the lateral canthus of the eye and the base of the horn. Five to 10 ml of 2% lidocaine is infiltrated subcutaneously and normally yields complete analgesia of the region in 5–10 minutes. The nerve lies superficially in young calves but may lie deeper as the animal matures. In older animals, cutaneous branches of the second cervical spinal nerve provide sensation to the caudal aspect of the horn base and are best anesthetized with an SC hemicircumferential infiltration of local anesthetic along the caudal aspect of the horn. When performing cosmetic cornuectomies in cattle, an SC ring block is performed at the horn base to anesthetize the skin.

In goats, a cornual nerve block alone is insufficient to provide adequate anesthesia for dehorning. In addition to the cornual nerve, the horn base is innervated by the cornual branches of the infratrochlear nerve. The infratrochlear branches are anesthetized by injecting 2–3 ml of local anesthetic midway between the medial canthus of the eye and the medial base of the horn as a line block due to the branching of the nerve. Alternatively, an SC ring block around the base of the horn may be performed but is likely to require a higher volume of local anesthetic and thus is less commonly used. Special care must be taken when dehorning kids and pygmy and dwarf goats due to their small size and the sensitivity of the goat to lidocaine toxicity. Dilution of lidocaine to 0.5–1% using sterile saline permits injections of larger volumes without compromising anesthesia of the region. General anesthesia using a combination of ketamine (3–5 mg/kg IM) and xylazine (0.1 mg/kg IM) or an inhalation anesthetic is also popular in older goats to minimize movement and vocalization while providing analgesia of the horn base and surrounding tissues.

9.4.2 Claw Amputation and Facilitated Ankylosis

Amputation of the claw or facilitated ankylosis in cattle are performed primarily as a procedure for septic arthritis of the distal interphalangeal joint or other disease processes with a poor prognosis for return to function. It is important to ascertain that the contralateral claw is healthy and capable of full weight-bearing before the procedure is attempted. General anesthesia is an option although not usually necessary. IV regional perfusion (Bier block) (Chapter 8) is performed easily by placing a tourniquet proximal to the fetlock and injecting approximately 20 ml of 2% lidocaine intravenously into the veins of the distal limb. Anesthesia of the foot occurs within 5–10 minutes and lasts until removal of the tourniquet, which can be safely left in place for up to 1 hour. Sedation can be provided as needed based on the available facilities and temperament of the patient.

9.4.3 Excision of Interdigital Fibromas

IV regional perfusion (Bier block) is the preferred anesthetic technique for interdigital fibroma excision. With a tourniquet in place proximal to the fetlock, 20 ml of 2% lidocaine administered intravenously will adequately desensitize all tissue distal to the tourniquet, including the interdigital area. Local infusion of 2% lidocaine around the periphery of the fibroma will also provide anesthesia to the surgery site. The presence of lidocaine at the incision site may delay healing, although this concern should not obviate the technique in cases where regional perfusion is unsuccessful. A metatarsal or metacarpal nerve block may also be used but is more technically challenging than the Bier block and is not commonly used.

9.4.4 Teeth Floating

The mandibular incisors of New World camelids commonly overgrow and extend beyond the lips. While most commonly a cosmetic defect, overgrowth can result in difficulty in the prehension and mastication of foodstuffs. Trimming of the incisors is performed easily with obstetric wire or a hand-held rotary tool. The pulp cavity is not entered when trimming is performed correctly and so anesthesia for pain management is not necessarily required. However, mild to moderate sedation is preferred depending on the fractiousness and anxiety level of the patient. In the opinion of the author, sedative choice is based on clinician preference as multiple drugs and multiple protocols work well for this minor procedure. Please see Chapter 3 for a list of commonly used sedation protocols in New World camelids.

9.4.5 Tail Docking

When performed in the first 2 weeks of a lamb's life, tail docking is a relatively simple and common procedure; proper analgesia can be achieved quickly with perfusion of a local anesthetic around the docking site. A caudal epidural is also effective but is time consuming and more technically challenging in small lambs. Occasionally, tail docking is requested for mature sheep that were previously overlooked or in cattle as a result of trauma. General anesthesia is recommended in sheep, though the procedure is often carried out in the field using local anesthesia. Perfusion of a local anesthetic or a caudal epidural can be performed using an 18- or 20-gauge needle at a dose of 1 ml of 2% lidocaine/50 kg (110 lb). Alternatively, a local ring block proximal to the amputation site may be employed to achieve analgesia of the surgical site.

Sacral fractures or coccygeal nerve damage in mature cows may cause a lack of tail tone and loss of function, leading to soiling of the tail and, potentially, unsanitary milking conditions. For anesthesia, 5–6 ml of local anesthetic is infused into the intercoccygeal space proximal to the site of the amputation after the placement of a tourniquet farther proximal for control of hemorrhage during the procedure. A caudal epidural is recommended for additive pain management but is insufficient by itself for analgesia to more distal surgical sites. The benefit of extended duration of analgesia when including an α_2 agonist or opioid in the epidural must be weighed against the risk of associated systemic effects.

9.4.6 Rectal Prolapse

Rectal prolapse in cattle and small ruminants can be corrected by a variety of procedures, including simple replacement, submucosal resection, and rectal amputation. Adequate restraint is necessary and sedation can be employed as necessary but is often not required depending on the temperament of the patient. A caudal epidural (Chapter 8) provides effective analgesia for each of these procedures. A dose of 1 ml of 2% lidocaine per 100 kg (220 lb) is used in cattle; in small ruminants, a dose of 1 ml per 50 kg (110 lb) is preferred although dosages of up to 1 ml per 15 kg (33 lb) have been reported [16]. When caudal epidural administration is difficult or unsuccessful in small ruminants, a perianal ring block of 2% lidocaine may be substituted to adequately desensitize the perianal region.

Rectal prolapse occurs relatively commonly in swine. In sows, it is most commonly observed during, or in the first weeks following, parturition. Manual reduction of uncomplicated cases is facilitated by the use of adequate restraint and sedation as needed. The perianal region is desensitized with a lumbosacral epidural (Chapter 8) or infiltration of a local anesthetic in a ring block around the rectum. Alternative corrective procedures are indicated when the rectal mucosa has become necrotic or otherwise unviable; the most commonly performed procedure is surgical amputation. General anesthesia is indicated for such procedures, and both inhalation and injectable anesthesia have been employed satisfactorily. Inhalation anesthesia, typically isoflurane, is preferred when available.

9.5 Wounds, Lumps, Bumps, and Abscesses

9.5.1 Wound Management

Appropriate anesthetic techniques for wound management will be determined by the extent of the wound(s) and the attitude of the patient. Adequate restraint for a thorough examination is essential, and sedation may be necessary for extended examinations or in patients that are fractious or aggressive. Xylazine is the most frequently used drug for sedation in large animals. General anesthesia may be required to appropriately examine small ruminants that suffer a severe predator attack and also may be useful for the performance of ancillary diagnostic tests such as imaging techniques to determine the extent of internal injuries.

Regional anesthetic techniques are desirable whenever possible as local anesthetics can delay wound healing. Additionally, when injected at the wound site, lidocaine can result in cell injury due to its acidic nature. The additional cell injury not only delays healing but acts as an additional painful stimulus to the animal. Buffering 2% lidocaine with 8.4% sodium bicarbonate in a 10:1 ratio will decrease the pain and discomfort of SC lidocaine injection without decreasing analgesic

efficacy. When regional techniques are impossible or impractical, local injections should be made through the wound to avoid the abundant pain receptors located within the epidermis. Use of longer needles allows deposition of the local anesthetic farther away from the wound margin and minimizes its negative effect on wound healing. Epinephrine, a potent vasoconstrictor, is sometimes added to lidocaine to enhance the efficacy and duration of action of the injection; this is contraindicated when providing analgesia around wound edges due to the risk of tissue necrosis.

9.5.2 Ocular Squamous Cell Carcinoma

Ocular squamous cell carcinoma is the most common indication for surgery of the periocular tissues in cattle. The surgical procedure utilized and the anesthetic techniques performed will be influenced by the surgeon's preference and the size, location, and involvement of local structures of the lesion. Local anesthetic techniques are almost always sufficient for routine cases; sedation with acepromazine (0.01 mg/kg IV, 0.1 mg/kg IM) or other sedatives can be of use when adequate restraint is not available, the animal is unusually agitated, or the lesion is extremely involved. Topical anesthetic can be applied to the cornea as desired. Local infusion of lidocaine around the lesion using an 18- or 20-gauge needle is recommended for removal of small lesions of the eyelids and conjunctiva by sharp dissection. When cryosurgery is the procedure of choice, the surgical area can be blocked using topical or local anesthetics. The nictitating membrane can be desensitized by injecting lidocaine directly into the base of the third eyelid using a 2.5-cm, 22- to 24-gauge needle.

9.5.3 Enucleation

Enucleation, or more commonly orbit exenteration, is frequently performed in farm animals to correct extensive inflammatory or neoplastic lesions of the eye or orbital structures. General anesthesia or heavy sedation may be beneficial for fractious animals or those with extensive lesion involvement. However, the procedure is commonly performed using physical restraint and local or regional anesthetic techniques. Sedation with acepromazine (0.01 mg/kg IV, 0.1 mg/kg IM) or xylazine (0.05 mg/kg IV, 0.1 mg/kg IM) prior to the procedure is recommended. An SC ring block is performed approximately 5 cm from the eyelid margins. The globe is desensitized by use of the Peterson block or retrobulbar technique (Chapter 8) according to the surgeon's preference. The author prefers a four-point retrobulbar injection using an 18-gauge, 15-cm needle. The needle may be bent manually to mimic the curvature of the globe before insertion through the eyelid or canthus at the orbital rim. Local anesthetic is injected in small increments as the needle is advanced, with 10–15 ml deposited at the back of the globe when the needle is fully inserted.

9.5.4 Entropion

Correction of mild cases of entropion in young ruminants is often performed without the use of sharp dissection and may not require anesthesia; infusion of a small amount of lidocaine locally can be performed if desired. When cases require more invasive techniques, general anesthesia is recommended. This is indicated most commonly in overweight potbellied pigs. In field situations, combinations of xylazine and ketamine (2 and 11 mg/kg IM, respectively) or *TKX-P* (Chapter 4) generally work well. *TKX-P* is a combination of tiletamine, zolazepam, ketamine, and xylazine formed by reconstituting one 500-mg vial of Telazol with 250 mg (2.5 ml) of ketamine and 250 mg of xylazine (2.5 ml). The resulting combination is dosed at 1 ml/35–75 kg (77–165 lb) in commercial

pigs or 1 ml/75–140 kg (165–308 lb) in potbellied pigs. Alternatively, general anesthesia may be maintained with inhalation anesthetics when the adequate equipment is available and circumstances warrant.

9.5.5 Abscess Removal for Caseous Lymphadenitis

Lymph node abscessation in cases of caseous lymphadenitis in small ruminants is the most common indication for surgical extirpation of lymph nodes in farm animals. Removal of the abscess in toto decreases environmental contamination and is frequently performed in valuable animals or on farms with strict biosecurity/biocontainment programs. General anesthesia is recommended for the procedure as complicated surgical dissection is often required due to the proximity to vital structures of the most commonly involved lymph nodes. Maintenance of anesthesia with inhalation anesthetics is preferred, but injectable anesthetic protocols may be suitable for some cases. Specific protocols are discussed previously (Chapters 4 and 6); selection should be based on the surgeon's preferences and the location of the targeted lymph nodes. Inhalation anesthetic protocols are recommended when removing lymph nodes in closer proximity to vital structures (e.g. carotid arteries, esophagus).

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10

Pain Management for Farm Animals

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Increased effort to manage pain has become standard practice in small animal medicine in recent years, but advances in pain mitigation in livestock species have been slower. Factors contributing to the slow progress are lack of analgesic drugs specifically approved for ameliorating pain of farm animals, known adverse effects, including excitation and decreased gastrointestinal (GI) motility caused by opioids or GI ulcer and impairment of renal function associated with nonsteroidal anti-inflammatory drugs (NSAIDs), fear that loss of pain prompts further damage to the injured tissue, requirement of record keeping by the Drug Enforcement Administration (DEA) when using scheduled drugs, inconvenient timing to administer the drugs for effective pain relief, the need for trained personnel to administer the drug via a specified route such as intravenous (IV) injection, and the increased cost to owners for analgesic drugs and their administration [1]. Untreated pain can delay wound healing and cause significant patient discomfort, stress, depression, and inappetence. When pain is severe and prolonged, the immune system can become impaired. A goal for appropriate patient care is restoration of normal physiological functions. Judicious use of analgesic drugs should be an essential part of the treatment plan to provide adequate pain relief and ensure comfort so that normal physiological functions are not impaired or are allowed to return. It should be kept in mind that pain is easier to treat before perception of pain actually occurs (preemptive analgesia) [2].

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in term of such damage.” Perception of pain involves transmission of electrical impulses in response to noxious stimuli received at the peripheral nociceptors located at the site of insult, which are A δ or C fibers; transduction of the impulses through the spinothalamic tract to the dorsal horn of the spinal cord, modification of these impulses by releasing central nervous system (CNS) neurotransmitters, for example substance P, neurokinin A, and brain-derived neurotrophic factor (glutamate), and activation of *N*-methyl-D-aspartate (NMDA) receptors. Projection of these neurotransmitters is mediated through specific pathways to the thalamus (neospinothalamic and paleospinothalamic tract neurons) and the limbic system (thalamocortical tract neurons). As a result, generation and awareness of the perception or emotion of pain occur [3, 4]. The initial response to acute pain tends to be well localized, short-lived, and proportional to the intensity of the insult. This response is usually a protective mechanism with the subject moving away from the

insult. Unlike acute pain, chronic pain is usually diffuse and persistent, and is often associated with hypersensitivity of the neural cells in the spinal cord and brain. Chronic pain may not involve injury to the tissue, but rather is often the result of inflammation associated with disease [4]. Hypersensitivity in the neural cells of the spinal cord and brain is reflected in the progression to central sensitization with increased sensitization of excitable nerve cells as evidenced by a disproportionately painful response to a normally mild noxious stimulation (wind-up syndrome) or greater perception of pain to a previously nonpainful stimulation (allodynia) [4, 5]. Surgery-induced pain often begins as acute pain but can progress to chronic pain as a result of prolonged inflammation.

Pain experienced by farm animals is often difficult to recognize due to their stoic temperament and the natural instinct of prey animals not to attract the attention of predators when injured. Behavioral indications of a farm animal in pain may include one or more of the following clinical signs: excessive grunting and bellowing (vocalization), lowering of the head, rigid posture, tail swishing, limping, kicking, or stomping of feet, teeth grinding, excessive licking on the affected area, reluctance to move or lay down, depression, decreased interest in surroundings, and inappetence. Physiological changes associated with pain include increased respiration, heart rate, body temperature, and pupil size. However, these physiological responses to pain can be misinterpreted since vital signs are often influenced by stress or other endogenous as well as exogenous factors [6]. Therefore, close observation and monitoring of the animal by regular caretakers or a veterinarian on-site are required for objective and unbiased judgment to institute appropriate and timely administration of pain-relieving treatment. Inadequate pain management in young livestock undergoing castration surgery was evident in a survey of Canadian veterinarians in 2004 and 2005, which showed that less than 0.001% in piglets, 6.9% in beef calves, and 18.7% in dairy calves received perioperative analgesics [7]. A similar survey done in the UK showed that only 57% of adult cattle that underwent cesarean section and laparotomy received epidural anesthesia and/or postoperative analgesics [8]. A web-based survey of members of American Association of Bovine Practitioners and Academy of Veterinary Consultants of the United States was conducted regarding castration methods, adverse events, and husbandry procedures [9]. The survey results indicated that only one of five surveyed participants provided an analgesic or local anesthetic at the time of castration [9]. In 2013, a survey of Brazilian large animal veterinarians indicated that 84% of them believed their knowledge of recognition and treatment of pain to be insufficient, and only 58.5% of the cattle they treated received preoperative analgesics for laparotomy as compared to the 72.9% for their equine patients [10]. Bradbury et al. [11] reviewed 233 papers on pain management in pigs undergoing experimental surgery, which would later transition to apply to human medicine due to the similarities of the physiology between pigs and humans. A total of 193 of the 233 papers described the use of drugs with analgesic effects but only 87 papers described the use of analgesics postoperatively. None of the papers described the justification for the analgesic chosen and only 23 papers provided an assessment of postoperative pain management. The authors concluded that postoperative pain management in pigs was either under-reported or underused even though the surgical procedures performed would have very likely caused a similar degree of pain in humans. Furthermore, the description of analgesics used, when given, were too limited to provide useful information to other researchers or veterinarians performing similar procedures [11]. In a recent report, multiple professional organizations and beef and dairy producers in the USA indicated via online survey that the frequency of use of analgesics increased as cattle age increased, regardless of the procedure or disease [12]. Veterinarians were more likely to administer analgesics, either locally or systemically, than producers for routine procedures such as surgical castration and dehorning. While all respondents recognized the long-term benefits of using analgesics in cattle, perceived federal regulations,

lack of trained personnel to administer analgesics, and cost of the analgesics continue to be the limiting factors for routine pain management in cattle [12]. Apparently, there is a need for animal caretakers, producers, and veterinarians to better recognize pain associated with disease and to promote pain management. Awareness of the need for proper pain management of farm animals has prompted researchers worldwide to promote studies of objective methods to recognize and evaluate pain responses, and develop effective and safe analgesics.

Analgesics commonly used in veterinary practice today include local anesthetics, α_2 agonists, NSAIDs, opioids, and NMDA antagonists. These analgesics can be administered alone or in combination. The advantage of combining different classes of analgesics is the potentiation of each drug's analgesic effect (synergism). Combining different classes of analgesics allows reduction of the dose requirement of each drug to produce effective analgesia, which then reduces the potential for side effects of each drug. Pain perception and its signal transmission occur at different levels, that is, peripheral nociceptor site, spinal dorsal horn, and central thalamic and limbic regions. Therefore, combining analgesics acting on different mechanisms and/or receptors maximizes analgesia (multimodal analgesia). A combination of local or regional anesthesia, NSAIDs, and low doses of an opioid and/or an α_2 agonist is the most commonly practiced multimodal treatment for intra- and postoperative pain management in farm animals [13]. Pain management should be included in the context of overall case management to optimize the patient's quality of life and early return of normal physiological functions. Although analgesics may be effective in relieving pain caused by disease, they do not cure the cause of pathological tissue damage resulting from the disease. Therefore, it is imperative that the disease causing pain be appropriately treated by medication and/or surgery to remove the origin of the pain.

Currently, no medications are approved by the US Food and Drug Administration (FDA) specifically for alleviation of pain in farm animals. Flunixin meglumine is approved for use in cattle only for treatment of pyrexia and inflammation [14]. Recently, transdermal flunixin meglumine was approved by the FDA for pain control in cattle, making it the only NSAID approved for pain control in cattle. Administering a drug not approved by FDA for pain relief is considered extralabel use [14]. Under the guidelines of the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) [15], extralabel drug use is permitted for relief of suffering of pain in food animals as long as the following specific conditions are met: (i) extralabel drug use is allowed only by or under the supervision of a licensed veterinarian; (ii) extralabel drug use is allowed only for FDA-approved animal and human drugs; (iii) extralabel drug use is permitted only when the health of the animal is threatened and not for production purposes; (iv) extralabel drug use in feed is prohibited; and (v) extralabel drug use is not permitted if it results in a violative drug residue in food intended for human consumption. Therefore, pain management using analgesics not approved by the FDA can be instituted to minimize pain and suffering of farm animals only as long as the aforementioned conditions are observed. Fortunately, analgesics used today, with the exception of phenylbutazone, are short-acting, but often require repeat dosing for long-term treatment. Thus, their administrations can be terminated accordingly to avoid violative residues and to ensure protection of animal and human health [6, 16].

10.1 Local Anesthetics

Local anesthetics, particularly lidocaine, can be administered locally or intravenously to produce pain relief. These drugs produce their anesthetic effects by blocking the propagation of action potentials along nerve axons via the reversible blockade of Na^+ channels. These anesthetics can be

injected into the tissue at the surgical site to produce local anesthesia, or they can be administered in the perineural area of major nerves to produce regional anesthesia. Local anesthetics block nerve fibers in the order β fibers (motor, touch) > nonmyelinated C fibers (pain, temperature) > A fibers (motor, proprioception), with the intensity of perception diminishing in the order of pain > cold > warmth > touch > deep pressure [17]. In domestic ruminants, many surgical procedures are performed safely and painlessly under local or regional anesthesia. All local anesthetics have similar physical properties and molecular structures. Most of these drugs are weakly basic tertiary amines, and they are generally available as acid solutions of the water-soluble salts. The acid salt is neutralized in the tissue, liberating the basic drug form, which then penetrates the cell membrane and interrupts the propagation of the action potential. Therefore, local anesthetics are less effective in inflamed tissue with lower pH because less liberation of the basic form of the drug occurs [18]. A painful, stinging sensation on injection has been reported due to the acid nature of local anesthetics. This stinging sensation can be ameliorated by adding 5 ml of 8.5% sodium bicarbonate to 50 ml of 2% lidocaine solution (1:10 ratio) [19]. There are two types of local anesthetics: ester local anesthetics (e.g. procaine, tetracaine) and amide local anesthetics (e.g. lidocaine, mepivacaine, bupivacaine, ropivacaine). Amide local anesthetics are the most commonly used.

Administration of local anesthetics prior to castration in young calves was shown to have beneficial effects such as reduced distress and improved incisional healing, though no significant improvement of average daily gain was observed [20–23]. Lidocaine in 2% injectable solution is the only local anesthetic approved by the FDA for use in cattle. It is approved for epidural administration with a maximal volume of 15 ml or for nerve blocks for volume up to 20 ml [16]. Lidocaine is the most popular local anesthetic, with onset of effect occurring within 5 minutes and a duration of 0.75–2 hours. Epinephrine induces vasoconstriction in the tissue surrounding the injected area and can be used with lidocaine to prolong the anesthetic duration of lidocaine by reducing absorption and removal of the drug by the blood circulation from the injection site. Epinephrine (1:200000–1:50000) at concentrations of 5–20 $\mu\text{g/ml}$ can be added to lidocaine solutions [24, 25]. For sheep, the maximum concentration of epinephrine that can be added to lidocaine is 12.5 $\mu\text{g/ml}$ of total solution [26]. However, potential side effects associated with addition of epinephrine to lidocaine include lack of revascularization of the wound edge and tissue necrosis when injected subcutaneously, and possible spinal cord ischemia when administered intrathecally or epidurally [27, 28]. When administered at 1.5 mg/kg intravenously to adult beef cows, lidocaine has a plasma half-life ($t_{1/2}$) of 1.06 ± 0.70 hours, a volume distribution of 4.6 ± 2.1 l/kg, and an elimination $t_{1/2}$ of 1.52 ± 0.94 hours. When 100 ml of lidocaine was infiltrated subcutaneously for inverted-L nerve blocks to Holstein cows, the maximum plasma concentration was reached at 0.52 ± 0.23 hours with a significant longer elimination $t_{1/2}$, compared to that when the drug was administered intravenously (4.2 ± 1.7 hours) [29]. Other amide local anesthetics such as mepivacaine (5 mg/kg, 1.5–3 hours) and bupivacaine (2 mg/kg, 4–8 hours) can be used for procedures that require a longer duration of local anesthesia [30]. Bupivacaine is believed to have greater cardiotoxicity than lidocaine and mepivacaine [31]. Bupivacaine is not recommended for routine clinical use in cattle because the drug is reported to be toxic to cattle, particularly in cases of accidental IV administration [19].

Administration of a large single dose or repeated small doses of local anesthetics can result in toxicity, particularly in neonates and young patients. Clinical signs of toxicity include nystagmus, muscle fasciculation, CNS stimulation progressing to opisthotonos and convulsions, hypotension, respiratory arrest, circulatory collapse, and death [18]. The maximum calculated safe dose of lidocaine was reported to be 13 mg/kg in one study [32]. In another study, accumulated IV doses of 5.8, 18, and 42 mg/kg induced signs of toxicity in adult, neonatal, and fetal sheep, respectively [33]. IV

infusion of mepivacaine in sheep induced convulsions at doses of 7.5–7.9 mg/kg and cardiovascular collapse at doses as high as 52–69 mg/kg [34]. Bupivacaine is approximately four times more potent than lidocaine. Therefore, a 0.5% solution of bupivacaine produces the same degree of neuronal blockade as a 2% solution of lidocaine. Anderson and Edmondson [19] recommended a lower maximum safe lidocaine dose of 10 mg/kg for cows undergoing cesarean section since a large volume of lidocaine is required to produce effective infiltration nerve blocks. Because small ruminants appear to be more likely to experience lidocaine toxicity, a maximum safe dose of 4 mg/kg is recommended [19]. Ewing [35] suggested a maximum dose of 6 mg/kg for lidocaine and mepivacaine, and 2 mg/kg for bupivacaine for small ruminants. With the maximum safe dose in mind, veterinarians should dilute lidocaine and mepivacaine solutions to 1 and 0.5%, respectively, to prevent overdosing in lambs and kids [35]. Diazepam (0.1–0.5 mg/kg IV) should be administered if seizure activity or convulsions caused by accidental overdose persist longer than 1–2 minutes [31, 36]. Ropivacaine is a newer local anesthetic with a duration of effect similar to bupivacaine (6–8 hours) but lower risk of cardiotoxicity than bupivacaine and less vasodilation than lidocaine [18]. Please refer to Chapter 12 for withdrawal times for lidocaine.

10.2 Systemic Pain Management

10.2.1 Opioid Analgesics

Opioid analgesics such as morphine, meperidine, fentanyl, buprenorphine, and butorphanol have been used for pain management in farm animal species. These drugs bind to μ , κ , or δ (OP3, OP1, or OP2) opioid receptors located on neuronal cell membranes. Binding of an opioid to these receptors triggers cellular changes that hyperpolarize the cell membrane and inhibit spinal pain transmission. Activation of μ receptors results in depletion of intraneuronal substance P, which reduces overall inflammation and neural pain transmission. There are opioid receptors located centrally in the hypothalamus, brain stem and spinal cord, and, peripherally, in joints and the cornea. Therefore, opioid analgesics can be administered either systemically for action on the brain or they can be deposited close to the site of action and produce their effects at all levels of pain pathways. For example, parenteral administration of an opioid provides analgesia at the central supraspinal level, intra-articular injection relieves joint pain, and epidural administration provides pain relief at the level of the spinal cord. Side effects of opioid analgesics such as respiratory depression, decreased GI motility and increased GI emptying time, increased appetite, sedation, euphoria, and nausea are also associated with activation of μ receptors [37]. Tachycardia and hyperexcitability develop occasionally when high doses of opioids are administered to farm animal species. Interestingly, hyperexcitability, though commonly observed in other species, does not occur as frequently in ruminants when administered at the recommended dose [38]. Most opioids used in veterinary practice are classified as either pure μ agonists (morphine, meperidine, and fentanyl), partial μ agonists (buprenorphine), or agonist/antagonist (butorphanol). Butorphanol is classified as agonist/antagonist because it possesses agonistic effects on κ receptors but antagonistic effects on μ receptors. Thus, butorphanol should not be administered at the same time as a pure μ agonist such as morphine because these two drugs compete for binding at μ receptor sites and butorphanol can antagonize the pharmacological effects of morphine, including analgesia. Unlike in other species, opioids have not been commonly prescribed for analgesia in farm animal species due to their controlled substance status and questionable effectiveness, although they have proven to provide effective pain relief in response to thermal and pressure stimulations [39–43].

Morphine, a pure μ opioid agonist, is effective in relieving mild pain in ruminants. Good analgesia only occurred in one-third of the farm animals receiving morphine [2]. Morphine should be administered parenterally, not orally, to ruminants because the drug is inactivated by the ruminal microflora. Doses of 0.05–0.5 mg/kg every 4–6 hours by IV, intramuscular (IM), or subcutaneous (SC) route are recommended [38, 44]. Superior analgesia produced by morphine was reported when administered at doses as high as 10 mg/kg to goats [38], even though 0.5 mg/kg IM is the dose recommended for use in goats [45]. Due to the slow onset of analgesic effect of morphine as a result of low lipid solubility (10 minutes IV, 20 minutes IM), an initial IV administration of the drug is recommended when significant pain is expected after surgery and maintenance of analgesia can be continued with IM administration or constant rate infusion (CRI) of a low IV dose of morphine. Large IV doses of morphine have been reported to cause a reduction of ruminoreticular contractions for up to 20 minutes [46]. However, GI side effects were not observed when morphine was administered intravenously at 0.1 mg/kg to cattle [46]. A low-dose CRI of morphine maintains constant effective blood level but minimizes the risk of inhibition of ruminoreticular contraction [44]. Please refer to Chapter 12 for withdrawal times for morphine.

