Chapter 20

Anesthesia and analgesia in ruminants

Jenelle Izer[1], **Cathy Dwyer**[2] and **Ronald P. Wilson**[1]

[1]Department of Comparative Medicine, College of Medicine, The Pennsylvania State University, Hershey, PA, United States; [2]Animal and Veterinary Sciences, Animal Welfare, Safe & Improved Food Challenge Centre, Scotland's Rural College, Edinburgh, United Kingdom

Chapter outline

I. Introduction

Sheep, goats, and calves are the most common ruminants used in biomedical research, testing, or training and this review will be limited to those species. As large animal models, they are docile, adapt well to frequent handling, restraint, and chronic instrumentation that may be dictated by research needs. They are readily available either as purpose-bred or farm-raised, conditioned animals. Sheep of any age and size are the most common small ruminants encountered in the research setting. This species, and to a lesser extent, goats are utilized in cardiovascular research, medical device implantation and testing, pharmacokinetic studies, regenerative medicine, orthopedic research, fetal surgery, and pulmonary studies. With recent advances in gene editing technologies, especially CRISPR, genetically modified sheep and goats are becoming important translational animal models of human disease (Kalds et al., 2019, 2020; Menchaca et al., 2020; Rogers, 2016). Sheep and goats are often used for the production of biologics and reagents used in experimentation, including red blood cells, sera, and antibodies. Calves are most often used for testing medical devices, especially mechanical circulatory support devices.

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II. Preprocedural considerations

A. Anatomic and physiologic influences on anesthesia of ruminant species

Attention to the unique anatomical and physiologic characteristics of the ruminant and taking steps to minimize potential adverse effects these differences may have on anesthesia, surgery, and recovery is paramount to a successful anesthetic and surgical outcome in these species. The unique structure, function, and volume of the ruminant gastrointestinal system present challenges for anesthesia and surgery not encountered in monogastric species. Preventing bloating, minimizing regurgitation, reducing rumen volume by judicious fasting, and protecting the airway are key factors in successfully anesthetizing the ruminant animal. Common complications encountered in anesthetizing ruminants are directly associated with the effects of the digestive system on adequate ventilation and include regurgitation and aspiration, inadequate oxygenation, and bloating. Addressing these potential problems by proper preparation of the animal and preventive measures is the key to a successful surgical outcome irrespective of the anesthetic regimen used.

The stomach consisting of the rumen, reticulum, omasum, and abomasum is unique to ruminant species and is the site of the production of volatile fatty acids, the primary energy source, through microbial fermentation (Leek, 2004). The ruminant stomach occupies approximately 75% of the abdominal cavity, filling most of the left half of the cavity and extending into the right half of the abdomen (Habel, 1975). The relative sizes of the four compartments of the stomach develop and change with the age of the animal. In the newborn calf, the ruminoreticulum contains less than half the volume of the abomasum and remains functionless while the animal is on a milk diet (Habel, 1975; Nickel et al., 1973). The capacity of the ruminoreticulum is approximately equal to the abomasum by 8 weeks of age, double the capacity of the abomasum by 12 weeks, and in adults, the capacity is approximately 9:1 that of the abomasum (Habel, 1975). In lambs, the stomach represents 22% of total gastrointestinal wet tissue mass but increases to 49% in adult sheep (Valverde and Doherty, 2008). In cattle, the volume of the stomach is approximately 115−150 L while in sheep and goats stomach volume is 15−18 L (Habel, 1975; Valverde and Doherty, 2008). The size and volume of the ruminant stomach can impede respiration and ventilation in the anesthetized animal by interfering with diaphragmatic excursion resulting in a reduction in the functional residual capacity of the lung, thus interfering with effective pulmonary gas exchange (Greene, 2003; Lee and Swanson, 1996). Positioning of the anesthetized ruminant may further exacerbate hypoventilation as recumbency shifts the rumen mass, leading to the displacement of the diaphragm into the thoracic cavity. Cattle placed in lateral or dorsal recumbency developed significant hypoxemia and hypercapnia (Jorgensen and Cannedy, 1996; Wagner et al., 1990). Furthermore, the displaced rumen may interfere with venous return, predisposing to decreased cardiac output and low blood pressure (Jorgensen and Cannedy, 1996; Valverde and Doherty, 2008). For these reasons, a key to successful anesthetic management and surgery of the small ruminant is taking preventive measures to minimize the potential for regurgitation and aspiration of stomach contents, prevent bloating and ensure adequate ventilation during anesthesia and surgery.