Meperidine hydrochloride is a synthetic opioid with an analgesic potency only 10–50% of that of morphine. Meperidine produces mild sedation and analgesia. Its administration has been associated with histamine release [47]. In yearling goats, meperidine (10 mg/kg IM) can be used as a preanesthetic analgesic given 10 minutes before induction of anesthesia with thiopental. After intubation, this combination provides 20 minutes of surgical anesthesia with complete recovery occurring in 90 minutes [48].

Fentanyl is a pure μ agonist similar to morphine with a potency that is approximately 75–100 times that of morphine. Fentanyl can be administered parenterally or transdermally. When administered parenterally, fentanyl induces analgesia within 5 minutes with a short duration of 20 minutes [38]. IV administration of fentanyl has been associated with abnormal behaviors and adverse effects such as pica, stall pacing, nystagmus, hyperexcitability, mania, ataxia, sedation, bradycardia, and respiratory depression [38, 49]. Transdermal patches are available at 0.025, 0.05, 0.075, and 0.1 mg/hour doses. A 0.05 mg/hour patch is an appropriate dose for a 30–50-kg (66–110-lb) goat [49]. Onset of analgesia is observed 18–24 hours after placement, and each patch lasts approximately 3 days. A new patch should be placed 48 hours after the first one has been applied. Variable absorption of fentanyl from the patch limits its clinical usefulness [49]. Contrary to the report in goats, transdermal fentanyl produced superior analgesia to intermittent administration of IM buprenorphine in sheep [50]. Maximum plasma concentration was reached at 12 hours following the placement of the patch with the concentration maintained above 0.5 ng/ml for 40 hours. In addition to effective analgesia, fentanyl-treated sheep required less preanesthetic sedation to allow for tracheal intubation [50, 51]. When compared to intermittent IM administration of buprenorphine (0.01 mg/kg every 8 hours), transdermal fentanyl (2 μ g/kg/hour) applied 24 hours prior to surgery in pregnant ewes produced more profound analgesia and a shorter anesthesia recovery time [52]. However, signs of excitement such as vocalizing, paddling, head jerking, and multiple unsuccessful attempts to stand were observed during the recovery period with fentanyl treatment but light manual restraint was sufficient to prevent the ewes from injuring themselves until signs of excitement subsided [52]. In cattle, application of 0.05–0.1 μ g/kg of fentanyl patch for pain relief was shown to be clinically beneficial [19]. Consistent skin absorption from fentanyl patches has also been reported when placed on the medial antebrachium in llamas [53]. In swine, a fentanyl 75–100 μ g/hour patch can be applied to the interscapular region to provide analgesia in 20–40-kg (44–88-lb) pigs postoperatively [38]. Effective plasma concentrations of 0.5 and 2 ng/ml can be achieved within 24 hours following application of the transdermal patch [38]. A fast-acting

analgesic should be given to provide pain relief due to slow absorption of fentanyl from a transdermal patch [2]. It is very important that the hair on the area intended for placement of the patch be clipped and the skin cleaned completely to ensure secure adherence of the patch. Excessive hair, dirty skin, or insecure adherence of the patch may result in inconsistent and unreliable absorption of the drug and subsequently suboptimal analgesic effect. Keep in mind that rumenosalivary recycling may result in bioavailability exceeding 100% and thus prolong the effects of fentanyl. This may pose a problem in establishing accurate withdrawal times [49].

Tramadol is a synthetic analog of codeine and morphine [54]. Tramadol produces analgesia by its action through central opioid, adrenergic, and serotonergic receptors [55]. It is classified as scheduled IV drug in 2014. Tramadol offers advantages over other opioids. It causes less respiratory depression and has low potential for human abuse [54, 56]. Furthermore, tramadol is reported to produce less CNS excitation in horses [57]. Tramadol has been shown to be effective in treating moderate to more severe postoperative pain in humans and dogs [58, 59]. However, clinical experience of this author indicated that only minimal analgesia was observed when tramadol was administered to dogs. Tramadol has low affinity for opiate μ receptors, and its dose requirement to produce similar degree of analgesia for moderate pain is 10 times that of morphine [60]. For more severe pain, tramadol administered at the same dose ratio is less effective than morphine [61]. One of the metabolites of tramadol, *O*-desmethyltramadol, is reported to be six times more potent in analgesic effect and 200 times more potent in binding ability to μ receptors than tramadol [62]. In calves undergoing a disbudding procedure, either IV tramadol (4 mg/kg) or rectal suppositories [200 mg/50–60 kg (110–132 lb)] provided effective analgesia to prevent head shaking, ear flicking, and head rubbing, indicators of pain from the application of caustic paste following disbudding [63]. Orally administered tramadol is well absorbed in humans, dogs, and cats with bioavailabilities of 70%, 65%, and 93%, respectively [64–66]. Lower absorption with a bioavailability of 23–37% and 5.9–19.1%, respectively, was reported following a single oral dose of 2 mg/kg in goats and 11 mg/kg in alpacas [67, 68]. A large volume-to-surface ratio, constantly high content of solid matter, and complex microflora and microfauna in the rumen were suggested to be the causes for the lower oral absorption of tramadol in goats and alpacas [67, 68]. A higher gastric pH of 6.8 in the rumen [69] as opposed to pH of 1.0–2.0 in the monogastric stomach [70] in the presence of a pK_a value of 9.41 of tramadol results in a greater percentage of nonionized tramadol in plasma and enterohepatic recycling in ruminants, which increase absorption of the drug and are believed to be the primary factors responsible for the high plasma tramadol concentrations in goats (542.9 ± 219.5 ng/ml) and alpacas (1202 ± 1319 ng/ml) [67, 68]. In humans, plasma concentrations of 100–150 ng/ml are recommended as the minimum effective concentration of tramadol in relieving mild to moderate pain [58, 64]. The elimination $t_{1/2}$ following oral administration was 2.67 ± 0.54 hours in goats, which is shorter than that of humans [56] but longer than that of horses and alpacas [57, 68]. However, IV administration of tramadol at 2 mg/kg to these goats did not provide effective pain relief as the plasma concentration rapidly declined below minimum effective concentrations [67]. Adverse effects such as hyperexcitability, hyperesthesia, tremors, and ataxia occurred soon after the start of IV administration of tramadol over a period of 5 minutes, but side effects quickly dissipated 15 minutes after the termination of IV infusion to alpacas [68]. These adverse effects were not observed following oral administration or slower IV administration over a period of 10 minutes. In alpacas, two of the metabolites, *O*-desmethyltramadol and *N*-desmethyltramadol, have slightly longer plasma $t_{1/2}$, 1.53 ± 0.68 and 1.38 ± 0.48 hours, respectively, than tramadol itself (0.849 ± 0.463 hours) [68]. Tramadol is capable of crossing the placenta and appears in the fetal circulation, and low concentrations of the parent drug and its active metabolites were also detected in human breast milk within 16 hours after administration [56]. A milk or

meat withdrawal time for tramadol has not been established at this time. In pigs anesthetized with xylazine (2.5 mg/kg IM) and ketamine (25 mg/kg IM), adding tramadol (5 mg/kg IM) to the anesthetic combination improved the quality of anesthesia and prolonged the duration of analgesia (43.7 ± 15.5 minutes vs. 32 ± 13.3 minutes) without alteration of physiologic parameters and prolongation of recovery from anesthesia [71]. Tramadol (1.6 mg/kg IM) has also been combined with xylazine (1.2 mg/kg IM) and telazol (3 mg/kg IM) to produce general anesthesia with excellent muscle relaxation and analgesia for approximately 80 minutes in pigs [72].

Buprenorphine is classified as a partial μ agonist with an analgesic potency that is 25 times that of morphine. Buprenorphine is poorly absorbed from the GI tract. Due to its high affinity and low specificity for the μ receptors, opioid antagonists are ineffective in reversing buprenorphine's effects. Onset of analgesia occurs in 45 minutes with a duration of 240 minutes following IM administration of buprenorphine (0.005–0.01 mg/kg). Propulsive walking, rapid and frequent head movements, chewing, and hypersensitivity to auditory and visual stimuli were observed in sheep receiving buprenorphine [39]. This author (Lin) has used IM buprenorphine at 0.01 mg/kg administered to goats every 6 hours following orthopedic surgery and observed satisfactory analgesia. No signs of CNS excitation as described in sheep were observed in the goats. A 3-day meat withdrawal is suggested for buprenorphine [38]. The recommended dose of buprenorphine in pigs is 0.01–0.05 mg/kg IM or IV every 6–12 hours [73]. When compared to etorphine (0.003 mg/kg IM) and pethidine (20 mg/kg IM), buprenorphine (0.12 mg/kg IM) produced longer duration of analgesia (7–24 hours) in pigs [74]. The analgesic effect of buprenorphine is deemed better than that of pethidine but not as good as etorphine [74]. Buprenorphine has been used in pigs following thoracotomy surgery at 0.01–0.04 mg/kg administered intramuscularly to provide adequate pain relief (Lin, personal observation).

Butorphanol is a κ agonist and μ antagonist with an analgesic potency approximately three to five times that of morphine. Butorphanol has a unique “ceiling effect”, that is, after effective action has been attained further increases in doses do not increase or enhance the degree of desirable pharmacologic effect [75]. Butorphanol may cause slight CNS stimulation in farm animal species, especially when administered to animals that are not in pain. Twitching of the facial muscles, lips, and head may occur. Butorphanol is the most frequently used opioids in farm animals. The recommended dose of butorphanol is 0.02–0.05 mg/kg IV or SC every 4–6 hours. Jones (2008) [2] commented that butorphanol is the best analgesic for ameliorating established pain and is capable of providing excellent visceral analgesia in 80% of the ruminant patients. Butorphanol can be given alone in sheep and goats to produce light sedation. No behavioral effects were observed when butorphanol was administered intravenously at 0.05 mg/kg in sheep, but ataxia was observed at 0.4 mg/kg while excitement occurred at 0.1–0.2 mg/kg [42, 76, 77]. In cattle, tremor and propulsive walking occurred following IV administration of butorphanol, but the signs disappeared within 30 minutes [38]. Butorphanol is frequently used in combination with a sedative or a tranquilizer to produce standing sedation and analgesia for minor surgery and diagnostic procedures. It can also be administered postoperatively for pain relief. In sheep and goats, xylazine and butorphanol can be administered simultaneously to produce deep sedation and recumbency lasting for as long as 60 minutes. In dairy cows, the $t_{1/2}$ of 0.25 mg/kg IV is reported to be 82 minutes [78]. Adding xylazine (0.05 mg/kg) and ketamine (0.1 mg/kg) to butorphanol (0.025 mg/kg) did not affect the elimination $t_{1/2}$ of butorphanol (71.28 ± 7.64 minutes) when the combination was administered intramuscularly to Holstein calves immediately prior to castration and dehorning [79]. This combination has been used successfully to provide analgesia for surgical procedures on very fractious cattle and also in cattle suffering extreme pain caused by disease [19]. Interestingly, when IV butorphanol (0.07 mg/kg) and xylazine (0.02 mg/kg) were administered to weanling bulls at the time of castration, the treatment did not offer significant beneficial effects in reducing distress and

improving growth performance after surgery [80]. In pigs, butorphanol is recommended at 0.1–0.3 mg/kg IV or IM every 4 hours, doses slightly higher than for other farm animal species [73]. Please refer to Chapter 12 for withdrawal times for butorphanol.

10.2.2 Nonsteroidal Anti-inflammatory Drugs

NSAIDs are used for their analgesic, antipyretic, and anti-inflammatory properties through inhibition on cyclooxygenase (COX), lipoxygenase, and thromboxane enzymes. The COX acts on arachidonic acid to release prostaglandins and other mediators of inflammation, and thus COX inhibitors like NSAIDs prevent the production of these mediators. There is evidence indicating NSAIDs may produce analgesia by central inhibition of pain response involving α_2 and μ receptors. There are two COX isoforms, COX-1 and COX-2. The COX-1 isoform is present in normal peripheral tissues and CNS. Its expression is enhanced by pain and inflammatory mediators. The COX-2 isoform is expressed in the CNS but only becomes the major enzyme for prostaglandin synthesis after induction by factors released from cell damage and death. Maximal COX-2 mRNA expression occurs in peripheral tissues 2–8 hours after induction [81]. NSAIDs appear to have differential activity according to their affinity for the two COX isoforms. For example, flunixin meglumine, ketoprofen, and phenylbutazone are nonspecific COX inhibitors, whereas etodolac and carprofen are selective COX-2 inhibitors. Flunixin meglumine is an excellent visceral analgesic, and phenylbutazone is very effective in relieving musculoskeletal pain. Clinical observation suggests specific COX-2 inhibitors are not effective analgesics in ruminants [2, 82]. NSAIDs are available in oral formulation, making oral administration an alternative route to provide pain relief. However, there are significant differences in the clearance of these drugs between animal species and age groups. Also, some of the NSAIDs have a narrow margin of safety in that therapeutic indexes are relatively close to their toxic indexes. Therefore, extrapolation of alternative NSAID dosing regimens from one species to another is extremely dangerous and not recommended [83].

Aspirin (acetylsalicylic acid) and sodium salicylate are both salicylic acid derivatives and were the first NSAIDs used for their analgesic, antipyretic, and anti-inflammatory effects. Though neither drug has been approved for use in food animals by the FDA, aspirin is frequently administered at 100 mg/kg, twice daily orally, for treatment of fever and minor joint and muscle pain. Aspirin ionized extensively in the rumen pH with an ionized-to-nonionized ratio of 1000:1, indicating a low oral bioavailability and slow absorption of the drug following oral administration in ruminants [84, 85]. It is believed that the rumen serves as a slow-release reservoir for oral aspirin absorption, reflecting the longer elimination $t_{1/2}$ of 3.70 ± 0.44 hours following oral administration of salicylic acid as compared to 0.54 ± 0.04 hours following IV administration of sodium salicylate to adult dairy cows [84, 86]. In humans, minimum effective serum concentration of salicylic acid to relieve mild pain resulting from headaches, aches, and pain is 30 $\mu\text{g/ml}$, but 100 $\mu\text{g/ml}$ is required to relieve pain caused by arthritis. In cattle, only oral administration of 100 mg/kg of aspirin resulted in a serum concentration above 30 $\mu\text{g/ml}$ while 50 mg/kg did not. Therefore, 100 mg/kg of sodium salicylate is recommended to maintain serum concentration above 30 $\mu\text{g/ml}$. However, conflicting reports showed that sodium salicylate relieved pain caused by nonsuppurative tarsitis in two cows but did not relieve pain in a bull suffering suppurative tarsitis [84]. There is no report on salicylic acid-induced clotting deficit in cattle [87]. For pigs, aspirin is recommended at a dose range of 10–20 mg/kg administered orally every 4–6 hours [73]. Please refer to Chapter 12 for withdrawal times for aspirin.

Flunixin meglumine (banamine) is a COX-1 inhibitor. It is approved by the FDA for use in beef and lactating dairy cattle for fever and inflammation associated with respiratory diseases,

endotoxemia, and acute bovine mastitis [14]. Recently, transdermal flunixin meglumine was approved by the FDA for pain control in cattle, making it the only NSAID approved for pain control in cattle. Flunixin meglumine is approved for IV administration at a dose of 1.1 mg/kg BID or 2.2 mg/kg SID, and this dosing regimen may produce analgesia for 6–12 hours. This dose can be repeated for up to 3 days. In calves undergoing castration with a Burdizzo clamp or surgical removal, effective pain relief was produced by flunixin meglumine administered IV along with epidural lidocaine. The report showed a significant decrease (50%) in plasma cortisol concentration and that the calves receiving flunixin meglumine had better steps and stride 6–8 hours into the postoperative period compared to the nontreated calves [88, 89]. Flunixin meglumine alone (2.2 mg/kg IV) administered 20 minutes before castration resulted in a mild decrease (20%) in plasma cortisol concentration. Several studies showed that concurrent administration of epidural lidocaine or xylazine enhanced the analgesic effect of flunixin meglumine [88–91]. Nonetheless, significantly better appetite, defecation, and milk production have been observed in cows receiving flunixin meglumine 24 hours before and after surgical correction of a left displaced abomasum [92]. In cattle, significant myonecrosis and prolonged tissue residues have been reported when flunixin meglumine is administered intramuscularly [14] (refer to Chapter 12 for drug withdrawal times). Thus, the drug should only be administered intravenously in cattle. However, this route of administration not only causes stress to the animal but also requires special training for personnel performing the task. Transdermal flunixin meglumine is given as a pour-on for transdermal absorption. It is reportedly to have a bioavailability of 37–48% and a plasma $t_{1/2}$ of 6.42–7.16 hours in calves without painful stimulations [93, 94]. In dehorning calves, Kleinhenz et al. [94] demonstrated that pain-induced sympathetic nervous stimulation with subsequent vasoconstriction caused a reduction of blood flow to the skin surrounding the horns. As a result, blood perfusion to the tissues surrounding the base of the horns decreased, which in turn decreased the absorption and bioavailability of the transdermal flunixin meglumine [94]. Furthermore, evaluation of pain biomarkers following dehorning indicated that transdermal flunixin meglumine alone did not provide effective analgesia to dairy calves either intraoperatively or postoperatively, as indicated by the lack of significant difference in the mechanical nociceptive threshold and plasma concentrations of cortisol and substance P [95]. However, local anesthetic blockade was not performed prior to dehorning in these two studies, as the intent of the studies was to assess the response of the biomarkers and the impact of pain on the pharmacokinetics of transdermally administered flunixin meglumine [94, 95]. Concurrent use of local anesthetic blockade and transdermal flunixin meglumine provided perioperative multimodal analgesia. The ease of administration and FDA-approved transdermal flunixin meglumine allows producers to formulate a method that does not require using a needle to provide analgesia without additional personnel training. Flunixin meglumine has become the second most common residue violation (the first being penicillin) in cull dairy cows. Veterinarians should address and emphasize the importance of following label instruction of the drug to farm personnel [96]. Doses of 2–4 mg/kg IV or SC once daily for flunixin meglumine are recommended for use in pigs [73]. However, 1–4 mg/kg IV, IM, or SC every 12 hours is recommended for pet pigs [97]. Please refer to Chapter 12 for withdrawal times for flunixin meglumine.

Phenylbutazone is clinically more effective in relieving pain associated with musculoskeletal injuries and chronic osteoarthritis than flunixin meglumine. Phenylbutazone is a drug with high level of regulatory concern due to lack of predictable withdrawal times. The drug is highly protein-bound with a very long elimination $t_{1/2}$ in cattle (30–80 hours) and sheep and goats (15–20 hours) when compared to that of other large animal species. When administered to cattle at a loading dose of 24 mg/kg followed by a single daily dose of 12 mg/kg, the drug was still detectable in milk 82 hours after administration. At this time, the use of phenylbutazone in female dairy cattle older

than 20 months of age is strictly prohibited, and its use in other milk- and meat-producing animals is strongly discouraged due to the concern over human consumption [98]. Phenylbutazone is capable of crossing the blood–placenta barrier, and concentration of the drug can be detected in calves born to treated cows. Continued exposure through the milk may lead to detectable plasma concentration in newborn calves with an elimination $t_{1/2}$ as long as 4 days [99]. In addition, the elimination $t_{1/2}$ of phenylbutazone has been reported to be age dependent, and it is twice as long in 1-month-old calves compared to 3-month-old calves [100]. Thus, the administration of phenylbutazone in very young calves is also discouraged. Phenylbutazone is believed to be a carcinogen and has been reported to cause blood dyscrasias (e.g. aplastic anemia, leukopenia, agranulocytosis, and thrombocytopenia), and the death rate in humans that develop aplastic anemia can be as high as 94% [101]. There are reports indicating that an idiosyncratic serum sickness, a type III hypersensitivity reaction, results from exposure to food residue of phenylbutazone, but no threshold concentration of phenylbutazone has been established [102]. Extralabel use of phenylbutazone is not justifiable under the AMDUCA guidelines because another NSAID (flunixin meglumine) is available and approved for use in food animals. It is recommended that phenylbutazone be reserved for valuable beef breeding stock with severe chronic disease when slaughter is not an option but temporary relief of pain is necessary for embryo or semen collection followed by euthanasia. A meat withdrawal time of a minimum of 45 days for the first dose of phenylbutazone with another 5 days added to each additional day of therapy beyond the first is recommended with a duration of up to 6–8 months if needed [2, 14, 83]. Although there are no NSAIDs approved for use in small ruminants, flunixin meglumine is labeled for use in food animals and should be used preferentially over phenylbutazone.

Ketoprofen is not approved by the FDA for use in food-producing animals. In Canada and European countries, ketoprofen is approved for use in alleviation of inflammation and pain associated with arthritis and traumatic musculoskeletal injuries, and also as adjunctive treatment for pain, fever, and inflammation associated with acute mastitis [103]. Compared to other NSAIDs, ketoprofen has a short plasma $t_{1/2}$ (30 minutes) and a small volume of distribution (0.21/kg), with 80% of the parent drugs eliminated in urine within 24 hours [103, 104]. Ketoprofen comes as a racemic combination of 50:50 ratio of R(–) and S(+) enantiomeric forms in the commercial formulation. It is reported that the S(+) isoform is approximately 250 times more potent than the R(–) isoform in its ability to inhibit prostaglandin E_2 (PGE₂). Approximately 31% of the R(–) isoform is converted to the S(+) isoform following IV administration in calves [105]. In sheep, the inhibition of PGE₂ by the S(+) isoform lasts four times longer than that of the R(–) isoform [106]. The concentration of ketoprofen in milk, even at peak plasma concentration, was below the sensitivity level of the analytical test, suggesting that the drug can be used safely in milk-producing ruminants with a short and predictable milk withdrawal time. The Food Animal Residue Avoidance Databank (FARAD) recommends a 24-hour and 7-day milk and meat withdrawal times, respectively [107]. Some clinicians believe that ketoprofen does not have any advantage over flunixin meglumine for treatment of inflammatory diseases in ruminants [83]. However, if the criteria for extralabel use can be met, ketoprofen can be administered at 3.3 mg/kg SID for up to 3 days. In 4- to 8-week-old calves, ketoprofen (3 mg/kg per os [PO]) has been shown to reduce pain-related behaviors when administered prior to and at 2–7 hours post the hot-iron dehorning procedure [108]. Combining ketoprofen and a cornual nerve block with or without xylazine greatly reduced the distress associated with dehorning and disbudding in calves as indicated by the reduction of the cortisol response to the surgery [109, 110]. Comparing intratesticular lidocaine alone to the combined technique of ketoprofen with intratesticular lidocaine for castration in calves less than 4 months old, the combined technique completely inhibited cortisol response to the surgery, while

lidocaine alone did not inhibit cortisol response [111]. In pigs, 1–3 mg/kg IV, IM, or PO of ketoprofen every 12 hours is recommended [73, 97].

Carprofen has greater potency and lower ulcerogenicity than phenylbutazone or aspirin [112]. Carprofen is approved in European countries for use as an adjunct treatment to antimicrobial therapy to reduce clinical signs in acute infectious respiratory disease and acute mastitis in cattle [113]. Similar to ketoprofen, carprofen has two enantiomer isoforms with the S(+) isoform approximately 100 times more potent than the R(–) isoform in inhibiting COX-2 enzyme in a canine study [114]. However, the effect of carprofen on both COX-1 and COX-2 enzyme activities is considered poor [112]. In sheep, the elimination $t_{1/2}$ of carprofen was 26.1 and 33.7 hours when administered intravenously at 0.7 and 4 mg/kg. Plasma concentration greater than 1.5 µg/ml corresponded to the effective analgesic effect of carprofen. When administered at 4 mg/kg IV, carprofen maintained therapeutic plasma concentrations for longer than 72 hours [115, 116]. Measurable amounts of carprofen were detected in the milk of cattle with mastitis following a single IV dose of 0.7 mg/kg [117]. In another study, no measurable milk concentrations of greater than 25 µg/ml were detected when carprofen was administered at 1.4 mg/kg IV to healthy cows. No milk withdrawal time for carprofen is needed in European countries. Based on a maximum residue level of carprofen of 500 µg/kg in muscle and 1000 µg/kg in liver and kidney, a meat withdrawal time of 21 days is recommended following a single injection of 1.4 mg/kg IV in European countries [118]. In calves, carprofen (1.4 mg/kg IV) alone administered 20 minutes before castration using a Burdizzo clamp technique decreased plasma cortisol concentration by 19% [119], but a 59% reduction was observed when carprofen was combined with epidural lidocaine [88]. Similar to ketoprofen, carprofen is believed not to have any advantage over flunixin meglumine, and its use in food-producing animals is not recommended due to its prolonged clearance time and detectable milk distribution. Doses of 2–4 mg/kg IV or SC once daily are recommended for administration of carprofen in pigs [73]. Wolff [97] suggested that administration of carprofen at 2–3 mg/kg IM, SC, or PO every 12 hours is appropriate for treatment of pigs. Carprofen administered orally at 2 mg/kg every 12 hours for 3 days provided effective analgesia in a pig suffering severe joint pain (Lin, personal observation).

Meloxicam preferentially, though not specifically, inhibits COX-2 enzymes. Meloxicam (0.5 mg/kg IM or SC) is approved as adjunct treatment of cattle with acute respiratory diseases, acute mastitis, or diarrhea in several European countries and the UK [120]. A small animal formulation is approved and marketed in the USA. Meloxicam has been proven to effectively relieve pain in calves resulting from castration, dehorning, and diarrhea [121–123]. Good oral bioavailability with maximum plasma concentration occurred at 10–12 hours with an elimination $t_{1/2}$ of 27.5 hours after oral administration of meloxicam at 1 mg/kg to 3-month-old Holstein calves [124]. Other evidence supporting the effectiveness of meloxicam (0.5 mg/kg IV) in ameliorating pain includes reduced heart rate and respiratory rate, and improved weight gain in treated calves when compared to untreated calves following dehorning and castration procedures [125–127]. In lactating goats, the elimination $t_{1/2}$ following IV and IM administration of 0.5 mg/kg of meloxicam was reported to be 9.96 and 10.83 hours, respectively. The study also showed complete absorption of the drug, as reflected in 105% bioavailability following IM administration [128]. The authors suggested that once-a-day dosing at 0.5 mg/kg may be sufficient to sustain long duration of analgesia based on the high IM bioavailability, long elimination $t_{1/2}$, and a mean plasma concentration at the steady state above the values of average therapeutic concentrations [128]. It is believed that meloxicam may be useful for sustained pain relief of greater than 3 days at 0.5–1 mg/kg orally every 24–48 hours [19]. A possible fatal anaphylactoid reaction in an Ayrshire cow to IV meloxicam was reported [129]. The cow appeared agitated and had profuse lacrimation, bilateral periocular edema, and chemosis within 10 minutes after IV administration. She became markedly ataxic and assumed

a recumbent position. Hyperventilation rapidly progressed to blood-tinted foaming at the mouth, tachypnea, and then dyspnea with cyanotic oral, nasal, and vulvar mucous membrane. The cow was euthanized due to the severity of the clinical signs [129]. Although manufacturers reported that the anaphylactoid reaction to NSAIDs is extremely rare with possibility incidence of less than 1 per 30 000 administrations, veterinarians should be aware of this possible reaction and be prepared to institute emergency treatment when an incident occurs [129]. Preemptive administration of meloxicam (0.4 mg/kg IM) to pigs not only reduces stress prior to castration but also provides analgesia following surgery [130]. Similar analgesic effects evaluated by vocal characteristics and cortisol response to castration was reported in piglets when meloxicam (0.4 mg/kg IM) with or without lidocaine local anesthesia was administered 15 minutes prior to surgery [131]. Meloxicam appeared to have wide margin of safety as evidenced by administration of five times the recommended dose (2 mg/kg) for 6 consecutive days to 5- to 6-month-old pigs with no lasting adverse effects observed [132]. Please refer to Chapter 12 for withdrawal times for meloxicam.

Diclofenac, a newly introduced NSAID, is an effective analgesic for post-traumatic pain, postoperative wound hyperalgesia, pain associated with movement and swelling, and joint pain resulting from lameness in horses [133–136]. Diclofenac was reported to be an effective analgesic for treatment of acute aseptic arthritis and myositis in cattle and buffalos [136, 137], and in relieving pain caused by castration in lambs [138, 139]. In sheep, diclofenac is proven to be effective against *Brucella* species and schistosomiasis when used in combination with streptomycin, rifampicin, or tetracycline [138, 140]. The elimination $t_{1/2}$ of diclofenac following 1 mg/kg IV and IM administration to sheep were 2.84 ± 1.94 and 2.12 ± 1.60 hours, respectively. Therefore, twice or three times daily doses will be ideal to maintain an effective plasma concentration of the drug [141].

Tolfenamic acid is an anthranilic acid class of NSAIDs. The drug is approved in European countries and Canada for use in cattle for treatment of acute mastitis and respiratory tract diseases. Although there are no proven data indicating any advantage of tolfenamic acid over flunixin meglumine, it has been occasionally used extralabelly. The pharmacokinetic study in cattle showed that tolfenamic acid has a large volume of distribution (1 l/kg) and a long elimination $t_{1/2}$ (8–10 hours) [16]. Prolonged, sustained therapeutic plasma concentration of tolfenamic acid following a single injection has been attributed to the unique enterohepatic recirculation in this species. Tolfenamic acid, when administered at the recommended dose of 4 mg/kg IV, has a milk withdrawal time of 24 hours [16]. The maximum residue levels of the drug in milk and muscle, kidneys, and liver have been set at 50, 100, and 400 $\mu\text{g/kg}$, respectively. Therefore, a meat withdrawal time of 7 days for a single IV injection of 2 mg/kg in beef cattle is recommended where the drug is approved [16, 142].

Metamizole, a pyrazolone derivative, is classified as a nonacid antipyretic analgesic. It is licensed for use in cattle in European countries. When administered at 40 mg/kg IV prior to umbilical surgery in calves, evidence of analgesia was supported by significantly lower heart rate and plasma cortisol concentrations for at least 150 minutes following skin incision into the postoperative period. Repeat dosing may be required if longer duration of pain relief is needed [143].

10.2.3 Alpha-2 Agonists

α_2 agonists such as xylazine, detomidine, medetomidine, dexmedetomidine, and romifidine have been shown to produce good visceral analgesia. These drugs produce analgesic effects via their actions on the peripheral and central α_2 receptors. There are α_2 receptors located in the dorsal horn of the spinal cord, whereas stimulation of the α_2 receptors located at the periaqueductal gray area of the midbrain (site of origin of the descending inhibitory pain pathways) is responsible for the

release of norepinephrine and modulation of pain at the spinal level. In sheep, it was shown that approximately 60% of analgesia produced by IV xylazine is mediated via spinal α_2 receptors and this was supported by the evidence of prior intrathecal administration of α_2 antagonists, idazoxan or RX811059A, which resulted in a reduction of IV xylazine-induced analgesia [144]. Therefore, α_2 agonists can be administered parenterally, epidurally, or intrathecally to produce analgesia. Xylazine or detomidine is often the first choice for treatment of severe abdominal pain in colicky horses. In ruminants, IV or IM administration of sedative doses of xylazine produces dose-dependent analgesic effects, which may last up to 60–90 minutes. IM administration of dexmedetomidine (0.1 mg/kg) with or without meloxicam (0.5 mg/kg IM) and local infiltration via ring block with lidocaine in disbudding goats was reported to result in the lowest pain score and least pain-related behaviors. Goats receiving dexmedetomidine alone had the lowest cortisol level even at 5 hours after disbudding, suggesting that the drug produced lasting pain relief long after the disbudding procedure [145]. Dexmedetomidine at doses of 5, 10, 15, and 20 μ g/kg and combined with telazol (2 mg/kg) was evaluated in alpacas following IM administration [146]. Doses of 15 and 20 μ g/kg inhibited motor response to claw clamping for 30 and 40 minutes, respectively. Transient hypoxemia was observed with higher doses of dexmedetomidine during the initial 5–10 minutes, which returned to normal at 15 and 20 minutes later [146]. α_2 agonists and opioids are often used in combination to provide good analgesia. The effects of these two classes of drugs are synergistic, thus greater analgesia can be achieved at lower doses of both drugs. The analgesic effects of the α_2 agonists have been described in detail in Chapter 2.

10.2.4 Ketamine

Ketamine, at subanesthetic doses, is effective in preventing or minimizing pain resulting from windup syndrome, which is mediated through the blockade of the NMDA receptors. In addition, ketamine and its active metabolite, norketamine, have been demonstrated to bind to opioid μ and κ receptors which may be in part responsible for the analgesic effect of the drugs [147]. Result of a study in rats indicated that norketamine has one-third of the analgesic potency of ketamine [148]. Coetzee et al. [149] showed a correlation between plasma norketamine and substance P concentration in that lower substance P concentration is correlated to higher plasma norketamine concentration in calves receiving low doses of xylazine (0.05 mg/kg IV) and ketamine (0.1 mg/kg IV) for sedation and analgesia during surgical castration [149]. Ketamine has been administered at 0.1–1 mg/kg IV to alleviate acute postoperative pain in humans [150]. A plasma ketamine concentration of 1000 ng/ml is considered the minimum effective concentration for the anesthetic effect, whereas a plasma concentration of 275 ng/ml or 1/10th–1/5th of the anesthetic concentration is correlated to the drug's analgesic effect [151]. Nonetheless, Grant et al. [152] suggested that analgesia occurred at plasma ketamine concentrations of 40–150 ng/ml. In cattle receiving xylazine (0.05 mg/kg IV) and ketamine (0.1 mg/kg IV), plasma ketamine and norketamine concentrations fell below 40 and 10 ng/ml within 30 and 60 minutes, respectively, after the administration of ketamine [153]. Ketamine can be administered alone intermittently at subanesthetic doses to produce analgesia. It can also be administered in combination with another class of analgesics such as an α_2 agonist or an NSAID or as CRI to maintain long-term analgesia. For example, ketamine has been used in combination with opioids or NSAIDs at 0.25–0.5 mg/kg IM every 6–8 hours to provide pain relief for goats suffering severe pain due to burn injury, polyarthritis, or osteomyelitis [154]. Ketamine is classified as a controlled schedule III drug, and record keeping of its use is closely monitored by the DEA, which may be viewed as a disadvantage over α_2 agonists and NSAIDs. Please refer to Chapter 12 for withdrawal times for ketamine.

10.2.5 Gabapentin

Gabapentin has become a popular antihyperalgesic drug for treatment of animals suffering chronic neuropathic pain or as treatment of windup syndrome in humans, dogs, and cats. Gabapentin has a chemical structure similar to the inhibitory neurotransmitter γ -amino-butyric acid (GABA) in the CNS. The drug was developed originally for use as an anticonvulsant drug [155]. Interestingly, gabapentin does not produce its pharmacologic effects through actions on the GABA receptors. There is evidence that gabapentin produces its analgesic effect by inhibitory action on $\alpha 2\delta$ -subunits of voltage-dependent calcium-channel complexes [156]. A decrease in calcium influx in the pre-synaptic nerve terminal and inhibition of the release of the excitatory amino acid are the results of gabapentin binding with $\alpha 2\delta$ -subunit. These inhibitory effects of gabapentin were only observed in patients with hyperalgesia but not in normal patients [156]. Gabapentin has been used frequently in small animal patients suffering from chronic pain, but its use in larger animals is still limited. Doses of 3–5 mg/kg PO every 8 hours have been recommended to produce satisfactory analgesia in goats. The dose can be titrated up or down depending on the patient's response to the initial dose or dosing interval. The oral bioavailability of gabapentin in goats is believed to be better than in horses. The only reported side effects of gabapentin in humans are sedation and dizziness [157], and in dogs are sedation and ataxia [158, 159]. However, sedation appears to be insignificant following IV administration of 20 mg/kg to horses [160]. Synergism of pharmacological effects has been observed when an NSAID is administered with gabapentin [155, 161]. In 6–8-month-old beef calves, oral gabapentin (15 mg/kg) was administered concurrently with meloxicam (0.5 mg/kg) with maximum plasma concentration and elimination $t_{1/2}$ occurring at 11.67 ± 3.44 and 20.47 ± 9.22 hours [162]. Comparable pharmacokinetics were reported with oral meloxicam (1 mg/kg) and gabapentin (10 or 20 mg/kg) to lactating Holstein cows [163]. Gabapentin at 10 mg/kg requires similar times to reach maximum plasma (8 hours) and milk (12 ± 6.69 hours) concentrations as meloxicam (11.33 ± 4.12 hours). Increasing the dose of gabapentin to 20 mg/kg doubles the maximum plasma concentration of gabapentin [163]. In cattle, orally administered gabapentin is useful in relieving pain caused by deep digital sepsis and septic arthritis at 10 mg/kg every 12 hours [19]. Residual milk concentrations were detected for as long as 48 hours in cows receiving 10 mg/kg and 64 hours in those receiving 20 mg/kg [19]. In lactating Holstein cows receiving gabapentin (10 or 20 mg/kg PO) with meloxicam (1 mg/kg PO), only 0.1% and 1% of administered gabapentin and meloxicam, respectively, were excreted in the milk [164]. The concentration of either drug in the milk fell below detectable level by 3 days, therefore it is reasonable to predict a milk withdrawal time of 72 hours for oral meloxicam administered at 1 mg/kg and gabapentin up to 20 mg/kg [164]. If gabapentin is prescribed for long-term treatment of chronic pain, a meat withdrawal time of 21 days can be assumed until further pharmacokinetic data for repeat dosing become available [6, 163].

10.3 Drug Combinations for Pain Management

Similar to the technique of using different classes of anesthetics to produce balanced anesthesia (i.e. unconsciousness, analgesia, and muscle relaxation), multimodal analgesia is used to produce effective analgesia using different classes of analgesics to prevent pain transmission at multiple levels and, at the same time, minimize the side effects of each drug by reducing the dose of each drug required when used alone. For procedures that likely produce intense pain, such as castration, combinations such as xylazine (0.02 mg/kg IV) and butorphanol (0.05 mg/kg IV),

detomidine (0.01 mg/kg IV) and butorphanol (0.05 mg/kg IV), or xylazine (0.02–0.05 mg/kg IM), butorphanol (0.01–0.025 mg/kg IM), and ketamine that are often used for standing sedation can be administered at a slightly higher recommended dose of each drug intravenously to induce appropriate analgesia in farm animals [2, 165]. In calves, 2.2 mg/kg of flunixin meglumine IV once daily and 0.01 mg/kg of buprenorphine IV every 8–12 hours have been used to provide pain relief after thoracotomy surgery. A bupivacaine line block at the site of thoracotomy can be added to enhance analgesia produced by IV flunixin meglumine and buprenorphine (Lin, personal communication). Combinations of meloxicam at 0.2 mg/kg PO with buprenorphine (0.01 mg/kg IM) twice daily or carprofen (2 mg/kg PO) with buprenorphine at 0.005–0.02 mg/kg IM have been used in pigs to relieve pain due to thoracotomy or joint disease (Lin, personal communication).

10.3.1 Constant Rate Infusion

An advantage of administering the CRI of an analgesic or analgesic combination is the ability to use a low dose of analgesic(s) to maintain steady-state plasma concentration, avoid peak and trough fluctuation of the drug effect, and, most importantly, provide continuous pain relief to the patient suffering severe chronic pain.

Systemic administration of lidocaine for treatment of postoperative ileus following colic surgery in horses has increased dramatically in recent years. In these cases, lidocaine is believed to provide beneficial effects, including analgesia, via its local anesthetic effect, prevention of intestinal adhesions and ileus by promoting GI movement (prokinetic effect), and minimizing reperfusion injury of ischemic areas by its anti-inflammatory effect. In cattle, lidocaine CRI can be administered to provide long-term analgesia following laparotomy at a loading dose of 1.3 mg/kg IV followed by an infusion of 3 mg/kg/hour [2]. Concomitant CRI administration of low doses of lidocaine (3 mg/kg/hour) with intermittent administration of detomidine (0.1 mg/kg IV) every 4 hours has also been recommended to alleviate abdominal and peritoneal pain in food animals [38]. A combination of ceftiofur (10 ml), 2% lidocaine (10 ml), and saline (40 ml) administered at an infusion rate of 2 ml/hour has been used to provide pain relief in Holstein cows with chronic septic arthritis of the flexor tendon sheath, although IV use of ceftiofur is no longer permitted in cattle [38]. Morphine, ketamine, and lidocaine combination CRI was administered to a Holstein heifer with severe burns over 40% of her body surface [166]. The heifer became more comfortable and was able to lie down and stand more easily with improved appetite during infusion [166]. Pharmacokinetic data of a CRI of 0.0048 mg/kg/hour of morphine, 2.1 mg/kg/hour of lidocaine, and 0.42 mg/kg/hour of ketamine were collected and analyzed immediately following induction of anesthesia and continued for 24 hours following umbilical herniorrhaphy surgery in calves [167]. Mean terminal $t_{1/2}$ was 4.1, 0.98, and 1.55 hours for morphine, lidocaine, and ketamine, respectively. Steady-state serum concentrations were achieved for lidocaine and ketamine, but steady-state serum concentration was not achieved for morphine in this study, which was believed to be due to the long terminal $t_{1/2}$ of the drug. The authors suggested that FARAD be consulted to establish an appropriate withdrawal time to avoid potential drug residue when morphine, lidocaine, and ketamine CRI is used for long-term pain relief in farm animal species [167]. In calves anesthetized for umbilical surgery, lidocaine with an initial bolus dose of 2 mg/kg IV followed by CRI of 3 mg/kg/hour enhanced the isoflurane anesthetic effect and reduced its dose requirement for surgical anesthesia by 16.6% as compared to that of control calves [168]. Similar

reduction for isoflurane requirement with CRI of lidocaine (0.12 mg/kg/hour) and ketamine (0.6 mg/kg/hour) combination has also been demonstrated in sheep undergoing orthopedic surgery [169].

Grant et al. [170] reported that in sheep (body weight 45–60 kg [99–132 lb]) sedated with a bolus dose of xylazine (5 mg IM) and a continuous IV infusion of xylazine (2 mg/hour) for 90 minutes, a steady-state analgesic effect as demonstrated by leg lifting in response to electrical stimulus was obtained 10 minutes after the start of the infusion until the end of the study [170]. Ketamine produces intense analgesia by blocking NMDA receptors and stimulating μ receptors. In addition, a potent anti-inflammatory effect by suppressing cytokines and neutrophil chemotaxis may also be associated with ketamine-induced analgesia. Ketamine is an effective analgesic for relieving established pain; it provides analgesia at a microdose of 0.4–1.2-mg/kg/hour CRI for long-term pain relief [2].

Butorphanol has proved to be an excellent visceral analgesic in ruminants. In adult cattle, long-term analgesia can be maintained with low doses of a butorphanol CRI. The solution for infusion is made up by adding 10–20 mg of butorphanol to 5 l of a balanced electrolyte solution, and the CRI is administered at 1–2 l/hour [2]. There is no report on the use of butorphanol CRI in sheep and goats. However, considering the concentration of butorphanol is only 0.002–0.004 mg/ml (10–20 mg in 5 l of solution), with an infusion rate of 1–2 l/hour for sheep and goats weighing 60 kg (132 lb), the total dose of butorphanol administered in an hour is only 2–4 mg (0.03–0.06 mg/kg). This dose would still be within the recommended dosage range for small ruminants [44].

A combination of an opioid, lidocaine, and ketamine (*trifusion*) has been administered as a CRI for long-term pain relief in ruminants. Either butorphanol or morphine can be used in the combination. Prior to infusion of the trifusion, a loading dose of butorphanol (0.05–0.1 mg/kg IV or IM in small ruminants, 0.02–0.05 mg/kg IV or IM in large ruminants) is administered for an instant increase in the plasma concentration of the drug. The loading dose for lidocaine is 1 mg/kg IV, and it is administered slowly to prevent lidocaine-induced cardiovascular and CNS effects. In preparing the trifusion solution for a 450-kg (990-lb) animal using 3 mg/kg/hour of lidocaine as base solution, add 4000 mg of ketamine (0.6 mg/kg/hour) and 170 mg of morphine (0.025 mg/kg/hour) or 148 mg of butorphanol (0.022 mg/kg/hour) into 1 l of 2% lidocaine solution. The infusion rate of the mixture is set at 67 ml/hour. The infusion rate can be adjusted to patient size using the formula $67 \text{ ml/hour} \times \text{animal kg}/450 \text{ kg (990 lb)}$ to calculate the desired infusion rate. For example, for a 300-kg (660-lb) animal, the infusion rate is 45 ml/hour ($67 \text{ ml/hour} \times 300 \text{ kg [660 lb]}/450 \text{ kg [990 lb]} = 45 \text{ ml/hour}$) [44]. Detomidine (0.004 mg/kg/hour) and acepromazine (0.0022 mg/kg/hour) have been added to trifusion, making it a five-drug combination, and this combination is termed *pentafusion* [44]. Pentafusion is used effectively to relieve the extreme pain of laminitic horses. This combination has not been investigated in ruminants. Dose adjustments of the drugs will be required if pentafusion is used in ruminants because of the difference in sensitivity of ruminants to the drugs included in this combination [44].

Tables 10.1 and 10.2 summarize the doses of drugs and drug combinations that can be used for systemic pain management in cattle, small ruminants, camelids, and pigs. Many options are available to relieve pain and ensure patient comfort. The choice of an appropriate analgesic or analgesic combination to be used for a patient depends on the type of pain, the patient's condition, and the experience of the veterinarian to maximize the beneficial effects of an analgesic or analgesic combination for patient comfort.

Table 10.1 Doses of drugs used for systemic pain management in cattle, sheep, and goats.

Drug	Dosage for cattle (mg/kg)	Dosage for sheep and goats (mg/kg)	Duration (hours)
<i>Local anesthetics</i>			
Lidocaine	–	1–2, SC	–
Lidocaine	–	2.5, IV	1
Lidocaine	200 mg in 40 ml saline, 2 ml/hour	Loading dose: 2–5, IV CRI: 3–6 mg/kg/hour	–
Lidocaine	Loading dose: 1.3–2, IV, over 5 minutes CRI: 1.2–3 mg/kg/hour	Loading dose: 2.5, IV CRI during isoflurane anesthesia: 6 mg/kg/hour	–
<i>Trifusion</i>			
Butorphanol	Loading dose: 0.05–0.1, IV CRI: 0.02 mg/kg/hour Loading dose: 1, IV	In sheep during isoflurane anesthesia –	–
Lidocaine	CRI: 3 mg/kg/hour CRI: 0.6 mg/kg/hour	CRI: 1.2 mg/kg/hour CRI: 0.6 mg/kg/hour	
Ketamine			
Or			
Morphine	0.025 mg/kg/hour		–
Lidocaine	Loading dose: 1, IV CRI: 3 mg/kg/hour Ketamine 0.6 mg/kg/hour	In goats CRI: 3 mg/kg/hour	
<i>Opioids</i>			
Buprenorphine	–	0.0015–0.006, IV, IM	0.75–3.5
Buprenorphine	–	0.005–0.01, SC	6
Buprenorphine	–	0.005–0.1, IV or IM	4, 8–12
Buprenorphine	–	0.005, IM	12
Butorphanol	–	0.05–0.5, IV or IM	2–4
Butorphanol	0.05, SC	0.05, SC	6
Butorphanol	–	0.05–0.5, IM, sedation	–
Butorphanol	–	0.4, IV, sedation and ataxia	–
Butorphanol	–	0.5, IM, IV	2–3
Butorphanol	–	0.005, IM	–
Butorphanol	–	0.05–0.2, IM, IV	1–3
Butorphanol	0.005, IM	–	–
Acepromazine/ butorphanol	0.03, IV 0.01, IV	–	–
Acepromazine/ butorphanol	0.022, IV 0.044, IV	–	–
Diazepam/ Butorphanol	–	0.1–0.5, IM or IV 0.01, IM	–

Table 10.1 (Continued)

Drug	Dosage for cattle (mg/kg)	Dosage for sheep and goats (mg/kg)	Duration (hours)
Midazolam/ butorphanol	–	0.05–0.025, IM or IV 0.01, IM	–
Fentanyl patch	–	0.2, transdermal	–
Fentanyl injectable	–	5 mg or 10 mg/70 kg, transdermal	72–96
Fentanyl injectable	–	0.001–0.006 µg/kg, IV; 0.001–0.005 µg/kg/hour, IV	1–2
Fentanyl injectable	–	0.01, IV in sheep	–
Meperidine	2, IM	2, IV, IM	2–4
Meperidine	3.3–4.4, IM, SC	3.3–4.4, IM, SC	–
Meperidine	–	10, IM in goats	0.25–0.5
Meperidine	5, IM	5, IM in sheep	0.25–0.5
Morphine	0.05–0.1, IM, IV	0.05–0.1, IV, SC	4–6
Morphine	0.4, IM, or 0.25–0.05, IM	0.1–0.5, IM	4
Morphine	0.05–0.5, IV, IM	0.5, IM, IV	4–6
Morphine	–	0.5–1, IV	12
Acepromazine/ morphine	0.02–0.04, IV 0.1–0.5 IV or IM	–	–
Oxymorphone	0.005, IM	0.005, IM	–
<i>α₂ agonists</i>			
Xylazine	0.05–0.2, IM, IV	0.05–0.2, IM, IV	2–4
Xylazine	0.1, IM	0.05–0.1, IM	–
Xylazine/ butorphanol	0.01–0.02, IV 0.01–0.02, IV	0.1–0.2, IV 0.01–0.02, IV	–
Xylazine/ butorphanol	0.05–0.1, IV 0.01–0.02, IV	0.02, IM 0.05–0.07, IM	–
Detomidine	0.003–0.01, IM, IV	0.003–0.01, IM, IV	2–4
Medetomidine	0.005–0.01, IM, IV	0.005–0.01, IM, IV	2–4
Romifidine	0.003–0.02, IM, IV	0.003–0.02, IM, IV	2–4
<i>NSAIDs</i>			
Aspirin	100, PO	50–100, PO	6–12
Aspirin	–	100, PO	12–24
Carprofen	–	2–4, IV, SC	24
Carprofen	–	1–2, IV, PO, SC	24
Carprofen	–	4, SC	24–48
Carprofen	–	0.7, IV, in sheep	–
Diclofenac	–	1, IV, IM	–
Flunixin meglumine	1–2, PO, IV	1–2.2, IV, PO, SC	12–24

(Continued)

Table 10.1 (Continued)

Drug	Dosage for cattle (mg/kg)	Dosage for sheep and goats (mg/kg)	Duration (hours)
Flunixin meglumine	1, IM	1, IV; 1–2, IV, PO	12
Flunixin meglumine	–	1, IM	–
Ketoprofen	2–3, IV	2, IV	12
Ketoprofen	–	3, IV, IM	24
Ketoprofen	2–3, IV, PO	2–3, IV, PO	12–24
Meloxicam	–	0.5, IV, SC, first day; PO, once daily for 5 days	12
Meloxicam	–	0.5, IV	8
Meloxicam	–	0.5, IM, PO	24
Meloxicam	–	2, PO, first day; 1 mg/kg, PO, SID	24
Phenylbutazone	2–6, PO, IV	–	24
Phenylbutazone	5, PO	5, PO	24
	10, PO	10, PO	8
Phenylbutazone	Prohibited in dairy cattle >20 months lame bull: 17–25, IV	–	24
<i>Others</i>			
Ketamine	CRI: 0.4–1.2 mg/kg/hour	CRI: 2.4 mg/kg/hour	–
Ketamine	CRI: 2.4 mg/kg/hour	CRI: 3 mg/kg/hour	–
Gabapentin	–	3–5, PO	8
Gabapentin	10, PO	–	12
Gabapentin/ meloxicam	15, PO 0.5, PO	–	6–12
Gabapentin/ meloxicam	10–20, PO 1, PO	–	–

Table 10.2 Doses of drugs used for systemic pain management in camelids and pigs.

Drug	Dosage for camelids (mg/kg)	Dosage for pigs (mg/kg)	Duration (hours)
<i>Local anesthetics</i>			
Lidocaine	Loading dose: 1.3, IV CRI: 3 mg/kg/hour	–	–
	Loading dose: 1–2, IV CRI: 1.2–3 mg/kg/hour	–	–
<i>Trifusion</i>			
Butorphanol	Loading dose: 0.05–0.1, IV CRI: 0.02 mg/kg/hour	–	–
Lidocaine	Loading dose: 1, IV CRI: 3 mg/kg/hour		
Ketamine	CRI: 0.6 mg/kg/hour		

Table 10.2 (Continued)

Drug	Dosage for camelids (mg/kg)	Dosage for pigs (mg/kg)	Duration (hours)
<i>or</i>			
Morphine	CRI: 0.025 mg/kg/hour	–	–
Lidocaine	Loading dose: 1, IV		
	CRI: 3 mg/kg/hour		
Ketamine	CRI: 0.6 mg/kg/hour		
<i>Opioids</i>			
Buprenorphine	–	0.01–0.05, IV, IM	6–12
Buprenorphine	–	0.005–0.01, IM	12
Buprenorphine	–	0.12, IM	7–24
Buprenorphine	–	0.02–0.03, SC	8–10
Buprenorphine	–	0.01–0.1, IM, IV	12
Buprenorphine	–	0.05–0.1, IM	–
Butorphanol	0.05–0.1, IV, IM	0.1–0.3, IM, IV	4–6
Butorphanol	0.1–0.5, IV, IM	0.1, IM	4–6
Butorphanol	–	0.1–0.4, IM, IV	–
Butorphanol	Loading dose: 0.05–0.1, IV	–	–
	CRI: 0.022 mg/kg/hour		
Fentanyl patch	Transdermal: 50 µg/hour for 30–50 kg (66–110 lb) 4 patches of 75 µg/hour/150 kg (330 lb)	Transdermal: 50–100 µg/hour	48–72
		–	–
Fentanyl	–	0.05, IV, IM	4
Fentanyl	–	Loading dose: 0.05, IV	–
		CRI: 0.03–0.1 mg/kg/hour	
Sufentanil	–	0.005–0.01, IV, IM	4
Sufentanil	–	Loading dose: 0.007, IV	–
		CRI: 0.015–0.03 mg/kg/hour	
Hydromorphone	–	0.05, IV	–
Meperidine	1–5, IM	0.4–1, IV	–
Meperidine	–	2, IM, IV	2–4
Meperidine	–	2–10, IM	4
Methadone	–	0.1–0.2, IV	–
Morphine	0.1, IV, IM	0.05–0.1, IV	4–6
Morphine	0.05–0.1, IV, IM	0.2–1, IM	4
Morphine	0.25, IV	–	4
Morphine	0.5–1, IM	–	3–6
Oxymorphone	–	0.02, IM	–
Oxymorphone	–	0.15, IM	4

(Continued)

Table 10.2 (Continued)

Drug	Dosage for camelids (mg/kg)	Dosage for pigs (mg/kg)	Duration (hours)
Tramadol	2, IV, IM	1.6, IM	2–3
Tramadol	4, IM	5, IM	–
Tramadol	11, PO	1–4, PO	8
<i>NSAIDs</i>			
Aspirin	–	10, PO	4
Aspirin	–	10–20, PO	4–6
Carprofen	–	2–4, IV, SC	24
Carprofen	–	2–3, PO, IM, SC	12
Carprofen	–	4, PO	24
Etodolac	–	10–15, PO	24
Flunixin meglumine	1.1, IV	1, IV, IM	12–24
Flunixin meglumine	1.1, IV	–	8
Flunixin meglumine	–	1–2, IV, SC	24
Flunixin meglumine	–	1–4, IV, IM, SC	12
Ibuprofen	–	10, PO	6–8
Ketoprofen	–	1–3, IV, IM, SC, PO	12
Ketoprofen	1–2, IV	3, IM	24
Ketorolac	–	1, IM, IV	–
Meloxicam	–	0.1–0.2, PO	24
Meloxicam	–	0.4, SC	24
Meloxicam	1, PO	–	72
Meloxicam	0.5, IV	–	–
Phenylbutazone	5, IV, PO	10–20, PO	24–48
<i>Others</i>			
Ketamine	CRI: 0.4–1.2 mg/kg/hour	CRI: 0.2–1 mg/kg/hour	–
Ketamine	CRI: 2.4 mg/kg/hour	–	–
Midazolam/ ketamine	–	0.5–1.5 mg/kg/hour	–
	–	8–33 mg/kg/hour	–
Xylazine	0.1–0.3, IV, IM, SC	0.5, IM	1–2.5
Xylazine	–	1, IM	–
Xylazine	–	10, IM	12
Xylazine/ ketamine	–	0.05, IV	1
	–	0.1, IV	–
Tolfenamic acid	–	2, IM	24

10.4 Local or Regional Analgesia

Local or regional anesthetic techniques in farm animal species are described in detail in Chapter 8. In this chapter, only the techniques commonly involved in pain management such as caudal epidural analgesia, lumbosacral epidural analgesia, and intra-articular analgesia are included. Topical application of local anesthetics in cattle is often ineffective due to the characteristic thick bovine skin, particularly at the flank and dorsal areas. However, an analgesic effect of 5% lidocaine gel has been observed when applied to the skin of injured teats to facilitate palpation and cannulation of the teat. Analgesia is evident within 10 minutes after application of the gel to dry skin [19].