1. *Fasting*

Withholding food and water prior to surgery decreases the rate of fermentation and the risk of regurgitation, and may decrease rumen volume (Swindle et al., 2002). Recommendations on the duration of fasting prior to surgery vary widely ranging from a few hours to 48 hours. Excessive fasting may lead to alterations in the rumen flora, reduced motility, and rumen stasis, resulting in a negative energy balance and complications during the postoperative period (Abrahamsen, 2009a, 2013). Furthermore, fasting may have adverse effects on acid-base status sufficient to cause cardiac arrhythmias (Abrahamsen, 2009a, 2013). In adult cattle, a 48-hour fast produced a 20%−30% reduction in heart rate, which persisted for 48 hours following recovery (Bednarski and McGuirk, 1986; McGuirk et al., 1990; Riebold, 2015). Fasting from food for 24−48 hours and withholding water for 12−24 hours in healthy sheep and goats resulted in better ventilation, less tympany, and reduced incidence of regurgitation (Carroll and Hartsfield, 1996). Other authors recommend shorter periods of no more than 12−18 hours fasting from food and either not withholding water or withholding for only 4−6 hours (Abrahamsen, 2009a, 2013; Swindle et al., 2002). In the authors' experience, withholding food and water from calves and adult sheep for 12−16 hours before surgery and supporting fluid balance with intravenous maintenance fluids supplemented with potassium decreases total rumen volume, and subsequently optimizing mechanical ventilation while avoiding the complications of prolonged fasting (Carney et al., 2009a, 2009b; Izer et al., 2018). Young animals that are transitioning from a functional monogastric to a ruminant should not fast for longer than 12 hours (Carroll and Hartsfield, 1996).

2. *Preventing regurgitation and bloat*

Regurgitation in the anesthetized ruminant may be either an active or passive process. Active regurgitation is most likely to occur due to inadequate or light anesthesia, whereas passive regurgitation results from increased transluminal pressure gradients and relaxed esophageal sphincters (Jorgensen and Cannedy, 1996; Steffey, 1986). In addition to fasting prior to anesthesia, induction techniques that quickly eliminate the gag reflex and position the animal in sternal recumbency with the head elevated reduce the risk of regurgitation during intubation (Abrahamsen, 2009a, 2013). Intubation with an appropriately sized endotracheal tube with the cuff inflated will protect the airway if regurgitation occurs during surgery.

In the ruminant animal, gases in the form of carbon dioxide (60%) and methane (30%−40%) are produced by the fermentation process in the rumen (Leek, 2004). The amount of gas production in adult cattle has been estimated to peak at a rate of 40 L/hour, 2−4 hours following a meal, and the accumulation of gas is normally eliminated by eructation, which occurs every 1−2 minutes (Leek, 2004). Heavy sedation or general anesthesia inhibits ruminoreticular motility and impairs eructation (Valverde and Doherty, 2008). The placement of an orogastric tube into the rumen at the time of anesthesia induction will minimize the accumulation of gas. A tube with an inflatable cuff, such as a foal urethral tube will assist in positioning the end of the tube at the gas-liquid interface in the rumen so that primarily gas and not rumen fluid will be suctioned off (Swindle et al., 2002). Removal of large amounts of liquid from the rumen will not eliminate gas production and is likely to result in a dry mass of ingesta that can impair the return to normal digestive function in the postoperative period. The orogastric tube may on occasion become clogged with ingesta or the wall of the rumen sucked onto the end of the tube causing it to no longer work. The authors' (JI and RW) have found that use of a low-pressure, intermittent vacuum is sufficient to minimize gas accumulation while avoiding the problems of clogging with solid food materials or suction of the rumen wall, thus occluding the tube. If the tube ceases to function and gas accumulates during surgery, the gas cap can be cannulated percutaneously with a large-bore (14−18 gauge) intravenous catheter connected to a sterile vacuum hose. The use of oral antibiotics such as neomycin prior to surgery to reduce fermentation will not significantly reduce the potential for regurgitation or bloating, can lead to problems with the return to normal gastrointestinal function following surgery, and is not recommended.

Detailed information on all aspects of anesthesia and analgesia for ruminants in the research setting is beyond the scope of this section; however, readers are referred to the excellent review of this topic by Valverde and Doherty (2008).

B. Animal welfare and the use of small ruminants in biomedical research

Animal welfare is generally considered to be the mental and physical well-being of an animal as it interacts with the environment. There have been many definitions and conceptions of animal welfare over the years, beginning with the Five Freedoms (Farm Animal Welfare Committee [FAWC], 1979), and considerations of the biological functioning, or feelings of the animal or the naturalness of the conditions under which it is kept (Fraser et al., 1997). However, more recently, this has been increasingly refined and centered on the capacity of the animal to feel or experience emotions, and therefore sentience. In this regard, the Five Domains concept (Mellor et al., 2020), which was initially developed specifically to assess welfare in biomedical research, is the most applicable to small ruminants used in research. The Five Domains framework, in this context, considers the impact of research practices on four physical or functional domains (nutrition, environment, health, and behavioral interactions; Mellor et al., 2020). Challenges in each domain influence the emotional state of the animal (positively and negatively), and these impacts provide information on the fifth domain, mental state. The cumulative balance of emotions elicited in the mental state domain leads to an overall welfare state assessment in the animal.