10.4.1 Caudal Epidural Analgesia

If properly performed, caudal epidural anesthesia desensitizes the perineum, vulva, vagina, and rectum. The injection site is usually between the first and second coccygeal vertebrae. As a general rule, 1 ml of 2% lidocaine per 45 kg (99 lb) of body weight is adequate, therefore a total dose of 1–2 ml is effective for most sheep and goats, and 5–7 ml for adult cattle. The onset of analgesia occurs within 1–5 minutes, and the duration is about 1 hour. The onset of perineal analgesia tends to be slower with epidural morphine or α_2 agonists, but the duration of analgesia is significantly longer as compared to that of lidocaine. Bupivacaine-induced caudal epidural analgesia was compared to lidocaine- and lidocaine–bupivacaine-induced analgesia in Holstein cows undergoing reproductive procedures [171]. The durations of analgesia produced by 0.05 and 0.06 mg/kg of bupivacaine were 226 ± 55 and 247 ± 31 minutes, respectively, which were significantly longer than that of lidocaine (0.2 mg/kg, 127 ± 25 minutes) and lidocaine (0.1 mg/kg)–bupivacaine (0.025 mg/kg) combination (181 ± 33 minutes) [171]. One cow receiving 0.05 mg/kg of bupivacaine developed profuse salivation, nasal discharge, hiccough, urination, and defecation, and all of these side effects subsided within 15 minutes. Accidental IV injection was thought to be the cause of the adverse reaction, which was supported by the lack of perineal analgesia following epidural injection of the drug in this cow [171]. In another study, bupivacaine (0.25 mg/kg, 192 ± 8 minutes), xylazine (0.05 mg/kg, 127 ± 8 minutes), medetomidine (0.015 mg/kg, 212 ± 10 minutes), xylazine with bupivacaine (206 ± 7 minutes), and medetomidine with bupivacaine (228 ± 9 minutes) were shown to produce longer duration of caudal epidural analgesia in buffalos than did lidocaine [172]. Bupivacaine (9–13 minutes) and ropivacaine (15 minutes) both have significantly slower onset but longer duration of perineal analgesia than lidocaine (5–7 minutes) in cattle [173]. Surprisingly, the duration of perineal analgesia produced by 0.11 mg/kg of ropivacaine (359 ± 90 minutes) was significantly longer than that produced by 0.06 mg/kg of bupivacaine (247 ± 31 minutes) [171, 173].

Caudal epidural injection produced by romifidine (0.05 mg/kg) and morphine (0.1 mg/kg) was capable of suppressing the response to noxious stimulation up to the flank area for 12 hours [174]. In sheep, epidural administration of fentanyl (0.0015 mg/kg) alone did not produce analgesia [175]. When adding fentanyl to xylazine (0.2 mg/kg), fentanyl was able to shorten the time of onset (4.5 ± 0.5 vs. 10 ± 1.1 minutes) and prolong the duration of epidural analgesia (315 ± 6 vs. 96 ± 6 minutes) of that of xylazine alone [175]. Compared to morphine, caudal epidural administration of an α_2 agonist not only produces excellent perineal analgesia, but these drugs also provide systemic analgesia and sensory blockade during surgery. The α_2 agonists, especially xylazine, have been used as the sole anesthetic to perform cesarean section in sheep [176]. The CNS-depressing effects such as sedation, ataxia, and sometimes recumbency can occur following caudal epidural or lumbosacral administration of an α_2 agonist [176]. These CNS effects are believed to be the result of (i)

absorption of the drug from epidural space into systemic circulation, (ii) cranial migration of the drug toward CNS, and/or (iii) local anesthetic effect of the drug, particularly xylazine. IV administration of an α_2 antagonist, atipamezole (0.005 mg/kg), reversed the CNS effects induced by epidural xylazine but did not affect the epidural analgesia [176]. Hind limb paresis/paralysis resulting from trauma to the spinal cord has been reported in both small and large ruminants after epidural administration of xylazine or medetomidine [38, 177–180]. It is very likely that trauma to the spinal cord on epidural injection is the cause for the hind limb paresis. However, this author (Lin) did not observe any adverse effects such as trauma to the spinal cord or hind limb paresis in adult cattle involved in a research project when five epidural injections of saline, lidocaine, clonidine, xylazine, or medetomidine were performed with at least a 2-week interval between each injection [181, 182]. The effects of three different doses of caudal epidural ketamine (0.5, 1, and 2 mg/kg, diluted to 5, 10, and 20 ml, respectively) have been investigated in standing cattle [2, 183]. Dose-dependent analgesia lasting from 17 to 62 minutes was observed. Ataxia but not sedation was observed throughout the study [2, 183].

10.4.2 Lumbosacral Epidural Anesthesia

Lumbosacral epidural anesthesia provides analgesia caudal to the diaphragm, including abdominal wall caudal to the umbilicus, inguinal region, flank, and perineal areas if properly performed. A dosage of 0.3–0.5 ml of 2% lidocaine solution per 10 kg (22 lb) of body weight is adequate for most surgery. The onset of analgesia and hind limb paralysis usually occurs within 5–15 minutes and lasts 1–2 hours [184, 185]. Dose-dependent duration of lumbosacral epidural analgesia with recumbency of ropivacaine has been reported from 5–6 hours with 0.29–0.35 mg/kg to 7–8 hours with 0.63–0.75 mg/kg [186].

Lumbosacral injection of xylazine (0.05 mg/kg) with lidocaine (2 mg/kg) and buprenorphine (0.005 mg/kg) with lidocaine (2 mg/kg) has been used to produce intrathecal analgesia for pain relief following stifle surgery in goats [187]. The result of this study showed that intrathecal buprenorphine with lidocaine produced more profound and longer-lasting analgesia but with less sedation than that of xylazine with lidocaine [187]. Both combinations produced satisfactory pain relief for goats following stifle surgery. However, the duration of analgesia for buprenorphine with lidocaine was at least 6 hours, which was approximately twice as long as that of xylazine with lidocaine [187]. In another study, lumbosacral epidural analgesia induced by morphine (0.1 mg/kg) or bupivacaine (1.5 mg/kg) was compared during abdominal surgery in goats [188]. Morphine produced 22 hours of intrathecal analgesia but only 3 hours was observed with bupivacaine [188]. Goats that received morphine stood within 59 ± 9 minutes following surgery, while those that received bupivacaine remained recumbent for 285 ± 49 minutes [188]. Although prolonged recumbency generally does not result in long-term adverse effects in goats, lumbosacral epidural morphine is believed to be more ideal when faster recovery to standing with longer pain relief is desired [189]. In sheep, intrathecal administration of morphine (0.1 mg/kg) resulted in hind limb ataxia and licking and chewing of the flanks and the hind limbs. The higher than recommended dose of intrathecal morphine was believed to be the cause of this adverse reaction [190]. Lumbosacral administration of morphine (0.1 mg/kg), bupivacaine (0.5 mg/kg), or morphine (0.05 mg/kg) with bupivacaine (0.25 mg/kg) following thoracic surgery produced analgesia durations of 40, 70, and 140 minutes, respectively. Lumbosacral bupivacaine alone or combined with morphine resulted in hind limb paralysis during the period of analgesia. No adverse reaction to morphine was observed in this study [191]. In goats, subarachnoid administration of buprenorphine (0.005 mg/kg) combined with lidocaine (0.1 ml/kg) resulted in more profound and

longer-lasting analgesia but with less sedation and ataxia than a combination of intrathecal xylazine (0.05 mg/kg) and lidocaine (0.1 ml/kg) [187]. Analgesic effects of lumbosacral administration of lidocaine (2.86 mg/kg), tramadol (1 mg/kg), and tramadol (1 mg/kg)–lidocaine (2.46 mg/kg) combination were evaluated in goats. Tramadol alone produced long duration of analgesia (235 ± 18 minutes) with a slower onset of action (12 ± 1 minutes) as compared to lidocaine [192]. Unlike xylazine and lidocaine combination, there was no synergistic or additive analgesic effect of lidocaine when combined with tramadol, which was reflected in the shorter duration of analgesia (140 ± 2 minutes) as compared to that of tramadol alone [192].

In goats, intrathecal administration of ketamine (2.5 mg/kg) combined with romifidine (0.05 mg/kg) and an added volume of saline to produce a total volume of 2 ml was reported to produce complete analgesia in the tail, perineum, and hind limbs for 2 hours [193]. In sheep, lumbosacral epidural ketamine alone (1 mg/kg, with saline added to produce a total volume of 7–9 ml) administered prior to recovery from orthopedic surgery delayed the time for the administration of first rescue analgesic (5 hours vs. 3.5 hours for the control). In addition, sheep receiving ketamine seemed to walk with less lameness [194]. Lumbosacral ketamine (2.5 mg/kg) alone in goats produced excellent analgesia, which completely abolished the response to pinprick for 5–20 minutes. Addition of xylazine (0.05 mg/kg) to ketamine prolonged the duration of analgesia to 60 minutes. Brief period of ataxia was observed with ketamine alone, whereas sedation and ataxia occurred throughout the xylazine and ketamine analgesic period [183].

The use of a combination of detomidine, ketamine, methadone, and bupivacaine administered extradurally into lumbosacral area was described for successful pain management in a Brown Swiss resulting from a pelvic limb lameness causing complex regional pain syndrome [195]. Epidural morphine (0.1 mg/kg) was originally administered to provide pain relief but was discontinued due to the development of pruritus. Initial doses of detomidine, ketamine, methadone, and bupivacaine were 7, 1640.6, 85.9, and 4.7 μ g/kg/day, respectively. Each drug was diluted with saline into 10 ml of solution, and the total volume of 40 ml of the mixture was infused over 24 hours. Due to significant sedation, detomidine was discontinued on day 5. The cow was monitored closely and the dose of each drug adjusted accordingly. The treatment was continued for 17 days and the cow was discharged only mildly lame with much improved physical condition [195].

10.4.3 Intra-articular Analgesia

In sheep, pain relief was obtained after stifle arthrotomy by intra-articular injection of lidocaine (40 mg, 2 ml) prior to incision and bupivacaine (10 mg, 2 ml) post closure. Additionally, phenylbutazone (1 g orally, once daily for 5 days) and transdermal fentanyl (15 mg) were initiated 24 hours prior to surgery [196]. Though this study did not evaluate the total duration of analgesia induced by the combination, a similar study in dogs suggested analgesia duration of approximately 24 hours [196]. A shorter duration of analgesia was observed in goats receiving intra-articular bupivacaine alone after stifle arthrotomy surgery [197]. Intra-articular injection of morphine has not been studied in adult cattle. However, the technique is proven to be an effective pain relief in dogs and horses. A dose of 0.05–0.1 mg/kg diluted with saline into 5–15 ml, according to the size of the joint, is recommended [198].

In recent *in vitro* studies, 0.5% bupivacaine was shown to cause cytotoxicity to bovine, equine, and human chondrocytes [199–202]. Approximately 90–99% chondrocyte deaths were reported in these studies after direct *in vitro* exposure to 0.5% bupivacaine for 30–60 minutes. Dilution of bupivacaine to 0.25% increased both human and bovine chondrocyte viability and reduced cell death to 41% as compared with the saline control group [201]. Further dilution of bupivacaine to 0.125%

resulted in similar chondrocyte viability to that of the saline control group [201]. When equine chondrocytes were exposed to 0.5% bupivacaine, 2% lidocaine, and 2% mepivacaine for 30 or 60 minutes, the cell viability was reported to be 28.73 ± 8.44 , 66.85 ± 6.03 , and $86.27 \pm 2.00\%$, respectively, whereas cell viability was $95.95 \pm 2.75\%$ after exposure to saline solution of a similar duration. Hence, intra-articular administration of mepivacaine, with its low cytotoxicity, appears to be a better choice to relieve joint pain [202]. Ropivacaine was shown to have less chondrocyte toxicity to *in vitro* human intact articular cartilage and cultured chondrocyte, as chondrocyte viability was reported to be $94.4 \pm 9.0\%$ for intact articular cartilage and $63.9 \pm 19\%$ for cultured chondrocyte, respectively, following exposure to 0.5% ropivacaine, whereas chondrocyte viability was $78 \pm 12.6\%$ for intact articular cartilage and $37.4 \pm 12\%$ for cultured chondrocyte respectively, when exposed to 0.5% bupivacaine [199]. There are no clinical reports that support the findings of these *in vitro* studies, and intact articular cartilage apparently offers some chondrocyte protective effects. However, the detrimental effects of bupivacaine and lidocaine on chondrocytes should be kept in mind, especially in patients with cartilage disorders, and mepivacaine and ropivacaine may be considered for intra-articular administration when indicated.

Tables 10.3 and 10.4 summarize the doses of drugs and drug combinations that can be used to produce local and regional analgesia for pain management in cattle, small ruminants, camelids, and pigs. Similar to the options available for parenteral administration of an analgesic or analgesic combinations, there are also different options of local or regional analgesic techniques available to relieve pain and ensure patient comfort. Careful selection of an appropriate local or regional analgesic or analgesic combination to provide maximal analgesia for the type of pain and the condition of the patient.

Table 10.3 Doses of drugs used to produce local and regional analgesia for pain management in cattle, sheep, and goats.

Drug	Dosages for cattle (mg/kg)	Dosages for sheep and goats (mg/kg)	Duration (hours)
<i>Local anesthetics</i>			
Bupivacaine	0.05	0.05, infiltration	2–3 in cattle
Bupivacaine	–	0.05, epidural	–
Bupivacaine	–	1, intrathecal	–
Bupivacaine	–	1.5–1.8 in goats	2–3 in goats
Bupivacaine	–	1.8, lumbosacral	11 in goats
Bupivacaine	–	10 mg, intra-articular, after surgery	–
Bupivacaine	–	1–2, SC	–
Lidocaine (2%)	0.2–0.4, epidural	0.05, infiltration	1–2 in cattle
Lidocaine (2%)	5–7 ml/450 kg (990 lb)	1–2 ml/50 kg (110 lb), epidural	1.2 in sheep and goats
Lidocaine (2%)	–	0.22, epidural	–
Lidocaine (2%)	–	1 ml/10 kg, lumbosacral	–
Lidocaine (2%)	–	1, intrapleural	–

Table 10.3 (Continued)

Drug	Dosages for cattle (mg/kg)	Dosages for sheep and goats (mg/kg)	Duration (hours)
Lidocaine (2%)/ethyl alcohol (95%)	1:1 ratio in 2–3-ml mixture, caudal epidural	–	–
Lidocaine	–	40 mg, intra-articular, presurgery	3–7 in goats
Lidocaine	20 ml/vein IVRA	3–4 ml/vein, IVRA	–
Lidocaine	20 ml/vein, IVRA	–	–
Morphine	40–100 mg IVRA		
<i>α₂ agonists</i>			
Detomidine	0.04 in 5 ml of saline, epidural	0.01, intrathecal in sheep, 2 ml of saline	3 in cattle 1 in sheep
Medetomidine	–	0.001–0.002, lumbosacral	–
Medetomidine	0.015 in 5 ml of saline, epidural	0.02 or 0.01–0.03 in 5 ml of saline, epidural	7 in cattle <3 in goats
Medetomidine	0.015	–	–
Mepivacaine	0.5–1 ml/50 kg (110 lb)		
Oxymorphone	0.005, IM	0.005, IM	–
Romifidine	0.05, epidural	0.05 in 4 ml of saline, intrathecal	12 in cattle 2 in goats
Romifidine/morphine	0.05/0.1 in 30 ml of saline, epidural	–	12 in cattle
Romifidine/ketamine	–	0.05/2.5 in 2 ml of saline, intrathecal	2 in goats
Xylazine	0.05 in 5 ml of saline, epidural	0.03, epidural	2–3 in cattle
Xylazine	0.07 in 5 ml of saline, epidural	0.07–0.4 in 2.5 ml of saline, epidural	1–2 in sheep
Xylazine	1 in 5 ml of saline	0.15 in 5 ml of saline, epidural	3 in goats
Xylazine	–	0.05 in 0.75 ml of saline, intrathecal	2 in goats
Xylazine	–	0.07–0.4 in 2.5 ml of saline, epidural	1–2 in sheep
Xylazine	–	0.1 in 2 ml of saline, intrathecal	1.5 in sheep
Xylazine/ketamine	–	0.05/2.5 in 1.5 ml of saline, epidural	0.5–1 in goats
Xylazine/ketamine	–	0.05/2.5 in 1.5 ml of saline, intrathecal	2 in goats
Xylazine/lidocaine (2%)	–	0.05/1.25 in 4 ml of saline, intrathecal	3 in goats
Xylazine/lidocaine (2%)	–	0.25 ml of 20 mg/ml/2 ml mix in 73-kg (161-lb) ewe, epidural	–

(Continued)

Table 10.3 (Continued)

Drug	Dosages for cattle (mg/kg)	Dosages for sheep and goats (mg/kg)	Duration (hours)
Xylazine/morphine	12 mg/0.1 for 500–600-kg (1100–1320-lb) cows, caudal epidural	–	–
<i>Opioids</i>			
Morphine	0.1 in 0.02–0.05 ml/kg saline, epidural	0.1 in 0.2 ml/kg saline, epidural	6–12
Morphine	–	0.05–0.1, epidural	24
Morphine	–	0.1–0.2, epidural	–
Morphine	–	0.1, epidural	–
Morphine/bupivacaine	–	0.1, epidural/1.5, epidural	–
Tramadol	–	1, lumbosacral	Slow onset, no ataxia
<i>Others</i>			
Ketamine	0.5–2 in 5–20 ml of saline, epidural	–	1 in cattle
Ketamine	–	1 in 7–9 ml of saline, epidural	5 in sheep
Ketamine	–	2.5 in 0.75 ml of saline, epidural	0.25 in goats
Ketamine	250 mg	–	0.28
Ketamine	500 mg	–	0.57
Ketamine	1000 mg	–	1.03

IVRA, intravenous regional anesthesia.

Table 10.4 Doses of drugs used to produce local and regional analgesia for pain management in camelids and pigs.

Drug	Dosage for camelids (mg/kg)	Dosage for pigs (mg/kg)	Duration (hours)
<i>Local anesthetics</i>			
Lidocaine (2%)	<4.4, IVRA	10 ml/vein, IVRA	–
Lidocaine (2%)	<1 ml/5 kg, IVRA	–	–
Lidocaine (2%)	1 ml/23 kg (51 lb), caudal epidural	0.5–1 ml/5 kg (11 lb), epidural	1–1.5
Lidocaine (2%)	1–2 ml/50 kg (110 lb), caudal epidural	–	–
Lidocaine (2%)	2–3 ml/adult llama	–	–
Lidocaine	3 mg/kg, lumbosacral	–	–
<i>α₂ agonists</i>			
Xylazine	0.1, caudal epidural	2 in 5 ml of saline, epidural	2

Table 10.4 (Continued)

Drug	Dosage for camelids (mg/kg)	Dosage for pigs (mg/kg)	Duration (hours)
Xylazine	0.17 in 2 ml of saline, caudal epidural	1 in 10 ml, >180 kg (396 lb), 2 in 10 ml, <50 kg (110 lb)	–
Xylazine	0.17	1 in 2% lidocaine to a total of 10 ml, lumbosacral	5–8
Lidocaine	0.22 Total 1.7 ml, caudal epidural		
Detomidine	–	0.5 in 5 ml of saline, epidural	–
Medetomidine	–	0.5 in 5 ml of saline	<0.5
<i>Opioids</i>			
Morphine	0.1, caudal epidural	–	12

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11

Fluid Therapy

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Fluid therapy prior to and during anesthesia is an important component of the anesthetic plan. Livestock affected with medical conditions that require anesthesia and surgical intervention commonly present with dehydration and different electrolyte and acid–base imbalances. Proper use of fluids can be beneficial and lifesaving in these cases. As with other medications, inappropriate use of fluids during anesthesia can lead to detrimental or lethal outcomes regardless of surgical expertise. Fluid therapy can be provided during the perioperative period, which is defined as the period of time beginning when the animal is examined on the farm or clinic and completed when the animal is returned to its normal environment or discharged from the clinic. In many situations, fluid therapy provided prior to and following anesthesia is more important to the outcome of the case than the fluids administered during anesthesia and surgery.

11.1 General Considerations

The physical state of the animal, especially the level of hydration, is an important consideration prior to anesthesia. Ideally, dehydration along with electrolyte and acid–base imbalances is corrected 12–24 hours prior to anesthetic induction; however, anesthesia and surgery might be necessary prior to completing fluid resuscitation. Under these circumstances, monitoring of cardiac, renal, and pulmonary function is critically important. Even when rehydration can be accomplished prior to anesthesia and surgery, another factor that impacts fluid balance is restriction of oral feed and water. Ruminants are prone to regurgitation and rumen tympany during general anesthesia, thus adult ruminants are often fasted for at least 12–24 hours prior to the procedure and restricted from oral water intake for a minimum of 8–12 hours. In very large livestock, or when greater reductions in rumen volume are preferred during abdominal surgery, longer periods of fasting of up to several days may be preferred. This restriction of oral water intake combined with ongoing fluid losses associated with a disease process makes consideration of perioperative intravenous (IV) or other parenteral fluid therapy imperative for successful management of anesthesia and surgery. Fluid loading, which is the administration of high volumes of IV fluids over a short duration prior

to induction of anesthesia and surgery, is one way to accomplish the goal of maintaining hydration while restricting oral intake of food and water to prevent regurgitation.

Dehydration as a result of excessive loss of body fluids or failure of fluid intake is the most common indication for fluid therapy in livestock. Examples of fluid intake failures include a lack of thirst as a result of neurologic depression or toxemia or inability to drink as would occur with esophageal obstruction. Diarrhea is the most common cause of excessive fluid loss, although vomiting and polyuria (renal disease) should also be considered, especially in small ruminants. Other indications for fluid therapy include hypovolemic shock, endotoxemia, electrolyte abnormalities, disturbances in acid–base balance, hypoglycemia, hypothermia, diuresis following toxin exposure, malnutrition, trauma, and failure in the transfer of passive immunity.

The overall goals of fluid therapy in sick livestock are to expand the circulatory volume to improve organ and tissue perfusion, correct life-threatening electrolyte abnormalities, and correct acid–base imbalances. Most drugs used for induction and maintenance of anesthesia decrease cardiac contractility and induce vasodilation, which result in a relative hypovolemia. These effects lead to decreased cardiac output and decreased arterial blood pressure. Benefits of the perioperative fluid therapy also include improvement of cardiac function, smooth muscle vascular tone, and blood flow distribution.

11.2 Physiology of Body Fluids

To administer fluids and electrolytes properly, a general understanding of the fluid composition of the patient and how this fluid is altered or lost during anesthesia, surgery, and disease states is necessary. Total body water comprises between 57% and 67% of body weight for ruminants, while pigs have less total body water (40–50%) as a percentage of weight likely due to less gastrointestinal (GI) water [1]. Most estimations of total body water approximate 60% of body weight [2]. This amount can vary slightly with age, body composition, and breed. In general, neonatal ruminants have relatively more body water than adults, and total body water in neonates may approach 75–80% of body weight. The larger total body water percentage is primarily due to a large extracellular fluid volume, but by 6 months of age the total body water and extracellular fluid space percent are similar to adult values. The larger total body water and extracellular fluid percent of neonatal ruminants does not provide a reservoir of fluid for the sick neonate [3]. Overweight animals have decreased total body water content as compared to lean animals since adipose tissue contains very little water. As an example, estimations of total body water for fattened sheep are approximately 50% of body weight [2].

Total body water is distributed within two major compartments, the extracellular fluid compartment and the intracellular fluid compartment. Approximately two-thirds of total body water is intracellular fluid (40% of body weight) and one-third is extracellular fluid (20% of body weight). The extracellular fluid compartment can be further subdivided into interstitial fluid (~15% of body weight), the intravascular fluid or plasma volume (~5% of body weight), and transcellular fluid (very small % of body weight). The interstitial fluid compartment consists of cerebrospinal fluid, connective tissue, and, most importantly, the contents of the reticulorumen and the remaining GI tract. The reticulorumen is an important reservoir of fluid for adult ruminants during periods of water restriction, and the GI tract can also be a site for water deposition during disease processes such as grain overload or endotoxemia. Dehydration causes a decrease in extracellular fluid volume secondary to a decrease in total body water and is characterized by an increase in packed cell volume and total protein. Hypovolemia is generally defined as a decrease in fluid in the

intravascular volume and can be treated rapidly by filling the vascular compartment to improve tissue perfusion. With dehydration, all fluid compartments are affected. Initially, dehydration results in reduction of the intravascular fluid compartment followed by contraction of the interstitial and intracellular fluid compartments. For dehydration, fluid deficits should be replaced more gradually to allow for fluid equilibriums to be reestablished between the various compartments of the extracellular fluid space.

Although the intracellular and extracellular fluid compartments differ in electrolyte composition, they are in osmotic equilibrium and water can freely diffuse between them. The movement of water and electrolytes between compartments is governed by hydrostatic and oncotic forces. Sodium is the most important cation within the extracellular fluid compartment, accounting for about 95% of the total cation pool. Potassium is the major intracellular cation. The concentrations of sodium and potassium are maintained within and outside of cells by the Na^+/K^+ -ATPase pump. Chloride and bicarbonate are the major anions within the extracellular fluid space, while phosphates, proteins, and other anions maintain electroneutrality with the potassium cation in the intracellular fluid compartment. Evaluation of blood electrolyte concentrations and acid–base status assess the extracellular fluid compartment. When fluids are administered to dehydrated animals, fluid losses are replaced within the extracellular fluid compartment, and thus the fluids being administered should contain concentrations of ions similar to what is found in the extracellular fluid compartment. Most disease processes in ruminants result in loss of fluids and electrolytes concurrently, and this is referred to as isotonic or iso-osmolar dehydration. In these cases, providing both fluid and electrolytes (mainly sodium) is important. Hypertonic dehydration or a relative water deficit occurs when water losses exceed losses of electrolytes, and water deprivation is an example. In contrast, hypotonic dehydration or relative water excess occurs when electrolyte losses exceed water losses. Hypotonic dehydration can occur in livestock with diarrhea, in which loss of electrolytes and water occurs concurrently (isotonic dehydration). Another example of hypotonic dehydration occurs in ruminants with obstructive urolithiasis, in which sodium depletion exceeds water loss as sodium moves into the peritoneal cavity [4].

11.3 Patient Assessment

A physical examination is very important prior to anesthesia to ensure that the correct fluid type is administered at an appropriate rate, as well as for identifying underlying disease processes that could complicate anesthesia. Intercurrent disease processes, hypothermia, and perinatal asphyxia can lead to difficulty in accommodating IV fluids during anesthesia and surgery. Fluid therapy can have adverse effects such as volume overload and pulmonary edema, so particular attention should be given to the cardiovascular, pulmonary, and renal systems. Respiratory disease is common in ruminants, especially weaning-age calves, kids, and lambs. In addition, mild, chronic lung pathology can be difficult to identify on clinical examination, yet this can negatively impact anesthesia and fluid therapy. Patients with respiratory disease have difficulty with gas exchange and are at greater risk of mortality, especially when general anesthesia and dorsal or lateral recumbency are utilized and the weight of the abdominal organs is further reducing lung capacity. Careful cardiac and pulmonary auscultation is important to identify animals at risk for anesthesia and fluid overload. Cardiovascular diseases may result in an inability to cope with an acute fluid load. Oliguric renal failure results in an impaired ability to excrete excess fluid. If concern exists following physical examination, preanesthetic diagnostic evaluation becomes important. A packed cell volume and total solids should be performed prior to induction of anesthesia for all cases. For cases in

which disease or organ dysfunction is suspected, a complete blood count, serum chemistry profile, blood gases, and radiographs should be performed. For suspected cardiovascular disease, echocardiography and electrocardiograms should be performed. Evidence of respiratory, cardiovascular, or renal disease should delay anesthesia until the problem is resolved or characterized as to the impact on anesthesia. Life-threatening abnormalities (dehydration and hypovolemia, hyperkalemia, metabolic acidosis) should be corrected prior to anesthesia if at all possible.