For small ruminants undergoing procedures potentially requiring anesthesia and analgesia, consideration of the welfare impact on the animal is critical to assess whether the costs to the animal of the procedure are acceptable when balanced against the benefits, and to address means to mitigate some of the impacts. For example, the costs to the animal of the withdrawal of food and water, up to 24 hours before anesthesia, will impact aspects of the nutrition domain (eliciting emotions of hunger, thirst, or frustration). Although small ruminants, particularly sheep, can cope with only small physiological impacts of food deprivation (Hogan et al., 2007), these species have evolved to spend large parts of their day searching for food and grazing. Thus, the behavioral motivation to feed is still present, and animals that are not fed show behavioral responses suggestive of negative affective states (Verbeek et al., 2011, 2014). Small ruminants are social species, and separation from conspecifics is associated with behavioral and physiological responses indicative of stress (Dwyer, 2004). Isolating an animal from conspecifics during recovery or to maintain a surgical site, thus affects the behavioral interaction domain, potentially eliciting emotions of fear, panic, anxiety, or boredom. Finally, surgical procedures are likely to cause at least transitory pain. Although some of these may be unavoidable or considered a necessary cost, consideration of whether they can be mitigated should always be part of experimental planning. For example, could an isolated animal be housed in sight and auditory communication with other animals, or a 'buddy' animal be housed with the experimental animal? For very young ruminants, being housed with their mothers can help reduce the impact of painful stimuli (Walker et al., 2003), and monitoring the potential presence of pain can ensure that these impacts are reduced.

C. The behavior of small ruminants

Ruminants are prey animals and have specific and highly motivated behavioral adaptations to deal with potential threats from predators. These are still maintained and expressed in the animal, regardless of whether a predator threat is present. For sheep, goats, and cattle, this involves highly organized social behavior, fear and anxiety when socially isolated, and flight from a threat (Dwyer, 2004). All species will also use aggression, particularly head threats and butting, particularly when cornered, although intact males will be more likely to attack than females. Sheep are generally the most fearful of the three species, although they are also the least likely to use aggression as a response, and, unless well-handled and trained from a young age, will regard humans as potential predators. Goats and young calves can be more curious and less fearful of human presence. All species are, however, very trainable, and if an animal is to be used in a study for a prolonged period, investing time in handling or 'gentling' the species, ideally with food rewards (Mellor, 2004), and habituating them to the experimental pens or apparatus can result in less stress and better cooperation from the animal and better experimental outcomes. All species respond well to stroking, hand feeding, and calm handling (Destrez et al., 2013), which can minimize the stress and difficulty of working with these species.

In agricultural practice, these species are almost always moved by driving away from the handler. All animals will tolerate the presence of humans (and indeed predators) at a distance but maintain a 'flight zone' around themselves, whereby encroachments into this space will elicit movement away (Grandin, 2014). The size of the flight zone will vary with species, experience, breed, and context, but for all species using low-stress handling techniques by working at the outer edge of the flight zone, such that the animal moves away slowly and calmly, is advised. Rapid movement into the flight zone will elicit panic and flight, which is counterproductive and can result in injury. As prey animals, these species have excellent peripheral vision, with the eyes located on the sides of the head, allowing 270° of vision, but with a blind spot directly behind (Piggins and Philips, 1996). The handler can speed up or slow down the movement of the animal by their position relative to the desired direction of travel (termed the 'point of balance' at the shoulder in cattle). Handlers positioned forward of the point of balance, in a 90° arc from the shoulder to the head, will slow down and stop movement, which can be started by moving caudally. When animals are in a chute or a confined space, moving backward along the line of animals will cause them to move forward. Calm and confident movement around animals is always advised, avoiding sudden or rapid movements which can elicit fear, panic, and flight. This is particularly relevant to larger males, which may carry horns, where a rapid movement toward the animal may result in charging and butting instead of flight, potentially causing serious injury to handlers. Although sheep and cattle will charge and butt with the head lowered, male goats rise on their hind legs and angle a head blow from above, so care must be taken when handling these animals.

In a laboratory setting, small ruminants can be trained to walk on a halter, and this can facilitate movement over short distances. Animals can also be easily trained to follow a bucket of feed, and this can be the simplest and least stressful method to move them. This method of encouraging movement makes use of the evolved following behavior, particularly of sheep, where the movement of another animal in front encourages other animals to follow. Designing movement routes to avoid dead-ends or sharp bends where the animal in front may suddenly disappear, and where there is only one easily observed route can facilitate animal movements (Starling et al., 2021). Unless specifically trained to tolerate handling and movements away from the social group, single animals are always difficult to move alone. Transporting these animals in a confined transporter may reduce the opportunity of a panicking animal injuring itself on obstructions.

1. *Restraint*

Any form of restraint and close confinement is stressful for small ruminants, eliciting fear, thus consideration of whether it is necessary and minimizing the time spent restrained is important. Sheep, goats and calves can often be caught and restrained manually by experienced animal handlers, as they are lightweight and, with training, relatively docile (Fonseca et al., 2019). Animals should be caught by gradually reducing the range of movement in the pen until the animal can be caught and restrained against the handler's legs or gently held against the side of the pen, usually by holding the chin with one hand, and pressing a knee against the lumbar vertebrae in front of the stifle. Animals should not be caught by the fleece, horns, ears, or tails, which can cause pain, bruising, and, in the case of horns, may break off and cause considerable bleeding.

Calves are usually restrained in a standing position, and for larger calves, this may require the use of a chute and head yoke to position the animal in a way that reduces the chance of injury. Sheep and goats can be cast (tipped onto their rump) if this is required for experimental procedures, but note that, although this usually causes the animal to remain still, this is still a stressful position for animals, and the time spent in this position should be minimized. Late pregnant ewes or does should not be cast.

Various forms of animal handling equipment, such as squeeze chutes, tilt tables, and rollover crates, are available which can make animal handling and restraint easier for the handler. These rely on physically restraining the animal within a crate or against a table, and then, for tilt tables and rollover crates, positioning the animal on its side or back as required. These have considerable benefits for the handler and may reduce the ability of the animal to struggle and injure themselves compared to manual restraint, but they are still associated with fear and stress in the animal. It is imperative that use of these devices is kept to a minimum in the conscious animal, which often cannot express its distress when restrained, and the ease for the handler should not be interpreted as a signal to keep animals restrained for longer than is necessary. Sheep or goats restrained on their backs are also susceptible to asphyxia, as fermentation in the rumen can put pressure on the lungs and impact the ability of the animal to breathe. Breathlessness has been identified as a significant cause of stress in ruminants (Beausoleil and Mellor, 2015), so avoiding the use of this position as much as possible will improve welfare.

III. Pain assessment and the need for analgesia

A. Pain assessment

In dealing with pain, the principles of the 3Ss (Suppress, Substitute, and Soothe) which have been developed for farm animals (Guatteo et al., 2012), should equally be employed when dealing with farm animals used in experiments. This approach is analogous to the 3Rs but focused on pain. It considers that those working with animals should suppress any source of pain that has no obvious advantage to the animal or those working with it. For example, consideration of whether common farming practices, such as castration or tail docking, are warranted in an experimental setting. Secondly, the substitution of a technique causing pain by another less painful method should be used wherever possible. This then requires a constant review of methods and consideration of less painful alternatives where these become available. Finally, in situations where a painful technique cannot be avoided then there is an expectation that all appropriate treatments to soothe that pain will be used. However, pain management in small ruminants is often inadequate, and this is frequently suggested to be because, as prey species, these animals may avoid showing overt signs of pain compared to other species (Anil et al., 2002). Studies of veterinarians in farm animal practice also suggest that some may believe that farm animals feel less pain than companion animals (Raekallio et al., 2003), perhaps due to an inability to adequately recognize signs that the animal is in pain. Experimentally, many studies have investigated methods to assess pain in ruminants, and a variety of different methods are used, often validated with the use of anesthesia or analgesia (Table 20.1). These suggest that there are well-validated and useful methods to assess pain, which can be applied when small ruminants are used in research.

The choice of which method of pain assessment, or combination, to use often depends on the type of pain expected or the type of procedure. Acutely painful stimuli, particularly those located in a somatic region, are often accompanied by well-defined behavioral and physiological responses, which can be readily scored or monitored. Changes in sensitivity to tactile stimulation of a specific site associated with injury or surgery can provide some information on the nociceptive responses of an animal, when associated with sensitive behavioral indicators of withdrawal, guarding, or other responses. However, chronic pain or more diffuse stimuli, which may be visceral in origin, are more challenging to assess, as they may be associated with alterations in daily time budgets, circadian rhythms of behavior, or physiological indicators, or more subtle changes in response. More recently the use of novel behavioral techniques, such as facial expressions, have been developed for use in ruminant species, following work on laboratory rodents (Table 20.1), and can give a more sensitive measure for assessing pain. An alternative approach, that of qualitative behavioral assessment (QBA), takes a holistic approach to assessing the whole animal, based on the dynamic expressivity of how that animal behaves, rather than what it does (Wemelsfelder et al., 2001). QBA has successfully provided a sophisticated understanding of the emotions associated with painful stimuli in sheep and cattle pain models, and further development of the use of this method in pain assessment is warranted. In general, however, while there is no one specific measure of pain, or pain assessment tool that works in all pain situations, there are a number of validated pain assessment scales that have greater value than single physiological measures, such as elevated heart rate. The use of a complementary combination of indicators, or a validated multidimensional or composite pain scoring system, can provide an accurate representation of the degree of pain experienced.

Pain, as an emotional state, can be experienced differently between different animals, and whereas some indicators in Table 20.1 attempt to understand the impact on

TABLE 20.1 A summary of the various types of behavioral and other indicators used to assess pain in small ruminants under different conditions.