Dehydration is most accurately assessed by changes in body weight before and after a disease event, but this information is not usually available to the clinician, therefore clinical assessment is utilized to assess degree of dehydration. The packed cell volume and total plasma protein can be used as tools to assess hydration status, and the packed cell volume also provides an assessment of oxygen-carrying capacity. However, measurements of packed cell volume and total solids cannot be used solely to replace an estimation of hydration status from physical examination. For example, the reference ranges for packed cell volume in healthy ruminants can be quite broad, which makes this measurement too variable to be useful for sole estimation of hydration status [4]. Total plasma protein concentration is dependent on colostral intake in neonates and can be elevated in patients with chronic inflammation. In addition, sheep, goats, and camelids with anemia and hypoproteinemia in conjunction with dehydration, as occurs with intestinal parasitism, can have a normal packed cell volume and total plasma protein concentration. Packed cell volume and total plasma protein concentrations are most useful in monitoring the progress of fluid therapy to prevent overhydration.

Percent dehydration can be easily estimated by assessing eyeball recession into the sockets (extent of enophthalmos), skin turgor, and the moisture of the mucous membranes (Table 11.1). In general, the presence of a gap between the eye and the orbit, decreased skin turgor, and dry/tacky mucous membranes are good indicators of dehydration in ruminants [5]. Results from one study demonstrated that the number of seconds of a cervical skin tent and the extent of enophthalmos are well correlated with the percent of dehydration in calves [5]. The extent of enophthalmos can be used to assess hydration in young small ruminants as well. The percent dehydration can be estimated by measuring the eyeball recession (in mm) and multiplying by 2. For example, a patient with eyeball recession of 4 mm is calculated to be 8% dehydrated. The duration of skin tenting can also be used to estimate hydration status. The percent dehydration is estimated by measuring the skin tent (in seconds), multiplying by 2, and then subtracting 4. For example, a calf with a skin tent of 6 seconds is estimated to be 8% dehydrated. Some caveats to this clinical assessment of dehydration exist, and it is important for the clinician to remember that emaciated ruminants usually have

Table 11.1 Estimating level of dehydration based on physical examination findings.

Percent (%) dehydration	Physical examination findings
<5	History of fluid loss but no findings on physical examination
5	Minimal depression, normal to mildly tacky mucous membranes, enophthalmos <4 mm, skin tent <2 seconds, normal capillary refill time (<2 seconds)
8	Depression, mild to moderate decreased skin turgor (skin tent 2–4 seconds), enophthalmos >4 mm, increased capillary refill time (3–4 seconds)
≥10	Severe depression, weakness, moderate to marked degree of decreased skin turgor (skin tent >5 seconds), dry and dark mucous membranes, enophthalmos >6 mm increased capillary refill time (>5 seconds), cold extremities

poor skin elasticity and enophthalmos, which can mimic dehydration [6]. Additionally, *Bos indicus* cattle with excessive skin on the neck have a prolonged skin tent regardless of hydration status.

In the absence of laboratory testing, acid–base and electrolyte abnormalities are more difficult to assess. Serum biochemistry and blood gas analyses can provide information on serum electrolyte abnormalities (sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus), acid–base disorders, or glucose abnormalities that require correction. A negative base excess (BE) in addition to low serum bicarbonate, low total carbon dioxide (TCO₂), and a high anion gap indicate metabolic acidosis. In contrast, a positive base excess in addition to increased TCO₂, increased serum bicarbonate, and hypochloremia indicate alkalosis [7]. However, the lack of laboratory equipment in the field usually makes the determination of acid base and electrolyte abnormalities challenging for the clinician. Under these circumstances, history, clinical signs, and presumptive diagnosis are essential tools to determine the metabolic status and electrolyte imbalances of the patient. In general, surgical conditions affecting ruminants present with consistent electrolyte and acid–base abnormalities that allow treatment without laboratory support.

11.4 Fluid and Electrolyte Therapy in the Perioperative Period

Fluid and electrolyte replacement therapy in livestock is required when fluid intake by the animal is not enough to meet their metabolic needs. Rehydration, replacement of lost electrolytes, and restoration of acid–base balance are the goals for fluid therapy. Provision of IV fluids can restore the circulatory capacity and mental status sufficiently that nutrition and replacement of ongoing losses can be provided through oral fluids. The aggressiveness of treatment is dictated by the severity of the condition as well as economic considerations. When developing the fluid and electrolyte replacement therapy plan, three basic assessments should be made: (i) quantity and rate of fluid administration, (ii) fluid type selection for such condition, and (iii) method of fluid administration.

11.4.1 Quantity and Rate of Fluid Administration

Patients that are to be anesthetized should ideally have IV access for administration of fluids and drugs. Fluid therapy is not always indicated for patients undergoing short duration of anesthesia and surgery [8]. When anesthesia and surgical time exceed 1 hour, fluid therapy is indicated to replace insensible water loss, counteract the hypotensive effects of anesthetics, and maintain tissue perfusion. Recipe-based and goal-directed fluid therapy is used to maintain vascular volume and tissue perfusion [9]. A recipe-based or liberal approach is the most often utilized method for fluid administration during anesthesia for farm animals. Fluid administration rates of 3–10 ml/kg/hour of crystalloid solutions (e.g. normal saline, lactated Ringer's solution), but not to exceed 20 ml/kg, are used when the surgical procedure does not result in significant blood loss [9]. In the majority of situations, the rate of fluid administration should not exceed 10 ml/kg/hour. If minor blood loss occurs (<20 ml/kg), patients should receive 3 ml of a balanced electrolyte solution for every 1 ml of lost blood. In surgical procedures in which significant blood loss occurs (>20 ml/kg), a colloid solution or whole blood should be administered for each volume of blood lost. Attempts should be made to maintain the packed cell volume greater than 20%, since a low packed cell volume in combination with hypotension can result in poor tissue perfusion and oxygenation. In cases in which the total plasma protein becomes less than 3 g/dl, plasma administration should be considered. Goal-directed fluid therapy involves administration of fluids during anesthesia and

surgery based on measurements of cardiac performance such as systolic arterial blood pressure. In this situation, combinations of crystalloids and colloids are administered to maintain mean arterial blood pressure in the normal range during surgery (90–120 mmHg) [9]. Colloids such as albumin, hetastarch, and dextrans are not frequently used in anesthesia or fluid therapy for farm animal patients.

For anesthesia and surgical cases that present with dehydration, the fluid therapy plan is calculated to replace deficits while supplying maintenance fluid needs and accounting for ongoing loss of fluids associated with the disease process (Table 11.2). The first priority for treating dehydration is to restore the extracellular fluid volume back to normal. Multiply the estimated percentage of dehydration by body weight in kilograms, which will provide the quantity of fluid in liters recommended to restore an animal to a normal hydration. IV fluid therapy is recommended in cases with clinical signs indicative of shock including tachycardia, increased capillary refill time (CRT >2 seconds), decreased mentation (depression, lethargy, absence or weakness of suckle reflex in calves), cold ears and extremities, and inability to stand. This is true for most ruminants affected with strangulating abomasal or intestinal disease, urinary tract obstruction or rupture, or severe endotoxemia. One report suggested that when dehydration is 8% or greater, IV fluids are necessary in ruminants because oral fluid therapy would not be effective [10]. Since the methods for precisely measuring dehydration are not available, it is important for the clinician to remember that replacing the exact fluid deficit is not of chief concern. Rather, the clinician should replace a fluid deficit to restore tissue perfusion and improve response to anesthesia and surgery.

Fluids given intravenously should be warmed prior to administration because cold fluids result in energy dissipation by the patient [11]. If rehydration can be accomplished prior to anesthesia, a general rule of thumb is to replace half of the fluid deficit over 4–6 hours with the balance given over 12–24 hours. More often, the fluid deficit (resulting in dehydration) is replaced more rapidly (6 hours); however, care should be taken in hypothermic neonates or in cases of sepsis/endotoxemia with increased vascular permeability and disseminated intravascular coagulopathy (DIC), as

Table 11.2 Components and formulas for perioperative fluid therapy.

Category	Amount/formula
Fluid rate during anesthesia	3–10 ml/kg/hour but not to exceed 20 ml/kg/hour
Fluid deficit	%dehydration × body weight in kg
Fluid maintenance	50 ml/kg/day (adults) 80 ml/kg/day (neonates)
Ongoing losses with disease process	Up to 5% of body weight in kg
Bicarbonate deficit	Body weight (kg) × 0.3 × base deficit (adults) Body weight (kg) × 0.6 × base deficit (neonates)
Shock rate	90 ml/kg/hour
Blood transfusion	Administer 1 ml of whole blood for every ml of blood lost during surgery when significant blood loss occurs ml of donor blood = recipient blood volume × desired PCV – actual PCV / PCV of donor blood
Plasma transfusion	30 ml/kg of body weight

PCV, packed cell volume.

generalized, pulmonary and cerebral edema may occur [12]. In these situations, the rate of fluid administration can be set at 40–50 ml/kg/hour, rather than the usual shock therapy rate of 90 ml/kg/hour to prevent such adverse effects.

Calculation of maintenance fluids is based on the physiologic requirements of the patient. The normal adult requires about 50 ml/kg/day to provide enough fluids for digestion and losses through urine and defecation (sensible water loss) and sweat and respiration (insensible water loss). As stated previously, neonates have higher total body water contents than adults and therefore have higher maintenance fluid requirements. The maintenance fluid needs for ruminant neonates can be up to 80 ml/kg/day. When developing the fluid therapy plan, replacement of the deficit is of primary importance, but including maintenance fluid requirements and accounting for ongoing fluid losses in the calculations are important if the animal is not taking in fluids on its own. Several factors including humidity, ambient temperature, dry matter intake, and lactation status affect the daily maintenance fluid requirements in ruminants. For example, lactating cows require 90% of their approximate daily milk production to be factored into their daily fluid maintenance calculations [13]. Care should be taken when patients are on continuous IV fluid therapy or when large volumes of fluids are given in a short period of time, as they can become hypoproteinemic and develop edema. Monitoring packed cell volume and total plasma protein help to prevent overhydrating patients.

Pathologic water losses continue to occur in livestock even while fluid therapy is initiated, especially in cases of infectious diarrhea. Losses may continue as well for third-space sequestration of fluids such as grain engorgement or ruptured urinary bladder. These expected losses should be included in the fluid therapy plan. While it is difficult to estimate these losses, up to 5% of the body weight per day may be estimated as extra fluid losses for animals with severe diarrhea.

11.4.2 Fluid Type Selection

Crystalloid fluids are the mainstay of fluid therapy during anesthesia and consist primarily of water with a sodium or glucose base. Crystalloid fluids can be categorized based on purpose: replacement, maintenance, hypertonic saline, hypertonic sodium bicarbonate, and dextrose in water. Alternatively, crystalloid fluids can be divided based on tonicity and include hypotonic, isotonic, and hypertonic. Replacement crystalloid fluids are required with deficits of either electrolytes, water, or, most commonly, both. The commonly used replacement crystalloids in farm animal medicine are isotonic solutions and include unbalanced solutions such as normal saline (0.9% NaCl) and sodium bicarbonate (1.3% NaHCO₃), and balanced electrolyte solutions such as Ringer's solution (with lactate or acetate), Normosol-R® (Hospira, Inc., Lake Forest, IL, USA), and Plasma-Lyte A® (Baxter Healthcare Corp., Deerfield, IL, USA). Balanced solutions resemble the composition of extracellular fluid while unbalanced solutions do not provide all electrolyte plasma components. All replacement and maintenance crystalloids have a similar osmolality to plasma and can enter all body fluid compartments. These fluids will equilibrate quickly with interstitial fluids, so only 20–25% of the infused fluid remains within the intravascular compartment 1 hour after infusion. During anesthesia, the balanced crystalloid fluids are preferred to the unbalanced crystalloids with few exceptions. Dextrose-containing solutions are indicated for treatment of primary water deficits or hypoglycemia, and normal saline can be used in cases of hyperkalemia (urolithiasis), hyponatremia, or hypochloremia. Although commercially available sterile solutions are ideal for the therapy of farm animals affected by surgical conditions that require anesthesia, some of these solutions are not commercially available (i.e. isotonic 1.3% sodium bicarbonate) or their use in treatment plans can become cost-prohibitive (i.e. when large cattle are being treated).

Table 11.3 Formulas for preparing local electrolyte solutions.

Component	IV solution to be made					
	0.9% NaCl	Nonalkalinizing solution	D ₅ W	0.45% NaCl +2.5% dextrose	1.3% NaHCO ₃	1.3% NaHCO ₃
NaCl	180 g	140 g		90 g		
KCl		25 g				
CaCl ₂		10 g				
50% dextrose			2 l	1 l		
NaHCO ₃					13 g	
8.4% NaHCO ₃ (sol)						0.155 l
Distilled water	20 l	20 l	18 l	19 l	1 l	0.845 l

A useful FDA-approved alternative in these circumstances is using locally prepared fluids with sterile water and reagent-grade salts. When using locally prepared solutions, preventing contamination and immediate administration after preparation is of paramount importance to avoid adverse effects on the patient. Examples of fluids that can be prepared locally with their respective components and amounts can be found in Table 11.3.

Irrespective of the condition affecting the farm animal patient, the decision to administer IV fluids to expand fluid volume is far more important than the specific choice of fluid type and rate; however, as stated before, surgical conditions affecting farm animals, and specifically ruminants, present with consistent electrolyte and acid–base abnormalities. Results from one study that evaluated blood gas analyses and serum biochemistry values in more than 500 cattle demonstrated that dehydrated animals older than 1 month of age were two times more likely to present with metabolic alkalosis than with metabolic acidosis. After excluding cases of pneumonia, acute ruminal acidosis, and diarrhea, only 16% of dehydrated cattle had metabolic acidosis. Hyponatremia and hypokalemia were observed in 20% of the patients and hypochloremia was observed in 40% [14]. In another study of 350 sick cattle, the authors reported that although 60% of dehydrated cattle had a blood pH within the reference range, a greater proportion of cattle (53%) had abnormally elevated serum bicarbonate concentrations compared with only 10% of cattle that had abnormally decreased serum bicarbonate concentrations [15]. Based on the results of these studies, at least for cattle, it would be only in few specific conditions that a truly alkalinizing fluid therapy is necessary.

Calves affected with diarrhea and adult ruminants affected with acute ruminal acidosis, choke, dysphagia, ketosis, pregnancy toxemia, and hepatic lipidosis have the potential to develop metabolic acidosis. Loss of sodium, loss of bicarbonate, increased L-lactate production by peripheral tissues, absorption of D-lactate from bacterial fermentation in the GI tract, and excessive accumulation of keto-acids in blood are some of the most important causes of metabolic acidosis in ruminants [16, 17]. Common electrolyte abnormalities in ruminants suffering from metabolic acidosis include hyponatremia, hyperkalemia, and hypocalcemia. In contrast, other GI and urinary tract conditions affecting cattle and other ruminants such as vagal indigestion, abomasal displacement or volvulus, abomasal impaction, traumatic reticulitis, small intestinal obstructions, and urinary tract obstruction/rupture usually present with metabolic alkalosis [7, 14]. In these cases, alkalosis is a consequence of chloride sequestration in the anterior GI tract or exchange of electrolyte

composition between urine and plasma [7, 18]. Results from one study of 108 goats with urolithiasis demonstrated that 44.8% had mild to moderate metabolic alkalosis. Only 10% of goats with urolithiasis presented with metabolic acidosis in the same study [18]. Different degrees of hyponatremia, hypochloremia, and hypokalemia or hyperkalemia can complicate the metabolic status of the patient in these cases. Strangulating abomasal or intestinal disease can initially present with metabolic alkalosis; however, as the disease process progresses and remains uncorrected, the metabolic status of the patient can become a mixed disturbance due to lack of blood perfusion and increased anaerobic metabolism in affected tissues.

Transition or early lactation high-producing dairy cows are prone to develop disease shortly after calving due to electrolyte imbalances, negative energy balance, and GI stasis. Small ruminants and beef cows carrying multiple fetuses or in a poor plane of nutrition during the last trimester of gestation are at risk of suffering from electrolyte abnormalities and negative energy balance before parturition. Hypocalcemia, hypokalemia, hyperketonemia, hypo/hyperglycemia, and displaced abomasum are common conditions that present around parturition and initiation of lactation in these animals. In any of these circumstances, the goal is to establish an appropriate fluid therapy plan to correct major acid–base and electrolyte imbalances prior to induction of anesthesia.

11.4.3 Fluid Therapy in Cases of Calf Diarrhea

In cases of calf diarrhea, restoring sodium and fluid deficit is insufficient to correct metabolic acidosis [12, 19]. The inclusion of an alkalinizing agent in the fluid therapy plan is necessary to rapidly correct acidemia. Sodium bicarbonate and metabolizable bases such as acetate, propionate, citrate, and lactate are options that can reduce acidemia by consuming the excess of hydrogen ions and increasing the strong ion difference. Acetate, propionate, and lactate are common components of commercially available balanced isotonic crystalloids such as Normosol-R®, Plasma-Lyte A®, and Lactated Ringers (Baxter Healthcare Corp., Deerfield, IL, USA), respectively. Citrate and acetate are common components of oral electrolyte solutions (OES) for calves. In contrast, only hypertonic 8.4% sodium bicarbonate is commercially available, and the clinician should prepare isotonic 1.3% sodium bicarbonate when needed as described in Table 11.3. Calculating base deficit (BD) in ruminants can be achieved by subtracting TCO_2 or total plasma bicarbonate from 25. In the absence of a laboratory biochemistry analysis, the practitioner can calculate BD in diarrheic calves by evaluating clinical signs such as posture, demeanor, presence of suckle reflex, and presence of palpebral reflex [20]. Most importantly, in systemically compromised diarrheic and acidotic calves, IV fluid therapy with sodium bicarbonate is warranted [21]. Using the formula described in Table 11.2, the clinician can estimate the bicarbonate needs of affected animals. After correction of metabolic acidosis, continuing with IV balanced crystalloid fluids or OES is recommended until diarrhea is resolved.

A common consequence of metabolic acidosis in diarrheic calves is hyperkalemia as potassium moves from the intracellular to the extracellular compartment in exchange for hydrogen ions. Correction of hyperkalemia is critical in severely acidotic calves due to its negative effects on cardiac function [19, 21]. Results from one study demonstrated that a small volume (6.4 ml/kg) of IV 8.4% sodium bicarbonate followed by 2l of OES was superior to 7.5% hypertonic saline or 46.2% dextrose solutions in reducing metabolic acidosis and hyperkalemia and resuscitating diarrheic calves [21]. Rapid administration of IV sodium bicarbonate has been associated with cerebrospinal-fluid acidosis in other species; however, results from one study demonstrated that IV administration of hypertonic (8.4%) sodium bicarbonate (10 ml/kg) to diarrheic calves without respiratory disease

over 8 minutes did not result in adverse effects [22]. Additionally, the authors of that study indicated that a single dose of IV hypertonic sodium bicarbonate (10 ml/kg) was better than a single dose of IV hypertonic (5.8%) sodium chloride (5 ml/kg) on reducing dehydration and acidemia when both treatments were followed with 3 l of isotonic OES [22].

After correction of metabolic acidosis, calves that continue to have diarrhea and are anorectic can develop hypokalemia and negative energy balance. In these cases, correction of hypokalemia can be achieved by adding a moderate concentration of potassium chloride (20–40 mEq) per litre of IV fluids. Ensuring milk or milk replacer feeding in smaller volumes at a higher frequency and/or adding 2.5–5% dextrose solutions to the fluid therapy can effectively prevent negative energy balance in these cases.

11.4.4 Fluid Therapy in Cases of Acute Ruminal Acidosis (Grain Overload)

Absorption of D-lactate from the rumen leads to D-lactic metabolic acidosis in affected ruminants [16]. Cases of acute ruminal acidosis usually present with severe dehydration and weakness. Accumulation of D-lactate within the rumen tremendously increases osmolarity and promotes movement of water inward, causing a third-compartment dehydration. Additionally, excessive production of acid causes damage to the ruminal mucosa and promotes translocation of bacteria, endotoxins, and D-lactate into circulation [23, 24]. Endotoxemia exacerbates dehydration and in some cases leads to further electrolyte imbalances such as hypocalcemia [25]. The main goals of the fluid therapy in cases of acute ruminal acidosis are to restore fluid deficit, expand circulating plasma volume, and correct acidemia. Nonacidifying IV fluid solutions such as balanced crystalloids (Normosol-R, Plasma-Lyte) or 1.3% sodium bicarbonate are good options for treatment. In the absence of laboratory testing, affected animals can be treated with an initial bolus of 20 ml/kg of 1.3% sodium bicarbonate IV followed by a constant rate infusion (CRI) of isotonic balanced crystalloids supplemented with calcium borogluconate (25 ml/l) and potassium chloride (20–40 mEq/l). Common effects of endotoxemia include reduced vascular resistance, increased permeability of peripheral blood vessels, vascular leaking, and DIC. In cases of severe systemic compromise as a result of endotoxemia, the addition of a colloid such as IV plasma (20–40 ml/kg) or hetastarch (50–100 ml/kg) can help to maintain oncotic pressure and expand the vascular space [26]. In cases of acute ruminal acidosis, administration of oral fluids should be avoided to prevent exacerbating ruminal distention.

11.4.5 Fluid Therapy in Cases of Hepatic Lipidosis/Ketosis/Pregnancy Toxemia

Dairy cows with subclinical or clinical cases of moderate ketosis usually respond well to treatment with oral propylene glycol (300–500 ml); however, animals affected with hepatic lipidosis, marked clinical ketosis, or pregnancy toxemia need IV dextrose-containing fluids to reduce free fatty acid mobilization and increase glucose availability. In cases of severe negative energy balance, excessive accumulation of ketones in blood can result in a high-anion gap metabolic acidosis and low serum bicarbonate [27]. Additionally, electrolyte imbalances such as hypocalcemia and hypokalemia are usually present. Isotonic 5% dextrose solutions are an option to treat ruminants with severe negative energy balance; however, additional metabolic and electrolyte abnormalities require a different fluid type selection. A 2.5% to 5% dextrose solution mixed with 0.45% sodium chloride or a balanced crystalloid can be effective in reducing negative energy balance and other electrolyte disturbances. The rate of dextrose administration should be 1–2 mg/kg/min. For an adult 500 kg body weight cow, this equates to about 1 l of a 2.5% dextrose solution per hour. For an adult 80 kg

body weight Boer goat, this equates to about 200 ml of a 2.5% dextrose solution per hour. In absence of laboratory testing, the clinician can start with an initial IV bolus of 10–50% dextrose at an approximate dose of 1 ml/kg of body weight to break the negative energy status and fat mobilization cycle and then follow treatment with a 2.5% dextrose CRI. Results from one study indicate that only 30% of hyperketonemic cows develop hypoglycemia, with a greater percentage of ketotic cows being normoglycemic or hyperglycemic [28]. The combination treatment of insulin and a dextrose CRI has been demonstrated to suppress fatty acid mobilization and total liver triglycerides in cases of ketosis [29, 30]. A low dose (200 IU) of protamine zinc insulin subcutaneously or Ultralente human insulin rDNA (Humilin) at a dose of 0.14 IU/kg intramuscularly every 24–48 hours can be effective in increasing tissue uptake of glucose and stimulating hepatic glycolysis [29, 31]. Corticosteroid treatment in cases of negative energy balance should be avoided to prevent hypokalemia resulting in intracellular potassium shifting and excessive renal excretion of potassium [32]; however, regardless of the use of corticosteroids, hypokalemia and hypocalcemia are common abnormalities in dairy cows with severe ketosis or small ruminants with pregnancy toxemia. The addition of potassium chloride (20–40 mEq/l), calcium borogluconate (25 ml/l) or oral calcium supplements, and B vitamins to the fluid therapy is beneficial in these cases. Oral phosphorus supplementation is recommended in cattle treated with dextrose solutions for prolonged periods due to a greater risk of hypophosphatemia [33].

11.4.6 Fluid Therapy in Cases of Abomasal and Small Intestinal Disorders

Uncomplicated left displacements of the abomasum usually do not present with significant hemodynamic or metabolic abnormalities that require aggressive IV fluid therapy. In these cases, oral electrolytes supplemented with calcium and propylene glycol are an excellent choice. In contrast, cattle with right abomasal volvulus or strangulating/obstructive intestinal disease (i.e. intussusception) usually present with severe dehydration, metabolic alkalosis, hypochloremia, hypokalemia, and hyponatremia [7, 14]. Treatment of these animals consists of 15–20 l of IV isotonic sodium chloride or another nonalkalinizing solution before or during surgery (Table 11.3). Regular isotonic sodium chloride or nonalkalinizing solutions rich in chloride and potassium are the best alternative to correct dehydration and electrolyte imbalances in ruminants with metabolic alkalosis. Hypertonic (7.2–7.5%) sodium chloride solutions at a rate of 4–7 ml/kg IV followed by water or isotonic OES are a good choice for fluid therapy in cases of abomasal surgery in the field. Subclinical hypocalcemia and ketosis are common complications of abomasal displacement in dairy cows [34]. Intravenous fluids should be supplemented with calcium borogluconate (25 ml/l) and potassium chloride (20–40 mEq/l) as needed, especially in early postpartum dairy cows. Alternatively, calcium chloride can be included in the preparation of a Ringer's solution (Table 11.3). Dextrose should be added to the fluid therapy in cases of severe ketosis, as described previously. Oral electrolytes can be supplemented with calcium, propylene glycol, and potassium chloride as needed.

11.4.7 Fluid Therapy for Cases of Sepsis (Septic Peritonitis, Septic Omphalitis, etc.)

Septicemia in ruminants usually results in endotoxic shock and hypovolemia. Therefore, expanding effective circulatory volume, improving cardiac output, and restoring tissue perfusion are of paramount importance in the fluid therapy goals of septicemic/endotoxemic ruminants. Ileus and GI stasis as a consequence of endotoxemia can lead to sequestration of chloride in the abomasum

and result in metabolic alkalosis. Intravenous balanced nonalkalinizing isotonic crystalloids supplemented with potassium chloride (20–40 mEq/l) are good alternatives for the treatment of endotoxemic patients. The combination of IV hypertonic saline (7.2–7.5%) at 4–7 ml/kg followed by water or isotonic OES (20l to adults to ~3l to calves) is a good choice for the treatment of these type of patients in the field. Hypocalcemia is a common consequence of endotoxemia in dairy cows [25, 35]. In these cases, the addition of calcium borogluconate (25 ml/l) to the IV fluids or oral calcium supplements are indicated. Additional side effects of endotoxemia are increased vascular permeability, reduced oncotic pressure, and coagulopathy (DIC). Plasma (20–40 ml/kg) or hetastarch (50–100 ml/kg) can be useful to maintain oncotic pressure and prevent pulmonary edema in endotoxic patients [26, 36].

11.4.8 Fluid Therapy in Cases of Urinary Tract Obstruction/Rupture

Farm animals affected by urolithiasis can present with metabolic alkalosis and different levels of dehydration, azotemia, hyponatremia, hypochloremia, and hyperkalemia. In some of these cases (i.e. bladder rupture), hyperkalemia can be life-threatening for animals undergoing general anesthesia and surgery of the urinary tract [18]. The main goal in these cases is to correct severe dehydration and hyperkalemia before surgery. When the plasma potassium levels are >6 mmol/l, draining urine by cystocentesis or removing free urine from the abdomen through catheterization is recommended before general anesthesia and surgery. The administration of IV fluids before correction of the obstruction (i.e. surgery) should be practiced with care to avoid exacerbating distention of the urinary tract (bladder or urethra) or further accumulation of urine within the abdomen. Isotonic sodium chloride or 5% dextrose solutions can help reduce hyperkalemia before surgery. Post-surgery or once the urinary obstruction has been resolved, the main goal of the fluid therapy is to reduce the azotemia and resolve hyponatremia and hypochloremia. Isotonic 0.9% sodium chloride at a higher fluid rate (1.5–2 times maintenance) is the best choice to increase diuresis and reestablish electrolyte balance.