Indicator or biomarker	Types of measures or responses	Examples of pain models where used	Example references
Specific pain-related behaviors	Kicking, stamping, rolling, looking at the site, head-shaking, vocalization	Castration, tail-docking, disbudding	Marini et al. (2017), Theurer et al. (2012) and Molony et al. (2002)
General behavioral changes	Daily activity budgets, feeding behavior, lying, social behavior	Chronic lameness, mastitis, metritis	Barragan et al. (2018)
Physiological indicators	Plasma or salivary cortisol, adrenaline/noradrenaline, substance P, haptoglobin, serum amyloid A, blood counts	Castration, tail-docking, disbudding	Sutherland et al. (2019), Kleinhenz et al. (2018) and Musk et al. (2017b)
Clinical indicators (often of SAM axis)	Blood pressure, respiratory rate, heart rate and heart rate variability, electromyography, EEG, assessment of lesions and healing	Castration, tail-docking, disbudding, surgical approaches	Harris et al. (2020), Sutherland et al. (2019), and Krohm et al. (2011)
Algometry	Von Frey hairs, thermal sensitivity, pressure plates	Castration, tail-docking, disbudding, lameness; reticuloperitonitis; keratoconjunctivitis	Troncoso et al. (2018), Kleinhenz et al. (2018), Musk et al. (2017c), and Dewell et al. (2014)
Facial expression	Orbital tightening, ear posture, shape of nares or muzzle, tension in cheeks	Lameness, mastitis, hot iron branding; osteotomy	Muller et al. (2019), McLennan et al. (2016) and Gleerup et al. (2015)
Qualitative behavioral assessment (QBA)	Terms associated with pain, irritation, uncomfortable, restlessness, anxiety and fear	Mastitis, castration	Maslowska et al. (2020), Grant et al. (2020), Vindevoghel et al. (2019) and des Roches et al. (2018)
Infrared thermography (IRT)	Surface eye temperature, inflammation	Castration in calves	Stewart et al. (2010), Kleinhenz et al. (2018) and Harris et al. (2021)
Numerical rating scales and visual analogue scales	Scores of perceived pain, such as gait scores for lameness, or more holistic assessments of pain	Lameness	Vieira et al. (2015), Kaler et al. (2009), Tuyttens et al. (2009) and Welsh et al. (1993)
Composite or multidimensional pain scoring systems	Multi-modal measures on various scales	Orchiectomy, stifle arthrotomy, thoracotomy	Izer et al. (2019), della Rocca et al. (2017), de Oliveira et al. (2014), Krohm et al. (2011) and Adami et al. (2011)

the animal at the emotional level (e.g., QBA), others, such as mechanical nociceptive threshold testing, for example, can be useful at understanding how stimuli are processed but do not provide an insight into the animal's perception of the painful stimuli. Pain can induce aversion to a place, people, or other stimuli because of the associations formed between the negative emotional state and another unconditioned stimulus. Pain-inducing stimuli may also affect the central processing of other stimuli, for example, resulting in more pessimistic-like behavior in cognitive or judgment bias testing in calves (Neave et al., 2014), or changes in responses to predator stimuli in fish (Ashley et al., 2009). Persistent or chronic pain can cause significant alterations in the central processing of stimuli, and more sophisticated assessments of behavioral responses may be required to understand the impact of chronic pain.

Relief of pain is a scientific imperative for any species used in biomedical research (National Research Council [NRC], 2011). Recognition and relief of pain are required by the Animal Welfare Regulations when these species are used in biomedical research (United States Department of Agriculture [USDA], 2008). In the research setting, anesthetic techniques and analgesic protocols often differ from those used in the field setting common to clinical practice, and certain experimental surgical procedures may require complex anesthetic and analgesic regimens. There is a growing body of literature on anesthesia, analgesia, and pain management specific to small ruminants (see, for example, Abrahamsen, 2009a, 2013; Carroll and Hartsfield, 1996; Carroll et al., 1998b; Coetzee, 2013; Gray and McDonell, 1986a, b; Greene, 2003; Lee and Swanson, 1996; Lin and Pugh, 2002; Lin and Walz, 2014; Riebold, 2015; Swindle et al., 2002; Valverde and Doherty, 2009). For some procedures, empirical use of anesthetics and analgesics reportedly used in humans, companion animals, or other species may be adopted and modified for the small ruminant. Cardiovascular studies in particular may require the use of cardiopulmonary bypass which is beyond the scope of clinical practice (see Carney et al., 2009b; Collan, 1970; Gerring and Scarth, 1974; Schauvliege et al., 2006). The attending veterinarian should be consulted for assistance in developing specific anesthetic protocols to meet study objectives.

B. Common husbandry procedures that cause pain

In normal agricultural practice, sheep, goats, and calves are subjected to painful procedures as part of routine management. These typically involve castration of all species, disbudding in calves and goat kids, and tail docking in sheep. In many cases, despite considerable research into methods to provide anesthesia and analgesia, these procedures can be done, legally, in many countries without the use of anesthesia or analgesia. When animals are used for biomedical research, as with all painful procedures, appropriate anesthesia and analgesia must be used, and justified on welfare, veterinary, or scientific grounds (Forbes et al., 2007).