11.4.9 Whole-blood Transfusions

Farm animals affected with conditions that result in acute whole-blood loss (i.e. trauma, lacerations, fractures), chronic whole-blood loss (GI parasitism, abomasal ulceration), or increased destruction of red cells (intravascular or extravascular) can benefit from a whole-blood transfusion. In general, whole-blood transfusions are recommended when clinical signs suggestive of tissue hypoxia exist, such as elevated heart and respiratory rates, weakness, and lethargy in the face of pallor of mucous membranes, or when the packed cell volume drops below 15%. Whole blood can be administered at a dose of 10–20 ml/kg; however, this will only result in an increase in packed cell volume of the recipient by 3–4%. For hemorrhagic shock, at least half of the estimated blood loss should be replaced by whole blood [37]. Whole-blood transfusions can also be used as a source of plasma and can be given at a dose of 40–80 ml/kg. Monitoring of the transfusion is important, and the whole-blood transfusion should be started at a slow rate (0.1 ml/kg/hour) with vital signs evaluated every 5 minutes. Although uncommon in ruminants, anaphylactic reactions to whole-blood transfusions are characterized by fever, dyspnea, hiccoughing, muscle tremors, salivation, and lacrimation. If a transfusion reaction is noted, blood administration should be ceased and epinephrine (1:1000) should be administered at a dose of 0.01–0.02 ml/kg intravenously.

11.4.10 Method of Administration

Administration of fluids is performed primarily by two routes, oral and IV. Subcutaneous, intra-peritoneal, and intraosseous routes are options but are not commonly used. Subcutaneous fluid therapy is limited by the volume that can be safely administered, therefore this route cannot meet the daily fluid needs of most livestock patients. In addition, subcutaneous fluids are contraindicated in animals that are severely dehydrated as blood is shunted away from the subcutaneous vasculature, leading to poor absorption of the administered fluids. With severe dehydration (>8%) and systemic compromise, the IV route is required. IV fluids can be given as bolus injections or as a CRI. Oral fluids have the advantage of being less costly but have the disadvantage of being less effective in cases involving GI stasis or severe dehydration. In addition, oral fluids should not be given to adult livestock within 8–12 hours of anesthesia.

Catheterization of the jugular vein is the most widely used approach for fluid therapy in livestock. A catheter should be placed prior to anesthesia in ruminant patients. In younger animals, the jugular vein is very superficial and easy to visualize. For small ruminants and calves, jugular catheterization is easiest with the patient positioned in lateral recumbency. As an alternative to the jugular vein, catheterization of the auricular vein for IV fluid administration in mature cattle offers easy accessibility. Large bulls with muscular necks can benefit from auricular vein catheterization because the catheter can be kept for longer periods while still allowing high flow administration rates [38].

Although the IV route should be the route of choice for fluid administration to preanesthetic and surgical patients, complete IV rehydration and correction of metabolic abnormalities in mature cattle requires a large amount of fluids and can become cost-prohibitive for producers. Oral fluid therapy can be utilized in these cases. In general, oral fluid therapy is preferred since it is the most physiologic but use of oral fluids is limited in cases set to undergo anesthesia and surgery. Oral fluids can be administered by orogastric or nasogastric intubation or through a rumenostomy surgery site. Orogastric tubes or self-retaining esophageal tubes (Magrath Cattle Pump System®, McCook, NE, USA) can be passed all the way down the esophagus into the reticulorumen in adult ruminants. For neonates, a nipple bottle, small red rubber feeding tubes or esophageal feeders are suitable. Deposition of milk and bicarbonate- or sodium-enriched fluids stimulate esophageal groove closure and diversion of the fluid to the abomasum for digestion and absorption. Oral rehydration solutions formulated for calves can be utilized for the treatment of small ruminants. All oral rehydration solutions must be mixed according to their label directions to avoid alterations in tonicity. Oral fluids can be administered at a dose of 3.5% of body weight at any one time.

Another alternative to address severe dehydration in ruminants while reducing the overall cost of fluid therapy is the use of a combination of IV and oral fluid therapy. A common practice among practitioners in the field is the administration of IV hypertonic (7.2–7.5%) sodium chloride solutions at 4–7 ml/kg over 5–20 minutes followed by oral/intra-ruminal water or isotonic OES. In one study, the administration of 5 ml/kg of hypertonic saline followed by ~3l of OES to diarrheic and acidotic calves was effective in rapidly correcting hypovolemia and metabolic acidosis compared with OES alone [39].

11.5 Monitoring Fluid Administration

Fluid administration during anesthesia and surgery is performed to expand the vascular volume in order to improve cardiac output, which will improve organ and tissue perfusion. As most drugs used for induction and maintenance of anesthesia decrease cardiac contractility and induce

vasodilation, hypovolemia is a common negative effect encountered during or after anesthesia. Use of monitoring equipment including electrocardiogram and arterial blood pressure analyzers is important to monitor the effects of inadequate or excessive fluid administration. Mean arterial blood pressure should be maintained at least above 60 mmHg, preferably 70 mmHg in adult cattle [8]. IV fluids in combination with judicious use of vasopressors can help to maintain adequate blood pressure. Please refer to Chapter 7 for treatment of hypotension. Close monitoring of heart rate, pulse strength, respiratory rate, and color of mucous membranes should be performed during anesthesia and recorded. Monitoring for fluid overload is also extremely important and can be evaluated by central venous pressure measurements and pulmonary auscultation. Central venous pressure or jugular venous pressure measurements are often not performed during anesthesia in farm animals, but if available and pressures are greater than 15 mmHg, volume overload occurs. Pulmonary auscultation is performed to detect increased bronchovesicular lung sounds that may be associated with pulmonary edema. Packed cell volume and total protein should be maintained above 20% and 3.5 g/dl, respectively, and serum electrolytes should be maintained within the reference ranges.

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12

Regulatory and Legal Considerations of Anesthetics and Analgesics Used in Food-producing Animals

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Veterinarians and animal owners who are involved in the production of animals for human consumption are charged with providing healthy, wholesome, and safe products. Consumers demonstrate an increased interest in the origin of their food and demand that it is produced under standards that ensure the well-being of food-producing animals and prevent contamination of food with harmful microorganisms or residues. While much misconception about the use of pharmaceuticals in food-producing animals exists in the general public, ensuring that edible animal products are free from harmful residues is the legal and moral obligation of producers and veterinarians. To achieve this goal, labels for all drugs approved for use in food-producing animals must provide a withdrawal time for meat, milk, and/or eggs, and animal products cannot be harvested until this time has elapsed. In the USA, this requirement is the result of amendments to the federal Food, Drug, and Cosmetics Act of 1906s, including the Delaney Clause of 1958 and the Kefauver-Harris Drug Amendments of 1962, which imposed that drugs must be safe and efficacious and must not leave unsafe residues in edible animal products [1]. Similarly, the directive 2001/82/EC has regulated the use of veterinary medicinal products in the European Union and created the legal framework for establishment of withdrawal periods following drug administration to food-producing animals. Directive 2001/82/EC has been repealed and replaced by Regulation (EU) 2019/6 with the goal of harmonizing and enhancing the regulatory framework among member countries [2].

In the USA, to achieve approval for marketing of a new animal drug, the sponsor must file a New Animal Drug Application (NADA) with the US Food and Drug Administration (FDA). The sponsor then must demonstrate in studies that the new drug is safe and efficacious in the target animal species, is safe for the environment, and can be manufactured to uniform standards of purity, strength, and identity. In addition, for food-producing animals, the sponsor must demonstrate that food products derived from treated animals are safe for human consumption. The goal of human food safety studies is a risk standard of “reasonable certainty of no harm,” which is assessed in toxicity and residue chemistry studies [3]. Toxicity studies are performed to assess the toxic hazard of a drug and its metabolites resulting from consumption of products from treated animals, and include genetic toxicity studies, 90-day feeding studies, and a two-generation reproduction study to assess the cross-generational toxicity and teratogenic potential of a new drug [3]. Residue and metabolism studies are performed to describe the fate of a drug following administration to the target species. For drugs

demonstrated to require a withdrawal time, residue depletion studies are performed. The drug is administered at the largest label dose for the longest label duration to evaluate residue depletion to below a tolerated concentration (tolerance). For withdrawal time calculations, the FDA, using parametric statistical methods, determines 99% tolerance limits with 95% confidence, indicating that there is only a 5% chance that 1 of 100 animals treated in accordance with label directions has tissue residues that exceed the tolerance value [3]. While similar in approach, the European Committee for Veterinary Medicinal Products (CVMP) determines withdrawal periods using differing statistical methods and suggests that 95% tolerance limits are more appropriate [4]. Support and criticism exist for these methods, and alternative statistical procedures have been proposed, including non-parametric methods that do not require the satisfaction of assumptions of parametric methods to estimate withdrawal times [5–8]. Additional concerns have also been expressed concerning withdrawal time calculations for injection sites, from which residues deplete extremely slowly and erratically [9, 10]. Various factors influence the metabolism and degradation of injectable pharmaceuticals at the injection site, which can result in differing residue depletion profiles as compared to other tissues [11]. In different countries, varying assessments are used by licensing authorities to evaluate the food safety implications of injection site residues, and the necessity for an internationally harmonized approach has been emphasized [11].

Veterinarians are commonly faced with the need to administer medications in a fashion or to a species that is not in accordance with label directions. When using pharmaceuticals in an extralabel fashion, the veterinarian assumes the legal responsibility of ensuring that the product is safe, efficacious, and will not leave harmful residues in animal products intended for human consumption. The Animal Drug Use Clarification Act (AMDUCA) of 1994 amended the Federal Food, Drug and Cosmetics Act to allow veterinarians to prescribe approved animal drugs in an extralabel fashion, but also defined several conditions and stipulations, including the following [12]:

- Extralabel drug use is permitted only by the order of a licensed veterinarian within the context of a valid veterinarian–client–patient relationship.
- No other approved animal drug is labeled and contains the same active ingredient in the required dosage and concentration, except when the veterinarian finds the approved drug to be clinically ineffective.
- The health of the animal is threatened, or suffering or death may result from failure to treat.
- Extralabel drug use is not permitted to enhance production or for feed additives.
- Extralabel use of an approved human drug is not permitted in food-producing animals if an approved animal drug can be used in an extralabel fashion.
- Appropriate labeling information, including withdrawal times for meat, milk, and/or eggs as specified by the veterinarian, must be provided.
- Ensure that the identity of the treated animal is recorded and records are maintained.
- Extralabel use that may result in residues above an established safe level or tolerance or present a risk to public health is not permitted.

The effects of antimicrobial use in food animals and resulting residues in animal products have received much attention, but human safety concerns unique to residues associated with anesthetic drugs exist. At least four idiosyncratic or allergic responses related to anesthetic or anesthetic adjuncts can occur in people, including malignant hyperthermia, halothane hepatitis, porphyria, and allergic reactions [1]. Violative residues of anesthetics are much less frequently detected than those of antimicrobials or anthelmintics, and adverse reactions in people exposed to anesthetic residues are not reported. While sensitive detection methods exist, the infrequency of detecting anesthetic residues in food animal tissues may in part result from paucity of routine testing.

Additional factors that decrease the risk of anesthetic residues include (i) short-term use for single procedures reduce the risk of accumulation, (ii) short half-life ($t_{1/2}$) of most anesthetics, (iii) common intravenous (IV) or inhalant administration results in more rapid absorption as compared to other routes of administration, (iv) potency of current anesthetics results in low doses, and (v) unlike many other drugs, anesthetics are usually used under direct veterinary supervision [13]. Following the use of an anesthetic for surgery, sufficient time for drug elimination usually elapses until slaughter; however, risk of violative residues exists when fractious animals are tranquilized for transport to slaughter or show animals are sedated in shows preceding sale.

As most anesthetic or anesthetic adjunct drugs are not approved for food animals, their use commonly falls under the regulations of AMDUCA. Considerable heterogeneity exists in the metabolism and excretion of pharmaceuticals within and especially between species, limiting the ability to extrapolate residue information from one species to another. Therefore, an extended withdrawal time should be considered when using a drug approved for one food animal species in another.

The primary resource for information for veterinarians using pharmaceuticals in an extralabel fashion is the Food Animal Residue Avoidance Databank (FARAD), which was established as part of the USDA FSIS Residue Avoidance Program of 1982 [14, 15]. On its webpage, veterinarians can search the database for approved food animal drugs and find recommended withdrawal times for extralabel use of some drugs. In addition, veterinarians can contact FARAD by email, or in emergencies by phone, and FARAD personnel will recommend an appropriate withdrawal interval according to the individual features of each case. Recommendations are based on available pharmacokinetic studies, and members of FARAD have developed an Extended Withdrawal Interval Estimator (EWE) algorithm that facilitates the calculation of extended withdrawal times in a repeatable and scientifically valid fashion [16]. The accuracy of the recommended withdrawal times is dependent on available pharmacokinetic data, and more conservative estimates are provided when little data is available.

When tissue residue depletion data are not available, the plasma $t_{1/2}$ can be used to calculate withdrawal times, and this approach is a viable alternative for many drugs [17, 18]. For other drugs, such as those that concentrate in target tissues or that have metabolites that are excreted at a slower rate than the parent drug, plasma $t_{1/2}$ -derived estimates of withdrawal time may be too short. Furthermore, pharmacokinetic studies are performed in healthy animals, and drug elimination in sick animals with compromised kidney or liver function may be prolonged [13]. The animal groups in which violative residues are most often reported are veal calves and culled dairy cows, in which elimination kinetics are often altered due to disease and reduced excretory function [19]. Considering the various factors that can influence drug elimination, adding a safety margin to the withdrawal time in sick and debilitated animals is prudent.

Some general rules apply when extrapolating withdrawal times in the absence of available information from FARAD [19, 20]:

- 1) For drugs that are eliminated in a linear fashion, doubling the dose will add an additional $t_{1/2}$ to the withdrawal time, provided the same route and volume per site are administered.
- 2) 99.9% of a drug is eliminated after 10 $t_{1/2}$, which can be a good rule of thumb to extrapolate the withdrawal time for many drugs. However, the remaining 0.01% must be below the tolerance level for tissue residues and tissue deposition must not occur.
- 3) In smaller species, $t_{1/2}$ are generally shorter than in larger species, and directly extrapolating withdrawal times from cattle to small ruminants is often appropriate.

With some exceptions, most anesthetics and anesthetic adjuncts have very short elimination $t_{1/2}$ and should be largely cleared from the body after 48–96 hours [13].

12.1 Alpha-2 Agonists and Antagonists

Alpha-2 agonists include xylazine, detomidine, and medetomidine, which induce sedation and analgesia. While xylazine and detomidine are commonly used in all farm animals, in the USA xylazine is approved only for horses and cervids, and detomidine is approved only for horses. In contrast to the USA, detomidine and xylazine are approved for use in food animals in various countries, and recommended withdrawal times vary (Table 12.1).

Cattle and small ruminants are very sensitive to the effects of xylazine. For systemic administration of xylazine, typical doses range from 0.05 to 0.3 mg/kg in cattle and 0.05 to 0.2 mg/kg in small ruminants. The pharmacokinetics profile of xylazine is best described by a two-compartment model with a rapid distribution phase and a large volume of distribution [21]. Following IV administration, the $t_{1/2}$ of distribution was 1.2 minutes in cattle and 1.9 minutes in sheep [22]. The elimination $t_{1/2}$ of xylazine following IV administration in cattle is 36 and 23 minutes in sheep, and is very similar when the drug is administered intramuscularly. Xylazine is rapidly metabolized to inactive compounds, and elimination occurs mainly by urinary excretion of these metabolites. In cattle, the primary metabolite of xylazine is 2,6-dimethylaniline, a toxic substance demonstrated to be carcinogenic in rats [21]. The toxicity of 2,6-dimethylaniline, which is used for many industrial manufacturing processes, has been extensively studied and its genotoxic and carcinogenic properties have prevented the FDA from establishing an acceptable daily intake (ADI) [21, 23]. However, there is currently no evidence that xylazine has carcinogenic potential for livestock at tranquilizing doses, and ingestion of edible tissues from xylazine-treated animals appears to pose an extremely low risk [24, 25].

Table 12.1 Examples of anesthetics and anesthetic adjuncts approved for use in farm animals outside of the USA (note that recommended withdrawal times can vary widely between countries).

Drug name	Country	Species	Withdrawal time
Acepromazine	Canada	Cattle, sheep, goats, pigs	Meat 7 days, milk 48 hours
Detomidine	Europe	Cattle	Meat 2 days, milk 12 hours
Ketamine	Europe	Cattle, sheep, goats, pigs	Meat 1 day, milk 0 hours
Meloxicam	Australia, New Zealand	Cattle, sheep, pigs	Injectable formulation: meat (cattle, pigs, sheep) 10 days, 3 days, 11 days milk (cattle, sheep) 84 hours, 11 days
	Canada	Cattle, sheep, pigs	Injectable formulation: meat (cattle, pigs, sheep) 20 days, 5 days, 11 days milk (cattle, sheep) 96 hours, 11 days
	Canada	Cattle (not in lactating animals)	Oral formulation: meat 35 days
	Europe	Cattle, pigs	Meat (cattle) 15 days Milk 5 days
			Meat (pigs) 5 days
Xylazine	Europe	Cattle	Meat 1 days, milk 0 days
	New Zealand	Cattle	Milk 3 days, milk 0 days

FARAD has updated its previous recommendations for xylazine withdrawal times (Table 12.2) based on approval of the drug for cattle in New Zealand [26]. In that study, a single intramuscular (IM) dose of 0.35 mg/kg of xylazine followed by 4 mg/kg of IV tolazoline were administered, and concentrations of xylazine and 2,6-dimethylaniline were below the limit of detection (10 µg/kg) by 72 hours in tissues and 12 hours in milk [27]. Currently, a withdrawal time of 4 days for meat and 24 hours for milk is recommended for doses of 0.05–0.3 mg/kg by IM administration [26]. For larger doses of xylazine (0.3–2.0 mg/kg) given intramuscularly, the recommended meat withdrawal time is 10 days and milk withdrawal time is 120 hours. For IV administration of 0.016–0.1 mg/kg of xylazine, recommended withdrawal times are 5 days for meat and 72 hours for milk. These recommendations pertain to single and multiple doses and are identical to those for sheep and goats [28]. For swine, a withdrawal time of 18 days is recommended for a single IM xylazine administration of up to 2.2 mg/kg [29]. For cervidae, including elk, fallow deer, mule deer, sika deer, and white-tailed deer, species-specific IM doses are provided. Xylazine should not be administered 15 days before or during the hunting season, and a minimum withdrawal time of 14 days is recommended [28]. In an emergency, xylazine is approved for use in organic livestock production, which requires a meat withdrawal time of 8 days and a milk discard period of 4 days [30].

The newer α_2 agonist detomidine has similar effects as xylazine, but, in contrast to xylazine treatment, animals usually remain standing after an IV dose of detomidine [24]. When intramuscularly administered at 50 µg/kg to facilitate castration of rams and bucks, detomidine affected body temperature, heart and respiratory rates, and blood pressure similarly, but provided superior analgesia to xylazine administered at 200 µg/kg [31]. Detomidine is labeled for IV or IM use in horses, but IV use has been recommended for most clinical scenarios [24]. An IV dose of 0.01 mg/kg is commonly used at a referral hospital [24]. A detomidine gel formulation approved for sublingual administration in horses was demonstrated to result in similarly deep sedation and approximately 34% bioavailability when administered to calves at 0.08 mg/kg sublingually as compared to IV detomidine administered at 0.03 mg/kg [32]. In goats, 0.01 mg/kg of detomidine produced sedation only when administered intravenously, and this dose does not result in observable analgesia. In contrast, doses of 0.02 or 0.04 mg/kg produced effective sedation and moderate analgesia by IV or IM routes, and ataxia and sternal recumbency were observed in all goats that were given 0.04 mg/kg [33]. In cattle, detomidine is characterized by rapid distribution and elimination, with elimination $t_{1/2}$ of 1.32 hours after IV administration and 2.56 hours after IM administration [34]. Excretion of detomidine in milk is very low, and concentrations of 0.4 ng/g were present at the first milking 11 hours after dosing, and no detectable amounts were present at 23 hours following administration [34]. Recommended withdrawal times for single or multiple IM or IV doses of up to 0.08 mg/kg are 3 days for meat and 72 hours for milk for cattle and small ruminants [28].

The pharmacologic effects of α_2 agonists are commonly reversed using the α_2 antagonist tolazoline, which is generally administered at 2–4 mg/kg by slow IV infusion. In 13 steers and 10 lactating dairy cows, tolazoline was administered 10 minutes after sedation with xylazine, and tissue and milk concentrations were evaluated [27]. Concentrations of tolazoline were below the limit of quantification (10 µg/kg) by 96 hours in tissues and 48 hours in milk. These data served as the basis for current FARAD withdrawal time recommendations, which are 8 days for meat and 48 hours for milk following a single IV dose of 2–4 mg/kg [26]. While demonstrated to be less effective than tolazoline or atipamezole [35–37], yohimbine can be used to reverse the effects of α_2 agonists. Relatively little pharmacokinetic data are available for yohimbine, and FARAD recommends a conservative withdrawal time of 7 days for meat and 48 hours for milk for cattle and small ruminants [15]. In organic livestock production, tolazoline can be utilized for the reversal of xylazine, and withdrawal periods of 8 days for meat and 4 days for milk are required [30].

Table 12.2 Recommended withdrawal times for anesthetics and anesthetic adjuncts in farm animals in the USA.

Drug class	Drug name	Cattle			Small ruminants			Swine	
		Meat	Milk	Dose	Meat	Milk	Dose	Meat	Dose
Alpha-2 Agonists	Detomidine	3 days	72 hours	≤0.08 mg/kg IV or IM	3 days	72 hours	≤0.08 mg/kg IV or IM		
	Xylazine	5 days	72 hours	0.016–0.1 mg/kg IV	5 days	72 hours	0.016–0.1 mg/kg IV	18 days	2.2 mg/kg IM
		4 days	24 hours	0.05–0.3 mg/kg IM	4 days	24 hours	0.05–0.3 mg/kg IM		
		10 days	120 hours	0.3–2.0 mg/kg IM	10 days	120 hours	0.3–2.0 mg/kg IM		
Alpha-2 Antagonists	Tolazoline	8 days	48 hours	2–4 mg/kg IV					
	Yohimbine	7 days	72 hours	≤0.3 mg/kg	7 days	72 hours	≤0.3 mg/kg		
Barbiturates	Thiopental	1 day	24 hours	≤9.4 mg/kg IV	1 day	24 hours	≤5.0 mg/kg IV		
Benzodiazepines	Diazepam	10 days		≤0.1 mg/kg IV	10 days		≤0.1 mg/kg IV		
Dissociative Anesthetics	Ketamine	3 days	48 hours	≤10 mg/kg IM	3 days	48 hours	≤10 mg/kg IM	2 days	10 mg/kg IM
		3 days	48 hours	≤2 mg/kg IV	3 days	48 hours	≤2 mg/kg IV	4 days	20 mg/kg
	Telazol*							30 days	≤2 mg/kg
Local anesthetics	Lidocaine	1 day	24 hours	≤15 ml epidurally					
		4 days	72 hours	≤100 ml SC					
Opioids	Morphine	14 days	48 hours	0.1 mg/kg once IV, IM, epidurally	14 days	48 hours	0.1 mg/kg once IV, IM, epidurally		
	Butorphanol	5 days	72 hours						
Non-steroidal anti-inflammatory drugs	Flunixin	4 days	36 hours	≤2.2 mg/kg IV, q24 hours for ≤3 days (label)				12 days	2.2 mg/kg IM

		7 days	84 hours	≤ 2.2 mg/kg IV, once				13–15 days	2.2 mg/kg IM, if product not labeled for swine
		10 days	96 hours	≤ 2.2 mg/kg IM, SC, PO once				21 days	2.2 mg/kg, IV or PO, ≥ 1 dose
		≤ 60 days		≤ 2.2 mg/kg IM, SC, PO multiple doses					
	Meloxicam	21 days		0.5–1 mg/kg PO single dose	15 days		1 mg/kg PO, single dose		
		30 days		≤ 1 mg/kg PO, multiple doses					
	Phenothiazine Derivatives	7 days	48 hours	≤ 0.13 mg/kg IV	7 days	48 hours	≤ 0.13 mg/kg IV	7 days	≤ 0.055 mg/kg IV
		7 days	48 hours	≤ 0.44 mg/kg IM	7 days	48 hours	≤ 0.44 mg/kg IM	7 days	≤ 0.44 mg/kg IM

IM, intramuscular; IV, intravenous; PO, per os; q24 hours, every 24 hours; SC, subcutaneous.
Further information and sources of recommendations are detailed in the text.

12.2 Barbiturates

The short-acting barbiturate thialbarbitone and ultra-short-acting barbiturate thiamylal are approved for food animal use, but are, like thiopental, not currently available. The short duration of narcosis following single IV infusion of *N*-methyl-barbiturates and thiobarbiturates is not a result of rapid metabolism but of redistribution to less vascularized tissues. After administration, the short-acting barbiturates almost instantly enter the brain and other organs that receive large proportions of the cardiac output. Subsequently, redistribution to larger, less vascularized tissues occurs and results in loss of narcosis. A large proportion of short-acting barbiturates can redistribute to adipose tissues, depending on the amount of body fat, and accumulation in adipose tissues can occur with repeated administration. FARAD has established withdrawal times of 1 day for meat and 24 hours for milk after administration of the ultra-short-acting barbiturates thiamylal (up to 5.5 mg/kg) and thialbarbitone (up to 9.4 mg/kg) [28]. In small ruminants, recommended withdrawal times for a single IV dose of up to 5 mg/kg of thiopental are 1 day for meat and 24 hours for milk [38]. Ultra-short-acting barbiturates are most commonly used for induction of anesthesia. For this purpose, they may be replaced by other injectable anesthetics such as propofol, which is discussed in section 12.9.

12.3 Benzodiazepines

The minor tranquilizers diazepam and midazolam are used for their anxiolytic, anticonvulsant, and centrally muscle-relaxing effects. They can be suitable for sedation or, in combination with another agent such as ketamine, for induction of anesthesia. Benzodiazepines can be especially useful for use in high-risk animals, such as geriatric or debilitated livestock, because of their minimal cardiovascular and pulmonary effects. Additionally, benzodiazepines have a short-lived appetite-stimulating effect, and an injectable formulation containing brotizolam (Mederantil®) is commercially available for the approved use of appetite-stimulation in cattle in some European countries.

Benzodiazepines rapidly penetrate the blood–brain barrier, and maximal brain concentrations are achieved within a minute of IV administration [39]. In sheep, diazepam reaches maximal serum concentrations in 14.6 ± 7.2 minutes following IM administration, which is much more rapid than in people [40]. Diazepam and midazolam are metabolized by the liver, and high concentrations of active diazepam metabolites are present in the bloodstream following administration. Elimination kinetics and other pharmacokinetic characteristics vary greatly between species [41], making the extrapolation of appropriate withdrawal times from other species difficult. The prevention of benzodiazepine residues in tissues of farm animals is critical because a variety of adverse effects can occur in people [13]. Pharmacokinetic and residue studies guiding withdrawal time recommendations for benzodiazepines in food-producing animals are currently lacking. Therefore, a conservative withdrawal time estimate of 30 days for meat should be used [13]. For IV doses of diazepam of up to 0.1 mg/kg in cattle and small ruminants, FARAD recommends a withdrawal of 10 days [29]. Benzodiazepines should not be used in lactating dairy cattle [13].

12.4 Dissociative Anesthetics

Dissociative anesthesia differs from narcosis induced by other drugs, as in addition to the depressive components such as unconsciousness and analgesia, catalepsy and spasms are also induced. The mechanism of action is understood to be a noncompetitive blockade of glutamate at the

N-methyl-D-aspartate (NMDA) receptor. Only two dissociative anesthetics are used in veterinary medicine, ketamine and tiletamine. Ketamine is usually administered in combination with other anesthetics and can be used in anesthesia induction and maintenance protocols. Tiletamine is available only in combination with the benzodiazepine-derivative zolazepam, and this combination (Telazol®) is widely used for immobilization and anesthesia in various species.

While tissue-residue data for ketamine are not available, the European Committee for Veterinary Medicinal Products concluded that a maximum residue limit (MRL) does not need to be established for ketamine, because “ketamine is rapidly absorbed and extensively excreted” and the drug is used only in individual animals which are not sent for slaughter during or immediately after treatment [42]. Different studies have investigated the pharmacokinetics of ketamine in food animals, demonstrating rapid elimination following administration. Ketamine is rapidly metabolized and its major metabolite, norketamine, contributes to the analgesic effects of ketamine [43, 44].

In calves administered 5 mg/kg of ketamine intravenously, the elimination $t_{1/2}$ was 60.5 ± 5.4 minutes. In the same study, other calves received ketamine 10 minutes after premedication with 0.2 mg/kg of xylazine, which did not significantly alter the elimination $t_{1/2}$ of ketamine. In contrast, premedication with xylazine resulted in a significantly lower volume of distribution and clearance of ketamine and prolonged the duration of anesthesia [45]. In calves administered a subanesthetic combination of xylazine (0.05 mg/kg) and ketamine (0.1 mg/kg) to provide sedation without recumbency (“ketamine stun”) prior to castration, similar pharmacokinetic parameters were determined [43]. In lactating dairy cows intravenously administered 5 mg/kg of ketamine the plasma elimination $t_{1/2}$ was 1.8 ± 0.5 hours and ketamine was undetectable at 12 hours of the study, with the last detectable concentration present at 8 hours after administration [46]. In milk samples, ketamine was detectable until 48 hours of the study and no residues were present at 60 hours after administration.

In sheep, a similar but shorter $t_{1/2}$ of 40 minutes was reported [44]. Ketamine and its metabolites are rapidly detectable in the urine of intravenously injected sheep, with peak concentrations occurring at 20 minutes. At 24 hours following injection, a large concentration of ketamine metabolites is present in urine samples, but only trace amounts of ketamine are present [44]. In swine, ketamine is highly bioavailable and rapidly absorbed following IM injection, and peak plasma concentrations are detected between 1 and 15 minutes [47]. Considerable individual differences of maximal plasma concentrations (1.5 to $12 \mu\text{g/ml}$) and total amount of ketamine ($\text{AUC } 14.5\text{--}42.5 \mu\text{g h/ml}$) were detected between swine. Immobilization and sternal recumbency were observed 1–5 minutes after IM injection. Lateral recumbency (sleep time) varied from 9 to 48 minutes in young pigs, and considerably longer sleep times were observed in adult sows (78–88 minutes). Elimination $t_{1/2}$ varied between 1.7 and 2.9 hours for ketamine and 1.4–3.2 hours for norketamine. Analgesic effects of ketamine varied between individual animals, and sleep time was directly correlated with plasma concentrations of ketamine [47].

Recommended withdrawal times following single and multiple IM administrations of up to 10 mg/kg of ketamine in cattle and small ruminants are 3 days for meat and 48 hours for milk. For IV doses of up to 2 mg/kg withdrawal time recommendations are also 3 days for meat and 48 hours for milk [28]. For larger doses of intravenously administered ketamine (up to 5 mg/kg), a milk withdrawal time of 48 hours is recommended by FARAD based on a previous publication [46]. However, as discussed above, ketamine was still present in the milk of five of six cows in that study, and the authors recommend adherence to a longer withdrawal time than currently provided by FARAD [46]. For swine, a meat withdrawal time of 2 days is recommended for ketamine doses of 10 mg/kg by IM or IV route [29]. Many anesthesia protocols for swine use larger doses of ketamine, prompting the necessity for longer withdrawal times. For IM doses of up to 20 mg/kg in swine a meat withdrawal time of 4 days was recommended [29].

While the use of Telazol is reported in various species, published studies reporting pharmacokinetics and tissue residues in cattle or small ruminants do not exist, and withdrawal time recommendations could not be made by FARAD [28]. In pigs administered a single IM dose of Telazol of 10 mg/kg, maximal plasma concentrations were detected at 31.92 minutes (range 15–75 minutes) for tiletamine and 65.17 minutes (range 15–135 minutes) for zolazepam. The $t_{1/2}$ was 3.67 ± 3.01 hours and 8.39 ± 5.67 hours for tiletamine and zolazepam, respectively [48]. A 30-day meat withdrawal time for Telazol up to 2 mg/kg by IM injection was recommended for swine by FARAD [29].

12.5 Local Anesthetics

Local anesthetics include lidocaine, mepivacaine, and bupivacaine, which can be used as local analgesics for minor or standing surgeries and for epidural anesthesia in farm animals. The mechanism of action is the blockade of fast voltage-gated sodium channels of neuronal membranes, thus preventing signal transduction. Only lidocaine is approved for use in food animals in the USA and it can be used in cattle for epidural anesthesia at a maximum volume of 15 ml or for direct nerve blocks with a maximum volume of 20 ml. However, larger volumes are frequently necessary when used for local tissue infiltration during surgery on adult cattle, which constitutes extralabel drug use. Similar to xylazine, the toxic metabolite 2,6-dimethylaniline (2,6-xylydine) is produced and can be detected in tissues and milk of animals treated with lidocaine [49]. However, in a risk assessment, any hazard to human health was deemed unlikely due to rapid excretion of lidocaine and 2,6-dimethylaniline, and the presence of insignificant concentrations in consumed food animal products [50].

In cattle, lidocaine is rapidly metabolized and excreted following administration [51]. In adult cattle, the plasma $t_{1/2}$ was 1.06 ± 0.70 hours following IV administration [52]. Following an inverted L-block using 100 ml of 2% lidocaine subcutaneously, maximal lidocaine concentrations were detected in plasma at 0.521 ± 0.226 hours [53]. The serum $t_{1/2}$ following subcutaneous (SC) administration was 4.19 ± 1.69 hours, which is considerably longer than after IV administration in the previous study [52, 53]. Lidocaine was detectable in serum for 8.5 ± 1.4 hours and milk for 32.5 ± 16.2 hours following administration as an inverted L-block [53]. The administration of 0.22 mg/kg of 2% lidocaine (approximately 6 ml per animal) for caudal epidural anesthesia did not result in detectable concentrations of lidocaine in serum or milk [53].

A study in fetal, neonatal, and adult sheep evaluated pharmacokinetic parameters after IV injection of 5 or 10 mg/kg of lidocaine and demonstrated a rapid decline of drug concentrations following administration [54]. The elimination $t_{1/2}$ of lidocaine was 30.9 minutes in adult nonpregnant sheep and 51.0 minutes in neonatal sheep. In another study, similar elimination $t_{1/2}$ were detected, which were 38.1 ± 2.1 minutes in nonpregnant and 31.9 ± 3.0 minutes in pregnant sheep [55]. Lidocaine rapidly crosses the placental barrier. IV injection of catheterized fetuses prompted detectable lidocaine concentrations in maternal blood within 2 minutes, indicating rapid equilibration of lidocaine between dam and fetus [54]. During constant rate infusion of lidocaine, fetuses receive approximately half of the maternal dose by weight (weight-normalized fetal-maternal dose ratio: 0.45) [56]. While toxic doses of lidocaine can cause neurologic signs, including convulsions, low doses of lidocaine can be used therapeutically as an anticonvulsant [57, 58]. A study evaluating the pharmacokinetics and toxicity of lidocaine in neonatal pigs determined an elimination $t_{1/2}$ of 2.67 ± 1.28 hours and, as in sheep, this is longer than in adult pigs, in which an elimination $t_{1/2}$ of 1.12 hours was described [57, 59].

While lidocaine is labeled for use in cattle, a withdrawal time is not provided. FARAD recommendations for withdrawal times in cattle at label indications and doses are 1 day for meat and 24 hours for milk following single and multiple doses by the epidural route using up to 15 ml. For single SC infiltrations (inverted L-block) using up to 100 ml (2 g) of lidocaine withdrawal times are 4 days for meat and 72 hours for milk, and these recommendations are based on a previous report in lactating dairy cows [53]. These recommendations should also be appropriate in other farm animals in which shorter elimination $t_{1/2}$ are typical. In horses, the lidocaine clearance time of 60 hours is longer than that for mepivacaine and bupivacaine but similar comparisons are not available for food animals [13]. The use of lidocaine and procaine as local anesthetics is allowed in organic livestock production, requiring a withdrawal period of 8 days for meat and 6 days for milk [30].

12.6 Opioids

The mechanism of action of opioids is binding of μ , κ , and δ opioid receptors, located in the central and peripheral nervous system, as well as other organs. Opioids used in veterinary medicine are either selective μ -receptor agonists or partially selective μ -receptor agonist or antagonist and include morphine, meperidine, fentanyl, oxymorphone, methadone, buprenorphine, and butorphanol [24]. While limited pharmacokinetics data are available in food animals, opioids exhibit rapid elimination and the elimination $t_{1/2}$ is approximately 3–4 hours in most species [13].

In food animals, morphine has poor analgesic properties when used parentally, and frequent readministration is necessary to maintain therapeutic blood concentrations [24]. Recommended analgesic doses for morphine in food animals include 0.05–0.1 mg/kg in cattle, 0.2 mg/kg intramuscularly (up to 20 mg) for swine, and up to 10 mg intramuscularly for small ruminants, but larger doses (up to 10 mg/kg in goats) have also been recommended [24, 60]. The elimination $t_{1/2}$ of morphine in farm animals is approximately 1–2 hours and was reported to be 87.9 minutes in horses and 86 minutes in sheep [24, 61, 62].

In addition to parenteral injection, morphine can be administered at 0.1 mg/kg epidurally to relieve pain of the perineum, posterior abdomen, or rear limb. This route of administration has two major benefits: (i) the duration of activity is prolonged, and thought to be approximately 12 hours in cattle, and (ii) unlike with local anesthetics such as lidocaine, epidural injections using morphine do not paralyze motor nerves [24]. Diffusion into the spinal cord is slow, and peak activity is observed after 210–250 minutes of administration. Epidural morphine can be administered via the lumbosacral space or as a caudal epidural, and should be readministered every 12 hours for the management of chronic pain. Withdrawal time information for food animals treated with morphine is not available. In a study in horses given one IV dose of morphine of 0.1 mg/kg, a serum elimination $t_{1/2}$ of 87.9 minutes was determined. Morphine was detected for 48 hours in blood and 144 hours in urine, and the authors concluded that horses should not be treated with morphine within 1 week of a race [61]. Because of lack of information regarding tissue pharmacokinetics, FARAD currently does not recommend the use of morphine in food animals [29]. From limited data in goats, morphine has a large volume of distribution, can be taken up into cells, and may persist in tissues after plasma clearance. For cattle, sheep, and goats receiving a single dose of 0.1 mg/kg by IV, IM, or epidural routes, FARAD recommends a meat withdrawal time of 14 days and milk withdrawal time of 48 hours. For repeated dosing, up to six doses, the recommended meat and milk withdrawal times are 28 days and 96 hours, respectively [29].

Butorphanol is likely the most commonly used opioid in farm animals and is administered either alone or in combination for analgesia or anesthetic protocols. Furthermore, butorphanol is used as an appetite stimulant, but this use is based on anecdotal efficacy [51]. In addition to affinity for μ -receptors, butorphanol is a κ -receptor agonist, and this affinity provides analgesia for visceral pain [39]. In farm animals, butorphanol is commonly used at doses between 0.02 and 0.25 mg/kg, and repeated dosing every 4 hours is necessary to maintain analgesic plasma concentrations [24]. In nonlactating dairy cows administered 0.25 mg/kg of butorphanol by a single IV route, rapid and extensive distribution followed by a slower elimination phase was observed [63]. The mean elimination $t_{1/2}$ was 82 minutes (range 69–115 minutes). In the same study, three lactating dairy cows received a smaller IV dose of 0.045 mg/kg, and trace quantities of butorphanol were detected in milk until 36 hours [63]. Butorphanol is commonly used in combination with other sedatives and enhances the analgesic effect of xylazine [64]. In calves coadministered xylazine (0.05 mg/kg), ketamine (0.1 mg/kg), and butorphanol (0.025 mg/kg) by IM injection, butorphanol was rapidly absorbed ($T_{\max}$ 9.5 ± 0.5 minutes) and rapidly cleared [65]. The elimination $t_{1/2}$ for butorphanol was 68.23 ± 7.13 minutes. Withdrawal times of 5 days for meat and 72 hours for milk or 4 days for meat and 72 hours for milk have been recommended following butorphanol administration in cattle [24, 51]. Butorphanol is an allowed substance for use in organic livestock production, which requires a meat withdrawal time of at least 42 days and a milk withdrawal time of at least 8 days [30].

Relatively little information is available regarding the use and pharmacokinetics of other opioids such as fentanyl in farm animals. In sheep, IV administration of 2.5 μ g/kg of fentanyl resulted in a short elimination $t_{1/2}$ of 3.08 hours [66]. In the same study, transdermal fentanyl patches were applied to sheep for 72 hours and provided a total dose of 12.8 ± 1.8 mg/kg per sheep. Adverse effects were not observed. The time of maximum concentration following topical application was 12 hours (range 4–24 hours), and the elimination $t_{1/2}$ was 15.6 hours (range 10.9–27.2 hours). An average concentration of 84.6 ± 45.7 pg/ml of fentanyl was detectable in samples 12 hours after patch removal. While the optimal concentration for analgesia has not been determined in sheep, maximal plasma concentrations in topically treated sheep ($C_{\max} = 1302.0$ pg/ml) were in the range of concentrations considered sufficient for analgesia in humans [66]. A similar study in goats determined an elimination $t_{1/2}$ of 1.20 ± 0.78 hours following IV administration of 2.5 μ g/kg of fentanyl [67]. Transdermal application (50 μ g/h) resulted in large variation of peak plasma concentrations (1.12–6.69 ng/ml, mean 6.99 ± 6.03 ng/ml) and time to peak plasma concentration (8–18 hours, mean 13 ± 4.5 hours). The elimination $t_{1/2}$ following transdermal patch removal was 5.34 ± 5.34 hours [67]. Because of large variability in pharmacokinetic data and lack of tissue residue studies, conservative withdrawal time recommendations should be made following treatment with transdermal fentanyl patches.

12.7 Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert antipyretic, anti-inflammatory, and analgesic properties by inhibition of cyclooxygenase enzymes that synthesize pro-inflammatory prostaglandins. Currently, only flunixin meglumine is labeled for use in food animals in the USA, but other NSAIDs are used by veterinarians, including aspirin, carprofen, meloxicam, and phenylbutazone [51]. In this chapter flunixin meglumine, aspirin, and meloxicam will be discussed in further detail. The administration of phenylbutazone is discouraged in food animals, and because flunixin meglumine is approved in the USA, the extralabel use of carprofen and ketoprofen would

be difficult to justify under AMDUCA. Carprofen, ketoprofen, and phenylbutazone are reviewed in detail elsewhere [51, 68].

In cattle, an injectable flunixin meglumine formulation is labeled for the control of pyrexia associated with bovine respiratory disease, endotoxemia, and acute bovine mastitis at a dose of 2.2 mg/kg every 24 hours or 1.1 mg/kg every 12 hours. Use of other NSAIDs in cattle for the same indications would be in an extralabel fashion and would be illegal under AMDUCA unless the veterinarian can justify that flunixin meglumine would not be effective. An injectable solution labeled for swine for the control of pyrexia associated with swine respiratory disease is also available. This product is labeled for IM administration at 2.2 mg/kg and is not intended for use in breeding swine [69]. Recently, a transdermal solution of flunixin meglumine for topical formulation was approved for control of pain due to foot rot and control of fever due to bovine respiratory disease [70]. Transdermal flunixin meglumine is labeled for single use; however, a recent study demonstrated that accumulation of the drug following three daily administrations was minimal and may not require changes from the label dose [71]. The drug was evaluated using the label dose for cattle in other species, including alpacas, goats, piglets, and sows [72–75]. Based on the achieved low bioavailability and lack of adequate treatment responses, these studies suggested that transdermal flunixin meglumine may not be adequate for use in other species, at least not when used as recommended for cattle [72–75].

In cattle, the injectable formulation of flunixin meglumine is labeled only for IV use in beef and dairy cattle, and not for use in dry dairy cows and veal calves [76]. In addition to causing significant tissue damage, administration by the SC or IM route prolongs the elimination of flunixin meglumine from tissues, likely resulting in violative residues [77, 78]. A recent *FARAD Digest* reviewed the contributing factors to prolonged withdrawal times associated with extralabel administration of flunixin meglumine [79], which resulted in updated recommendations by FARAD [15]. When used according to the label, flunixin meglumine is an allowed substance for use in organic livestock production, with a required withdrawal period of at least twice as long as required by the label [30].

Multiple studies demonstrated prolonged elimination $t_{1/2}$ for flunixin meglumine when administered subcutaneously or intramuscularly as compared to the IV route. The elimination $t_{1/2}$ following a single IV dose of flunixin meglumine (1.1 mg/kg) in dairy cattle was 3.1 hours, but it was 5.2 hours after IM administration of the same dose [80]. In a study evaluating the plasma pharmacokinetics and milk residues of flunixin meglumine and its metabolite 5-hydroxy flunixin meglumine in dairy cows administered two doses of 1.1 mg/kg of flunixin meglumine, significantly longer terminal $t_{1/2}$ were detected following IM or SC administration (4.48 ± 1.77 hours and 5.39 ± 2.48 hours) as compared to IV administration (3.42 ± 0.98 hours) [81]. While 5-hydroxy flunixin meglumine was undetectable in milk of all intravenously injected cows at 36 hours after the second dose, violative residues were detected in one intramuscularly and one subcutaneously injected cow. Cows producing less than 20 kg of milk per day eliminated 5-hydroxy flunixin meglumine more slowly than those with greater production. The authors concluded that the large number of reported flunixin meglumine residues in culled dairy cows is likely related to administration by an unapproved route, and that low-producing cows may be a contributing factor to the occurrence of violative residues [81]. The current tolerance for flunixin meglumine concentrations in milk is 2 ppb (2 ng/ml), which is exceeded following IV administration of 2.2 mg/kg per day for 3 days in the first, second, and third milking in which concentrations of 66, 20, and 14 ppb are detected, respectively [51, 82].

In weaned dairy calves, flunixin meglumine administration at the time of dehorning improved average daily gains, reduced biomarkers of pain, and reduced circulating cortisol levels [83]. The

median plasma $t_{1/2}$ of flunixin meglumine in these calves was 6.0 hours (range 3.4–11 hours) following an IV dose of 2.2 mg/kg [83]. In tissues, the reported elimination $t_{1/2}$ of flunixin meglumine were 9–51 hours for liver and 22–37 hours for kidney after IV administration of three daily doses of 2.2 mg/kg, which is up to 10-fold longer than plasma elimination $t_{1/2}$ [51]. In sheep, plasma elimination $t_{1/2}$ for flunixin meglumine were reported to be 229 minutes (3.82 hours) and 205 minutes (3.42 hours) after IV administration of 1.0 and 2.2 mg/kg [84]. Very similar plasma elimination $t_{1/2}$ were reported for goats following IV (3.6 hours, range 2.0–5.1 hours) and IM administration (3.4 hours, range 2.6–7.1 hours) [85]. In swine, the elimination $t_{1/2}$ of flunixin meglumine following administration of a single IV dose of 2.0 mg/kg was 7.76 hours, and the authors concluded that enterohepatic recycling may occur in swine as reported in other species [86]. The recommended withdrawal time for flunixin meglumine in cattle following administration at the approved dose and route for up to 3 days is 4 days for meat and 36 hours for milk [76]; however, as mentioned above, FARAD has recently updated its withdrawal recommendations [51, 79]. For the transdermal formulation of flunixin meglumine, a meat withdrawal time of 8 days was recommended [70]. In swine, a meat withdrawal time of 12 days following a single IM administration of 2.2 mg/kg of flunixin meglumine specifically formulated for swine was established [69]. Longer withdrawal times were recommended when using flunixin meglumine formulations that are not labeled for swine, even at the label dose, or when administering one or more doses by IV or oral routes (see Table 12.2 for details).

While aspirin is believed to fall under the grandfather clause of the Animal Drug Amendments of 1968 by some veterinarians, this is not the position of the FDA [78]. There are currently no approved veterinary products containing salicylic acid available in the USA, and the use of commercially available products in food animals is of questionable legality and discouraged by FARAD [68, 78]. Following oral administration to cattle, aspirin is slowly absorbed (half-time of absorption 2.91 hours) and rapidly eliminated (half-life of elimination 32 minutes), but oral doses of 100 mg/kg every 12 hours maintained serum salicylate concentrations that were considered therapeutically effective (30 μ g/ml) [87]. In calves treated with 50 mg/kg of oral aspirin, plasma salicylate concentrations remained below 10 μ g/kg and failed to mitigate an effect on acute cortisol response [88]. In the same study, an elimination $t_{1/2}$ of 0.63 hours was detected following IV administration of 50 mg/kg of sodium salicylate prior to castration. In calves treated with 2.5–5.0 mg/l of sodium salicylate in drinking water for approximately 5 days, the time to maximal plasma concentration was 41.7 hours and the mean plasma salicylate concentration was 32.2 μ g/ml. Plasma concentrations rapidly declined after removal of salicylate from drinking water and were undetectable within 24 hours [65]. Elimination $t_{1/2}$ of aspirin in sheep and goats (38.2 ± 4.0 minutes and 27.3 ± 3.6 minutes) are similar to those reported in cattle, and a dose of 20 mg/kg by IV or IM route achieved therapeutic plasma concentrations [89]. Recommended withdrawal times for aspirin following oral administration to cattle are 1 day for meat and 24 hours for milk [78].

Meloxicam, an NSAID of the oxicam class, is commercially available as an injectable formulation for use in cattle and pigs in Europe [90], and there are injectable and oral formulations labeled for large animal use available in Australia, Canada, and New Zealand [91, 92]. In the USA, meloxicam is commercially available as oral and injectable formulations for use in small animals, and several generic tablet formulations (7.5 and 15 mg) are available for relief of signs and symptoms of osteoarthritis in people. The use of oral meloxicam as an analgesic compound in US livestock could be considered under AMDUCA, as FDA-approved drugs for this purpose in food animals are currently unavailable [68].

In cattle, meloxicam was demonstrated to be effective in alleviating pain associated with painful procedures, including branding, castration, disbudding and dehorning, and resection of the coffin

joint [83, 92–97]. Furthermore, clinical efficacy was demonstrated when meloxicam was included in therapeutic protocols for medical conditions including respiratory disease, mastitis, musculoskeletal lameness, and calf diarrhea [98–103].

In studies evaluating the pharmacokinetics of oral meloxicam in calves, the drug had a good bioavailability and approximate mean peak plasma concentrations of 3.0–3.5 µg/ml were achieved at 10–12 hours. In these studies, the plasma $t_{1/2}$ was approximately 25 hours [104, 105]. The bioavailability of meloxicam was significantly different in calves administered meloxicam in milk replacer as compared to administration by stomach tube [106]. In lactating dairy cattle, the plasma pharmacokinetics of meloxicam were similar to those described for calves [107]. Meloxicam was detectable in milk for up to 80 hours, and the $t_{1/2}$ in milk was 10.38 ± 1.20 hours [107]. Following a single oral administration of meloxicam to lactating cows, milk concentrations decreased to below the maximum residue limit by 72 hours and below the limit of quantification by 120 hours in all animals [102]. However, meloxicam pharmacokinetics are significantly affected by age and stage of lactation, possibly requiring dose adjustments and longer withdrawal times [108–110]. A conservative meat withdrawal time of 21 days was proposed based on 10 terminal $t_{1/2}$ in the plasma of calves [51], and was supported by another study evaluating repeated oral administrations to beef calves [111]. Currently, FARAD recommends a meat withdrawal time of 21 or 30 days for calves treated once or with multiple doses, respectively, of oral meloxicam ≤ 1 mg/kg [15]. For small ruminants, a meat withdrawal time of 15 days following a single oral dose was recommended [15].

12.8 Phenothiazine Derivatives

The mechanism of action of phenothiazine derivatives is by antagonism of dopaminergic receptors of the ascending reticular formation and other central nervous systems [39]. Despite its common use as a tranquilizer and anesthetic adjunct, little information regarding the disposition of acepromazine in food animals is available. In horses, the elimination $t_{1/2}$ was determined to be in the range of 50–150 minutes following a dose of 0.15 mg/kg in one study [112]. In another equine study, the elimination $t_{1/2}$ was 184.8 minutes, and acepromazine was detectable in plasma for 8 hours after administration of 0.3 mg/kg [113]. Acepromazine is not approved for use in food animals in the USA, but is approved in Canada and Australia, and withdrawal time recommendations provided by FARAD are primarily based on foreign approvals [28]. For cattle, FARAD recommends a withdrawal time of 7 days for meat and 48 hours for milk for doses of up to 0.44 mg/kg by IM injection or up to 0.13 mg/kg by IV injection [28]. Identical recommendations are provided for small ruminants [38]. For swine, a 7-day meat withdrawal time is recommended for up to 0.055 mg/kg by IV route or up to 0.44 mg/kg by IM route [28].

12.9 Propofol

Propofol is a highly lipophilic, injectable, short-acting anesthetic used for the induction and maintenance of anesthesia. Propofol crosses the blood–brain barrier very rapidly and, unlike short-acting barbiturates, re-dosing to maintain anesthesia does not result in tissue accumulation. In general, propofol has a very large volume of distribution, rapid clearance, and short terminal $t_{1/2}$ [39]. In a pharmacokinetic study in calves, propofol was administered at 3 mg/kg following the administration of xylazine (0.1 mg/kg) to induce general anesthesia for umbilical hernia repair [114]. Following administration of propofol, plasma concentrations decreased rapidly in all

calves. However, propofol was still detectable in the plasma of three of five calves at 8 hours after administration and in one calf at 12 hours after administration. The volume of distribution was 330.7 ± 171.1 ml/kg, clearance was 1182.61 ± 443.24 ml/h/kg, and the elimination $t_{1/2}$ was 3.27 ± 2.34 hours. Because of paucity of sufficient plasma and tissue pharmacokinetics in food animals, FARAD recommends the use of other anesthetics instead of propofol [29]. A meat withdrawal time of at least 72 hours was recommended, but due to lack of data a milk withdrawal time could not be determined [51].

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13

Euthanasia of Farm Animals

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As implied by the Greek terms “eu” meaning good and “thanatos” meaning death, the process of euthanasia should end the life of an animal by procedures that eliminate or minimize pain and distress [1]. When a decision to euthanize an animal has been made, three phases of the process must be considered in an effort to achieve this ideal balance: (i) appropriate animal handling prior to euthanasia to minimize pain and distress, (ii) appropriate technique of euthanasia, and (iii) legal and safe disposal of the carcass. The decision to euthanize a farm animal is often not exclusively influenced by the desire to relieve animal suffering, as factors such as financial costs and practicality of continued therapy have to be considered; however, it is the veterinarians’ and caregivers’ responsibility to utilize a method of euthanasia that provides the ideal balance of minimal pain and distress while considering the environment in which the euthanasia is performed.

13.1 Considerations Prior to Euthanasia

Veterinary guidance is critical in forming the decision to euthanize a farm animal, as the prognoses for life and function based on the veterinary examination can establish whether euthanasia is the most appropriate option, or whether salvage by slaughter of a chronically ill animal is a morally and financially sound option. While euthanasia is easily recognized as the only viable option in certain conditions such as fractures of the spine or severe painful trauma that cannot be relieved by treatment, the necessity for euthanasia may not be as easily appreciable with other disorders, especially by farm managers and caregivers [2]. An increasing body of research has evaluated physiological and behavioral indicators of pain in farm animals (e.g. [3–6]), but the accurate and objective assessment of pain and resulting physical suffering remain difficult. In surveys assessing perceptions of bovine veterinarians on pain in cattle, significant variation existed among individuals about the perceived amount of pain associated with disease or veterinary procedures, and the utilized methods of pain control also differed significantly among veterinarians [7–9]. Veterinarians’ opinions also vary on the topic of which health conditions necessitate immediate euthanasia, continued therapy, or salvage by slaughter [10]. Therefore, it is reasonable to infer that for animal caregivers, who have varying degrees of knowledge and experience, the accurate assessment of pain and need for euthanasia can be even more challenging [11]. Some diseases may be more

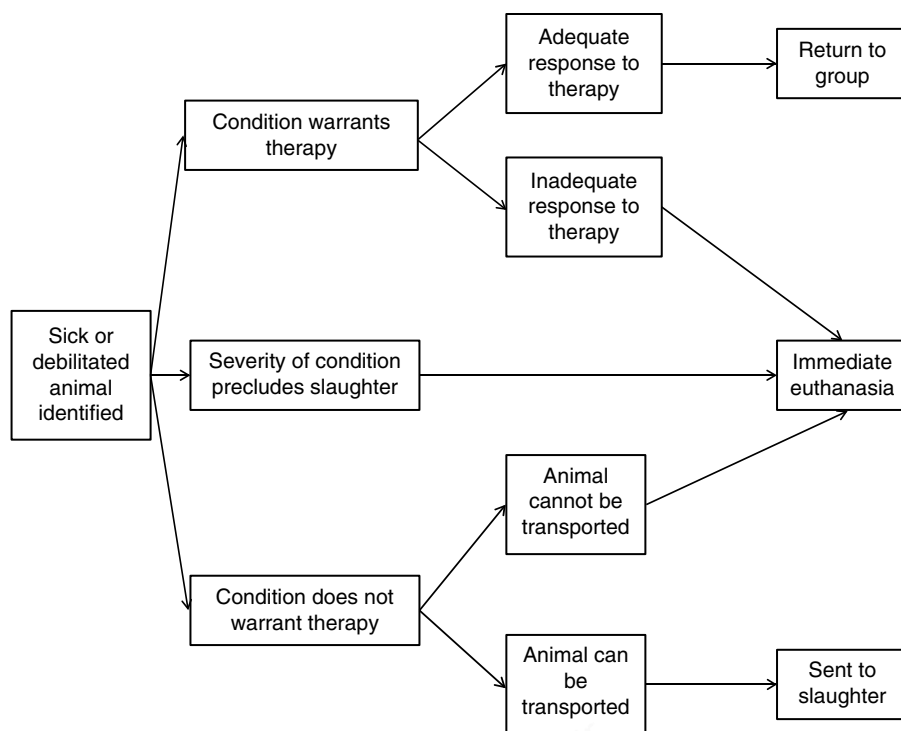


Figure 13.1 Example of a decision algorithm that can be implemented as part of an on-farm euthanasia plan to provide farm personnel with clear direction for the handling of sick and debilitated animals. Source: adapted from [14].

visually striking but less painful (e.g. rectal prolapse), while others are more painful but inconspicuous (e.g. chronic arthritis) [12], and misinterpretation of clinical signs could result in inappropriate administration of euthanasia procedures. When immediate and direct veterinary advice is not available, and the decision to euthanize is made by animal caregivers, creation of clear criteria for euthanasia in the form of standardized euthanasia protocols can help to alleviate employee stress associated with euthanasia and improve the overall welfare of a herd [12, 13].