Castration is usually carried out in agricultural practice within a few days of birth to reduce unplanned matings, to avoid taint or changes in other sensory characteristics of meat in postpubertal males, and/or to reduce the risk of injury to humans and other animals in managing intact male animals (Sutherland and Tucker, 2011). Several different techniques are routinely used, including the use of tight rubber rings (elastration), banding, instruments designed to crush the spermatic cords (known as bloodless castration), and surgical approaches. In many countries, the method or timing of the use of some of these methods without appropriate anesthesia or analgesia may be restricted. For example, in the UK, castration using tight rubber rings is only permitted for lambs or kids under 7 days of age, without anesthesia or analgesia, and is forbidden in some European countries. Castration by any method has been shown to be associated with behaviors indicative of pain (e.g., rolling, kicking, stamping, abnormal postures), and elevations of plasma cortisol and heart rate (Graham et al., 1997; Kells et al., 2020; Molony et al., 2002; Paull et al., 2009). These behaviors can persist for several hour after the procedure and can be significantly reduced using local anesthetics (lidocaine) injected into the testes and scrotal neck, but not completely abolished (Kells et al., 2020; Stewart et al., 2014). Subcutaneous, but not intramuscular, meloxicam reduced pain behaviors in the 12 hours after castration (Paull et al., 2012), although it did not affect acute pain responses (Kells et al., 2020). Topical application of local anesthetic has been shown to reduce the pain associated with surgical castration (Paull et al., 2009), but this method of castration is prohibited in many countries as it causes the greatest behavioral pain responses. More recently, formulations to deliver NSAIDs through a buccal route in small ruminants have been developed and can help to reduce pain expression to a greater degree than is achieved through local anesthetic alone (Small et al., 2018).

1. *Disbudding*

Disbudding is usually carried out in young calves or goat kids soon after birth but is rarely practiced with sheep. Dehorning refers to the removal of the developing or mature horn in older animals. In agriculture, this is done to avoid handler or between-animal injury, especially when animals are kept in confined spaces. This might be a relevant issue for research uses of animals. However, all species have several polled breeds; thus, unless there is a very specific and justifiable reason for using a horned breed, the use of polled varieties would be greatly encouraged to avoid the need for this procedure. When required, disbudding of the young animal (<2 months of age) is preferred over dehorning and should be in compliance with applicable regulations (ASAS, 2020).

Disbudding can be carried out using caustic paste, scoops, or thermal cautery (Brooks et al., 2021; Hempstead et al., 2018a). In general, pastes and scoops are not recommended methods due to the pain associated with these approaches, and with paste, the potential for causing burns to other parts of the animal. In many countries, disbudding can only be carried out by a veterinarian, and requires the use of at least local anesthesia, and often postoperative analgesia. In goat kids, the skull is thin around the site of the horn bud, and disbudding is often carried out under general anesthesia as the risk of inadvertently causing brain damage is considerable. Even with the use of local anesthesia and analgesia (such as lidocaine and flunixin meglumine) or general anesthetic and NSAIDs (isoflurane and meloxicam), there is evidence of pain in the animals, such as head shaking, a reduced growth rate, and pessimistic behavioral responses in cognitive bias testing for a number of days after the procedure (Ajuda et al., 2020; Hempstead et al., 2018b; Neave et al., 2014).

2. *Tail-docking*

This procedure is only commonly carried out on sheep in agricultural practice. For sheep, tail docking is routinely carried out to reduce the risk of fecal soiling of the breech area, which can be a risk factor for cutaneous myiasis (flystrike). This is a painful and unpleasant condition, which can cause distress and mortality in sheep if not treated (French et al., 1994). However, the evidence that tail-docking can reduce the incidence is unclear (Orihuela and Ungerfeld, 2019; Sutherland and Tucker, 2011), and the use of other practices, such as regular shearing of the perineal area, insecticides, and topical applications of deterrents, may be at least as effective.

Tail docking is generally carried out by the same methods as described for castration, but also using hot docking irons. Similar restrictions apply in many countries, and the procedure is associated with behavioral and physiological evidence of pain in the lamb, albeit at a lower level than seen for castration (Molony et al., 2002). The use of subcutaneous local anesthetic drugs, such as bupivacaine, administered immediately before docking is effective at reducing these responses (Graham et al., 1997).

IV. Sedation and premedication

Sedation of small ruminants prior to the induction of anesthesia is advantageous in that sedatives and tranquilizers may help minimize stress and anxiety and allow for better control of the animal. Often the dose of the induction agent(s) and the amount of maintenance anesthetic are reduced with the use of sedative premedications. Depending on the choice of sedative or tranquilizer selected, some drugs may provide analgesic effects as well. Common doses of sedatives and anesthetic induction agents used in calves and small ruminants are presented in Tables 20.2 and 20.3, respectively.

A. α_2 agonists and antagonists

In ruminants, α-2 adrenergic receptor agonists produce reliable, dose-dependent sedation that can range from mild sedation to complete recumbency (Valverde and Doherty, 2008). Xylazine can be used as a single agent or combined with an opioid for sedation prior to anesthesia, or alternatively, it may be administered with a dissociative agent such as ketamine or tiletamine-zolazepam to induce anesthesia (Flecknell et al., 2015). All α-2 agonists yield a quick onset of sedation with ruminants being particularly sensitive to the effects of xylazine. One-tenth or less of the xylazine dose used in other species is required to produce sedation in cattle and small ruminants (Valverde and Doherty, 2008). Goats appear to be more sensitive to the effects of xylazine than sheep (Taylor, 1991). The difference in sensitivity between species appears to be of pharmacodynamic origin and is likely due to G-protein binding affinity in ruminants species compared to nonruminant species (Törneke et al., 2003).

In sheep, hypoxemia and the formation of pulmonary edema are well-known adverse effects of α-2 agonists, with the exact pathophysiology largely unclear. These hypoxemic reactions appear to be highly variable, potentially individual- and breed-dependent, making it difficult to predict whether an individual animal will react adversely, and the degree of hypoxemia which may develop (Kästner, 2006; Kutter et al., 2006). In addition to the development of hypoxemia and pulmonary edema, bradycardia, hypercapnia, hypotension, hyperglycemia, hypoinsulinemia, and increased urine production have been reported following xylazine administration (Greene and Thurmon, 1988). Combining xylazine with methadone, morphine, or

TABLE 20.2 Common doses for sedative drugs in small ruminants.

Variable	Calf (mg/kg)	Sheep (mg/kg)	Goat (mg/kg)
Acepromazine	0.02; IV, IM	0.01–0.02; IV	0.01–0.02; IV
	0.04–0.09; IM	0.04–0.09; IM	
Medetomidine	0.03; IV, IM	0.001–0.007; IV	0.001–0.007; IV
	0.04; IM	0.04; IM	
Xylazine	0.05–0.3; IV, IM	0.01–0.02; IV	0.01–0.02; IV
	0.1–0.3; IM, SQ	0.1–0.3; IM, SQ	
Detomidine	0.03; IV, IM	0.001–0.007; IV	0.001–0.007; IV
	0.04; IM		
Dexmedetomidine		0.005; IV	
Diazepam	0.25–0.5; IV	0.25–0.5; IV	0.25–0.5; IV
Midazolam	0.1–0.3; IV, IM	0.1–0.5; IV, IM, SQ	0.1–0.5; IV, IM, SQ

Modified from Valverde and Doherty (2008).

TABLE 20.3 Common doses for induction drugs in small ruminants.

Variable	Calf (mg/kg)	Sheep (mg/kg)	Goat (mg/kg)
Propofol	4–6	4–6	4–6
Methohexital	3–5	3–5	3–5
Ketamine	5–10	5–10	10
Xylazine[a]/ketamine	0.05–0.1/3–5	0.03–0.05/3–5	0.05–0.1/3–5
Ketamine/midazolam	4/0.4	4/0.4	4/0.4
Ketamine/diazepam	4/0.4	4/0.4	4–5/0.4–0.5
Xylazine[a]/ketamine/diazepam	0.05/3/0.4	0.03/5/0.4	0.03/5/0.4
Tiletamine-zolazepam (1:1 mixture)	4	1–4	1–4
Xylazine[a]/tiletamine-zolazepam	0.05/2	0.05/2	0.05/2
Xylazine[a]/ketamine/guaifenesin	0.05/2/75	0.05/2/75	0.05/2/75

[a] *Can be substituted by equipotent dose of another alpha$_2$ agonist.*
Source. Valverde and Doherty, 2008.

tramadol resulted in cardiopulmonary changes similar to those induced by xylazine alone in sheep; however, these combinations produced enhanced sedation at 15 and 30 minutes following administration (de Carvalho et al., 2016). Xylazine also has an oxytocin-like effect in ruminants (Greene and Thurmon, 1988). Xylazine administered to ruminants in the final trimester of pregnancy may cause premature parturition and retention of fetal membranes (Rosenberger et al., 1968), which is important to note as sheep are often used as models in reproductive and fetal research studies. Increased myometrial tone and increased intrauterine pressure have been reported in cows following xylazine administration (Leblanc et al., 1984).

Detomidine may be used as a safer alternative to xylazine in pregnant sheep and goats as it is unlikely to induce abortion in pregnant ruminants (Jedruch and Gajewski, 1986; Pyörälä et al., 1986). While the pharmacologic effects of detomidine are comparable to those of xylazine, ruminants seem to be less sensitive to detomidine than to xylazine (Celly et al., 1997). Because detomidine is more α_2-specific than xylazine, a lower dose is required to achieve adequate sedation with less adverse effects (Singh et al., 1994). The severity of hypoxemia and pulmonary edema induced by detomidine is less in comparison to other α_2 agonists (Kästner, 2006). Detomidine administered at 20 μg/kg intravenously as a bolus dose followed by an infusion of 60 μg/kg/hour produced satisfactory sedation for minimally invasive procedures with no significant cardiorespiratory effects in sheep (de Moura et al., 2018).