On-farm euthanasia plans should be part of the overall herd-health management program and should include specific planning for the three phases of euthanasia. A decision tree can be used to determine the approach to a sick or debilitated animal (Figure 13.1). This decision tree can be modified to include treatment modalities, duration of attempted therapy before deciding on euthanasia, and methods of euthanasia as part of a farm-specific herd management plan. Developing clear criteria for sick animals can ensure consistent decisions among farm personnel and timely implementation of euthanasia procedures [14].

General guidelines have been proposed to aid in the decision-making process on whether an animal should be euthanized [14–16]. These guidelines commonly include specific endpoint criteria that form indications for euthanasia such as:

- fractured leg (irreparable)
- severe trauma
- loss of production and quality of life (severe mastitis, etc.)
- inability to stand or walk (disabled livestock)

- diagnostic (e.g. potential for human disease, such as rabies)
- advanced ocular neoplasia (cancer eye)
- debilitating or toxic conditions
- cost of treatment prohibitive and poor prognosis
- extended withdrawal time for sale of meat and poor prognosis.

In adaption for euthanasia guidelines for small animals, generalized guidelines for use in swine operations have been proposed [12]:

- weight loss of 20–25% of total body weight, characterized by muscle wasting
- extreme weakness or the inability or lack of desire to eat or drink, persisting for 24 hours or more
- suffering from any infection/disease that fails to respond to treatment.

As part of an on-farm euthanasia plan, procedures for handling debilitated animals prior to euthanasia should be reviewed. The prevention of pain and distress during handling before euthanasia can often be achieved by simple environmental changes, and animal welfare recommendations for cattle transported and handled for slaughter apply [17–20]. Separation of the animal to be euthanized from healthy conspecifics is generally advisable to prevent distress and safety concerns, such as from a missed or ricocheting gunshot. Stress responses including vocalization, fearful behavior, and olfactory stress signals can communicate anxiety and apprehension among animals [21–23], and it is often easiest to remove all healthy animals from the area in which euthanasia will be performed. While ambulatory animals may be moved for short distances to a location where euthanasia procedures and carcass removal can be more effectively performed, fractious or recumbent animals may best be euthanized at their present location. Ensuring the prevention of pain and distress, animals that tolerate human contact can be moved using appropriate carts or sleds. As most methods of euthanasia require close contact to the animal, animals must be restrained by a halter or chute. The required restraint should be chosen based on the disposition of the animal and the method of euthanasia. Restraint by a halter can be adequate for small and large farm animals accustomed to human handling and allow intravenous administration of barbiturates or accurate placement of a penetrating captive bolt. Premedication with sedatives or tranquilizers should be considered to ensure safety of personnel and reduce distress when euthanizing fractious animals. Premedication can be administered in a chute if possible with minimal pain and distress, or can be administered by blow-dart or dart-gun. For some animals, gunshot may be the most appropriate form of euthanasia, as it requires the least amount of human contact.

13.2 The Process of Euthanasia

Any appropriate method of euthanasia is aimed at inducing unconsciousness as rapidly as possible. Unconsciousness is defined as the loss of individual awareness and occurs when the brain's ability to integrate information is blocked or disrupted [1, 24]. The underlying mechanisms that achieve unconsciousness in anesthetized individuals are still incompletely understood, but most anesthetic agents appear to induce an unconscious state by deactivation and disintegration of the posterior corticothalamic complex [25]. In animals under general anesthesia, movement can be observed despite the presence of a state of unconsciousness and amnesia, which is a result of continued spinal cord activity, as memory and awareness are abolished at anesthetic concentrations which are less than half of those needed to abolish movement [26]. While much more pronounced deactivation of cortical function and rapid loss of consciousness are expected with methods of

euthanasia, it is important to ensure that all activities observed in an animal to which a method of physical or chemical euthanasia has been administered occur subsequent to unconsciousness. In animals, the loss of unconsciousness is defined as loss of the righting reflex [24]. By means of electroencephalography (EEG), various studies have evaluated brain function in animals at slaughter and although data obtained with EEG are limited in their ability to precisely determine the onset of unconsciousness (e.g. [27–30]), indicators of successful stunning in slaughtered animals also apply to euthanasia. While weakly present in rare cases, the corneal reflex is expected to be absent after successful stunning by captive bolt [27, 31]. After stunning, immediate collapse, followed by a period of tetanic spasticity and then clonic slow hind limb movements with increasing frequency occur [24]. In cattle and small ruminants, loss of righting reflex, loss of rhythmic breathing, protrusion of tongue, absence of corneal reflex, and absence of nystagmus indicate successful stunning by captive bolt [31, 32].

During euthanasia, loss of residual muscle movement and cardiac and respiratory arrest occur subsequent to loss of unconsciousness. Before movement and disposal of the carcass, death must be confirmed. A combination of criteria is most reliable to confirm death, which includes absence of pulse and corneal reflexes, failure to respond to strong pinches to the nose or interdigital space, inability to auscultate respiratory and heart sound by stethoscope, graying of mucous membranes, and rigor mortis. Only the presence rigor mortis can, by itself, serve as confirmation of death, and other criteria must be verified in combination [24].

13.3 Methods of Euthanasia

The American Veterinary Medical Association (AVMA) Panel on Euthanasia categorizes methods of euthanasia as being acceptable, conditionally acceptable, or unacceptable [24]. Additionally, the panel provides species-specific adjunctive methods that can be used in conjunction with other methods to produce a humane death and ensure death in an unconscious animal. An acceptable method of euthanasia is one that consistently produces a humane death when used as the only means of euthanasia. For all farm animals, euthanasia by injection of barbiturates and barbituric acid derivatives is categorized as an acceptable method. Methods that are considered conditionally accepted vary by species and age, but for all farm animals, including cattle, small ruminants, and swine, physical methods such as gunshot and penetrating captive bolt are conditionally accepted. Properly administered, conditionally accepted methods ensure a humane death, but because of the greater potential for operator error or safety hazards, they might not do so as consistently as acceptable methods. Additionally, conditionally acceptable methods include those not well documented in the literature [24].

13.3.1 Injectable Euthanasia Agents

In addition to barbiturates and barbituric acid derivatives, the AVMA Guidelines on Euthanasia discuss other injectable euthanizing agents, including tributame, T-61, and ultrapotent opioids. Unavailable in the USA, T-61 was evaluated in German cattle and induced death less rapidly and with more excitatory events than a sodium pentobarbital-containing euthanasia solution [33]. Availability and practicality make barbiturate-containing solutions the most commonly used injectable method of euthanasia in farm animals. Barbiturates rapidly induce unconsciousness by depressing the function of the cerebral cortex and result in collapse of the animal. In a step-wise fashion, other central nervous system (CNS) functions are subsequently depressed, with reduction

in blood pressure, depression of the medullary respiratory center and apnea, cerebral death, and subsequently cardiac arrest.

Various manufacturers currently provide commercially available euthanasia solutions containing sodium pentobarbital at similar concentrations and sometimes in combination with local anesthetics and other CNS depressants such as phenytoin sodium. Additionally, euthanasia solutions contain a dye to ensure ease of identification. Unlike sodium pentobarbital, which is a Drug Enforcement Administration (DEA) schedule II drug, many commercially available euthanasia solutions are categorized as schedule III drugs, enabling less strict regulations concerning their availability and storage.

Most euthanasia solutions are labeled only for dogs or dogs and other small animals, and dosing information for farm animals is extrapolated. Product information from a euthanasia solution labeled for large animals recommends a dose of 1 ml/4.5 kg (10 lb) of body weight, to a maximum of 100 ml, in accordance with its small animal dosage and label information for other products (40 mg of sodium pentobarbital per kg [2.2 lb] of body weight) [33, 34]. Barbiturate solutions should always be administered by intravenous route, which ensures rapid distribution to the CNS. However, intravenous injection can be complicated in fractious or aggressive animals. In these cases, tranquilization or identification of alternative methods of restraint prior to euthanasia should be considered. Alternatively, intraperitoneal administration of nonirritating formulations of sodium pentobarbital may be a substitute to intravenous injection and is considered acceptable by the AVMA Panel on Euthanasia; however, it is not practical for many large farm animals [24]. For euthanasia by intraperitoneal route, larger quantities of barbiturate solution should be administered, which can be cost prohibitive. Intraperitoneal injection of euthanasia solutions results in a significantly greater duration until loss of consciousness as compared to intravenous administration [35]. While some solutions without an added local anesthetic are labeled for intraperitoneal injection, this route of administration may result in pain, which can be reduced by addition of lidocaine to sodium pentobarbital formulation (e.g. 10 mg of lidocaine per ml of sodium pentobarbital) [36]. Failure of injecting the peritoneal cavity was reported in 6.7% and 58% of intraperitoneally injected piglets and adult cats, respectively, and subsequent necropsies demonstrated that the euthanasia solution was delivered into the urinary bladder, gastrointestinal tract, or spleen [35, 37]. While nonvascular administration of injectable euthanasia agents, including subcutaneous, intramuscular, or intrathoracic, is not acceptable, in unconscious animals injection into organs such as intracardiac injection is considered conditionally acceptable.

Unacceptable as the sole method of euthanasia, saturated solutions of potassium chloride, magnesium chloride, or magnesium sulfate are categorized as adjunctive methods of euthanasia for large and small ruminants [24]. These can be used in anesthetized or unconscious animals and induce cardiac or respiratory arrest following intravenous or intracardiac administration. Prior to administration, the surgical plane of anesthesia must be confirmed [24]. While injectable anesthetic protocols such as ketamine/xylazine are able to induce unconsciousness, sole use of alpha-2 agonists such as xylazine prior to potassium chloride or magnesium sulfate administration comprises an unacceptable method of euthanasia [24, 38].

13.3.2 Physical Methods

The AVMA Panel on Euthanasia categorizes euthanasia by gunshot and penetrating captive bolt as conditionally acceptable methods for cattle, small ruminants, and all age groups of swine, except suckling pigs [24]. Firearms are widely available and gunshot is often the most practical method of euthanasia, especially when veterinary assistance is unavailable. On dairy farms, on-farm

euthanasia is most commonly performed by gunshot (85–90%), and only a minority of farms utilized barbiturates or captive bolt for euthanasia [39, 40]. On dairy farms, decisions regarding euthanasia were made in absence of veterinary consultation in 67.7% of surveyed farms, and larger farms were less likely to seek veterinary assistance for euthanasia [40]. The absence of veterinary supervision, safety concerns for personnel that perform euthanasia, and the emotional effects of the procedure on farm personnel are challenges of on-farm euthanasia by physical methods [12]. These challenges should be addressed by providing adequate training by veterinarians and farm managers because physical methods of euthanasia may be best suited to ensure rapid relief of pain and suffering in different situations [12, 41].

The goal of euthanasia by gunshot or captive bolt is the immediate loss of consciousness by inducing massive damage to the cerebral hemispheres and vital regions of the brainstem [42]. To reliably achieve this goal, accurate placement of the shot or captive bolt on the animal's head is critical, and has been reviewed [24, 43]. For cattle, the appropriate point of entry is the intersection of two imaginary lines drawn from the top of the eye or lateral canthus to the opposite horn (Figure 13.2). This placement differs from older recommendations that suggested that the imaginary lines be drawn from the medial canthus to the horn base, which can result in improper stunning due to penetration of the frontal sinus. While breed variations exist, using the lateral canthus to determine the point of entry results in larger frequencies of brainstem disruption and proper stunning [44, 45]. The shot should be placed perpendicular to the skull, aiming at the foramen magnum to reduce the risk of ricochet and increase brain damage [41]. Due to smaller brain size, accurate placement of a gunshot or penetrating bolt is more difficult in calves. Placement at the intersection of an imaginary line from the lateral canthus to the site of horn formation on the contralateral site also applies to calves, and aiming the shot at the foramen magnum is critical [24]. Alternate stunning locations such as the poll position are less effective in cattle, and can result in misdirection of the shot into the spinal cord and prolonged presence of consciousness [29, 46]. The frontal placement of a gunshot or penetrating bolt is effective in most groups of cattle, but reduced effectiveness of stunning has been observed in animals with thick frontal bones such as adult bulls or water-buffalo [47]. For these animals, selection of firearms with greater muzzle energy or the use of penetrating captive bolts with larger bolt velocities are necessary.

The optimal point of entry for gunshot or penetrating captive bolt for sheep and goats has been recently updated from previous recommendations (e.g. previous edition of this chapter and *AVMA Guidelines for the Euthanasia of Animals*, 2013 edition), based on two recent studies

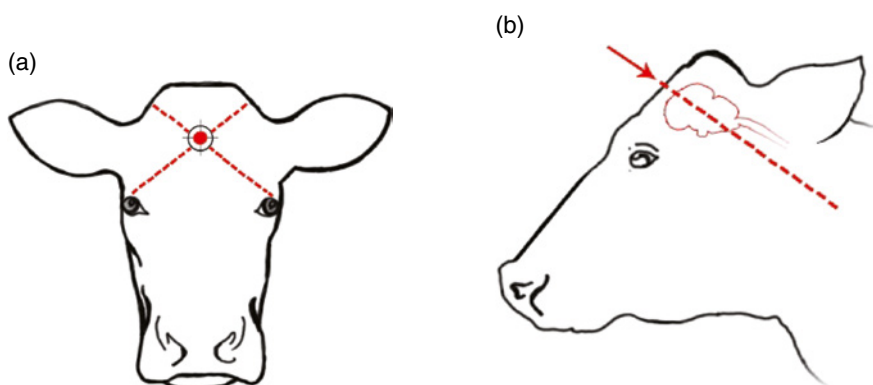


Figure 13.2 (a) Frontal and (b) lateral views of the accurate site and angle for placement of a gunshot or captive bolt in cattle. Source: adapted from [16].

performed in goats [42, 48]. The optimal site for small ruminants can be the intersection of two imaginary lines drawn from the lateral canthus of the each eye to the middle base of the contralateral ear, resulting in placement of the shot near the poll (Figure 13.3) [24, 42]. Another approach, resulting in similar shot placement, identifies the optimal site by placing the captive bolt on the dorsal midline of the head at the level poll, while aiming downward toward the most cranial portion of the intermandibular space [24, 48]. Placement of a shot or captive bolt at frontal positions may result in inconsistent outcomes due to varying sizes of the sinus cavities in small ruminants and should be reserved for euthanasia of heavily horned animals while using a firearm [24]. In addition to the described changes, the most recent edition of the *AVMA Guidelines for the Euthanasia of Animals* has been expanded to include recommendations for American bison, water buffalo, camelids, and cervids [24].

For pigs, three points of entry for a gunshot or penetrating captive bolt can be used. The frontal position is preferred and can be used for gunshot or captive bolt methods. On the midline of the forehead, the shot is placed approximately 0.5 inch (1.25 cm) above eye-level, aiming at the tail or spinal cord (Figure 13.4). Alternatively, a gunshot can be placed in the temporal region, or from behind the ear, aiming at the opposite eye [16, 24, 43].

Figure 13.3 Dorsal view of the proper placement of a gunshot or captive bolt for euthanasia of small ruminants. *Source:* adapted from [42].

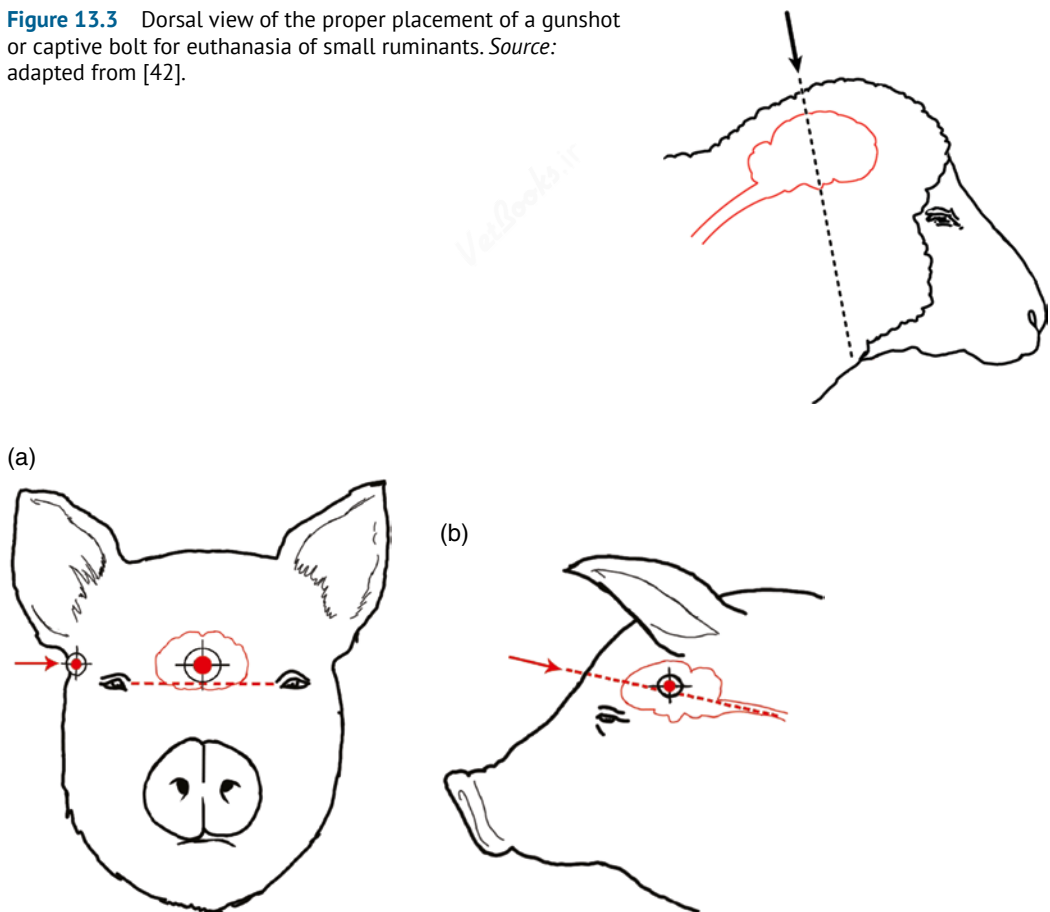


Figure 13.4 (a) Frontal and (b) lateral views of the proper placement of a gunshot or captive bolt for euthanasia of swine. *Source:* adapted from [16].

While widely available, .22 caliber handguns or rifles are not sufficient to euthanize most farm animals as they lack the muzzle energy necessary to penetrate the skull and induce severe brain damage reliably [1]. Muzzle energy is a function of bullet weight and velocity, and can be calculated as E (in ft-lb) = bullet weight (in grains) $\times$ bullet velocity² (in ft/s)/450450 [1]. While .22 caliber firearms provide only approximately 150 ft-lb of muzzle energy, a minimum of 300 ft-lb energy is recommended for animals weighing up to 181.8 kg (400 lb), which should be available from various handgun cartridges such as .38 special, 9 mm, or .45 ACP. For animals larger than 181.8 kg (400 lb), firearms providing muzzle energies greater than 1000 ft-lb are recommended [1, 49]. Solid-point bullets should be used, especially when euthanizing adult cattle and other animals with thick frontal bones. In contrast to hollow-point bullets, which fragment on contact with the skull, solid-point bullets more reliably penetrate the frontal bones [1]. A study evaluating various firearm-ammunition combinations for the euthanasia of yearling cattle determined that a 9 mm pistol-fired 124-grain total metal jacket round and a .22-caliber rifle-fired hollow-point cartridge were poor choices for this purpose, but also identified various reliable firearm-ammunition combinations [50]. A recent study demonstrated that a multipump air pistol firing a .22 gauge projectile was insufficient for the euthanasia of dairy goat kids [51].

As an alternative to handguns and rifles, shotguns can be ideal for effective euthanasia of animals at close ranges [50]. Unlike for captive bolts, a secondary kill step is usually not necessary for shotguns or other appropriate firearms. Shotguns are safer than handguns or rifles, as the shot disperses in the cranium and is less likely to exit, reducing the risk for the shooter and bystanders. For small farm animals such as calves, lambs, or kids, smaller bore shotguns (.410 or 28 gauge) are sufficient; however, for adult cattle and other large livestock larger gauges should be used (20 gauge or larger) [24, 52, 53].

When using physical methods of euthanasia, sufficient training, comfort with the technique, and awareness of safety hazards are critical. While penetrating captive bolts must be placed firmly against the restrained animals head, firearms must be held off the animal's head to prevent build-up of pressure and catastrophic barrel failure. To reduce the risk of ricochet, firearms should not be used in enclosed spaces or on hard surfaces, and bystanders should always be behind the shooter or removed from the area. While less restraint is necessary and animals can be euthanized at greater distances with firearms, patience is critical for accurate placement of the shot. Means of a secondary kill step such as a second cartridge or shell, knife for exsanguination, or potassium chloride solution should be available regardless of whether a firearm or captive bolt is used.

Although massive brain damage sufficient to cause death can be inflicted using penetrating captive bolts, they are considered stunning devices and secondary kill steps need to be implemented immediately following stunning and determining unconsciousness. A study evaluating a penetrating captive bolt device with a built-in air-channel pithing mechanism demonstrated its effective use as a one-step euthanasia method, which may be useful when large numbers of cattle must be euthanized [54]. Stunning effectiveness is determined by accuracy of placement, bolt velocity, and depth of bolt penetration. Ineffective stunning and misfires are most commonly caused by poor maintenance [41]. Captive bolt guns require regular maintenance, and guns and powder charges must be stored in a dry location to ensure proper function [55].

Use of nonpenetrating captive bolts is a conditionally acceptable method of euthanasia for euthanasia for calves, kids, lambs, and young pigs. Species-specific purpose-built and general non-penetrating captive bolts are available and deliver a controlled blunt-force trauma to the head [24]. Immediate loss of consciousness results from concussive forces to the brain with greatest efficacy in young animals, which have not developed thick frontal bones. Adjunctive methods of euthanasia are applied immediately after unconsciousness has been confirmed to prevent return to sensibility and eliminate pain or distress.

13.3.3 Adjunctive and Other Methods of Euthanasia

Adjunctive methods of euthanasia include intravenous administration of potassium chloride or magnesium sulfate, second shot, exsanguination, and pithing, and are administered to unconscious animals to ensure a humane death [24]. Adjunctive methods must be prepared prior to inducing unconsciousness and administered immediately after loss of consciousness is confirmed. During administration, violent involuntary movements can occur and pose safety concerns to personnel. The safest location for personnel is at the dorsum, close to the head of the recumbent animal and away from the extremities [16].

Saturated solutions of potassium chloride or magnesium sulfate are prepared using hot water, and frequent agitation enhances the solubility of the salt. Both salts are readily available as water softener (potassium chloride) or Epsom salt (magnesium sulfate). Potassium chloride solutions can be made by adding 30 g of potassium chloride to 100 ml of water. For adult dairy cattle, 120 ml of saturated potassium chloride given rapidly by intravenous route should be sufficient to cause death [41]; however, salt solutions are administered to effect. When magnesium sulfate is used, larger volumes may be required and death may not occur as rapidly.

Exsanguination is performed by severing the common carotid artery, jugular vein, and trachea using a pointed very sharp knife. The knife is inserted into the neck just behind the jaw and ventral to the neck bones. A deep incision is then made away from the neck which allows rapid loss of large blood volumes and death. Bleeding may continue for several minutes, but increased blood flow can be achieved by dissecting the vessels closer to the thoracic inlet, where they are larger [1]. Alternatively, exsanguination can be performed by severing the brachial vasculature by deeply incising the axillary area until the limb can be reflected dorsally [16]. The large amount of accumulating blood can be challenging and esthetically displeasing, therefore internal exsanguination can be achieved by severing the aorta by the transrectal route.

Pithing using commercially available disposable pithing rods can be performed following use of a firearm or penetrating captive bolt. The pithing rod is inserted into the entry site and manipulated to maximize destruction of brain and spinal cord and ensure death. Pithing prevents the necessity to exsanguinate stunned animals during euthanasia or is used to reduce involuntary movement during exsanguination [16].

In addition to the injectable and physical methods discussed above, swine can be euthanized by inhalant agents including carbon dioxide, nitrous oxide, and argon, as well as by electrocution. These methods are commonly used to stun pigs at slaughter and are considered conditionally accepted methods of euthanasia by the AVMA Panel on Euthanasia [24]. Specialized equipment, which is generally unavailable to most veterinarians and farm managers, is required for both methods, precluding their discussion in this chapter. For suckling pigs, manually applied blunt force trauma meets the definition of euthanasia and is classified as a conditionally accepted method. As uncertainty of success and fatigue during repeated application can lead to inconsistency in the success of this method, the AVMA encourages the identification of alternatives to manually applied blunt force trauma to ensure that criteria for euthanasia are reliably met [1].

13.4 Considerations Subsequent to Euthanasia

After confirmation of death, appropriate means of carcass handling and disposal in accordance with local, state, and federal laws have to be followed. Disposal of farm animal carcasses may be regulated by a state's solid waste, medical waste, agriculture, or emergency management regulations. In many states, carcasses have to be disposed of within 24 hours of death [56]. Depending on

the size of the animal, method of euthanasia, and environmental conditions, disposal in an approved landfill or by rendering, burial, burning, or composting may be appropriate. Important concerns when disposing of euthanized animals include the protection of ground and surface water, containing the spread of infectious diseases, and protection of domestic and wild animals from pharmaceutical residues.

While little information is available on the effects of most pharmaceuticals and other residues such as heavy metals from carcasses on environmental parameters and health of scavengers, increased residues are detected in apex predators such as bald eagles and are cause for concern [57, 58]. Of most immediate concern is the presence of pentobarbital in euthanized animals, and label information for all commercially available euthanasia solutions must contain environmental warnings [59]. Barbiturates are characterized by high stability to biotic and abiotic degradation and they are highly stable in aquatic environments [60]. Barbiturates remain toxic in carcasses of euthanized animals for extended periods following death. The carcass of a horse remained lethally toxic for domestic dogs more than 2 years following euthanasia, emphasizing the necessity for proper disposal of euthanized animals [61]. Multiple reports on secondary pentobarbital intoxication exist in the literature, affecting domestic, zoo, and free-ranging animals [61–67]. Owners have been held responsible for the death of raptors killed by the presence of sodium pentobarbital in euthanized animals and are legally responsible for proper carcass disposal [56, 67].

The presence of barbiturates in pet food from rendered animal products has also raised concerns. While barbiturates are stable through the rendering process and are distributed approximately equally between meat, bone, and tallow fractions, combination with other raw materials results in low concentrations that are unlikely to cause adverse health effects [68, 69]. Renderers have become reluctant to accept carcasses from euthanized animals and alternatives for carcass disposal should be considered.

Disposal in approved landfills is accepted by many authorities, but can also expose scavengers to residues of pentobarbital when carcasses are not covered [70]. If not prevented by close vicinity to water or high ground water tables, deep burial can be used for carcass disposal. Carcasses should be buried at least 2 ft below ground level. For carcasses of diseased animals that could be potentially contagious, incineration in licensed facilities is preferred and also abolishes concerns regarding barbiturate residues.

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