Other α-2 agonists commonly used in small ruminants in a research setting include medetomidine and dexmedetomidine. Because α-2 agonists also have analgesic and muscle relaxant effects, they are often used as preanesthetics or as anesthetic adjuncts in ruminants (Lin, 2015). Medetomidine induces dose-dependent sedation, and when administered at a dose of 0.005 mg/kg, produces analgesia in sheep that is comparable to that of fentanyl dosed at 0.015 mg/kg (Muge et al., 1994). Intravenous xylazine produced significant decreases in pulmonary function in ventilated isoflurane-anesthetized sheep in comparison to an equipotent dose of medetomidine, suggesting that medetomidine may be the preferred α-2 agonist when optimal pulmonary function is essential (Raisis et al., 2021). The onset of sedation produced by medetomidine is more rapid and lasts longer than that produced by xylazine in calves and goats (Carroll et al., 2005; Rioja et al., 2008). Cardiopulmonary effects such as increases in heart rate, mean arterial blood pressure, and pulmonary arterial blood pressure have been reported following IV or IM administration of medetomidine in ruminants (Carroll et al., 2005; Kästner et al., 2003; Rioja et al., 2008). Medetomidine also results in increased cortisol and glucose levels in ruminants by having a profound effect on the stress response (Carroll et al., 1998, 2005; Ranheim et al., 2000).

While racemic medetomidine has a binding ratio of 1620:1 (α_1:α_2), its D-enantiomer, dexmedetomidine, is even more selective (Murrell and Hellebrekers, 2005; Virtanen et al., 1988). Dexmedetomidine is twice as potent as medetomidine, with a dose of 5 μg/kg IV being equipotent to 10 μg/kg IV of medetomidine for sedation in sheep (Kästner et al., 2001a). Cardiopulmonary depression and moderate-to-severe hypoxemia are adverse effects of dexmedetomidine administration, and similar cardiopulmonary and sedative effects have been reported in comparing dexmedetomidine and medetomidine in sheep (Kästner et al., 2001a, 2001b, 2005, 2007a, 2007b). Compared to the use of dexmedetomidine alone in sheep, combining dexmedetomidine with an opioid (butorphanol, methadone, morphine, or tramadol) resulted in the same degree of cardiopulmonary depression without a significant impact on the degree or duration of sedation achieved (Borges et al., 2016). In regards to sedation, these results suggest no real added benefit in combining an opioid with dexmedetomidine.

The sedative and adverse effects of α-2 agonists can be reversed with specific α-2 adrenergic antagonists. Atipamezole, yohimbine, tolazoline, and idazoxan have been used to reverse the effects of α-2 agonists and curtail recovery time. It is important to note that the use of α-2 adrenergic antagonists will also reverse the analgesic effects provided by the α-2 agonists, so supplemental analgesia should be provided as necessary upon reversal. Yohimbine dosed at 1 mg/kg IV will reverse the sedative effects of xylazine in sheep (Riebold, 2015). Yohimbine is less effective than other α-2 antagonists, as tolazoline dosed at 0.5–2 mg/kg IV has been shown to reverse the effects of xylazine in calves more rapidly than yohimbine (Thurmon et al., 1989; Valverde and Doherty, 2008; Young et al., 1989). Ketamine-medetomidine sedation can be successfully reversed using tolazoline (2.2 μg/kg IV) and atipamezole (20–60 μg/kg IV or IM) in calves (Lin et al., 1999; Raekallio et al., 1991). When administered rapidly, tolazoline has been reported to cause tachycardia, increased cardiac output, vasodilation, and coronary vasodilation (Yellin et al., 1975). The risk of central nervous system excitement and adverse cardiovascular effects are reduced when α-2 antagonists are administered intramuscularly (Abrahamsen, 2008).

B. Phenothiazines

Acepromazine maleate produces mild sedation and skeletal muscle relaxation in ruminants (Lemke, 2007). When administered at a dose of 0.02–0.1 mg/kg IV or SQ, acepromazine provides mild tranquilization with minimal respiratory depression (Swindle et al., 2002). Although acepromazine does not provide any analgesic effects, it does have a sparing effect on inhalant anesthetics and may protect against the arrhythmogenic effects of anesthetics (Flecknell et al., 2015). The drug has minimal effects on heart rate but may result in hypotension in volume-depleted animals due to its alpha-adrenergic blocking properties (Lin et al., 2012; Valverde and Doherty, 2008). When combined with an opioid as a preanesthetic, sedation and preemptive analgesia can be achieved prior to the induction of anesthesia. Acepromazine alone administered to sheep resulted in a level of sedation similar to that observed when administered in combination with the opioids methadone, morphine, and tramadol without causing clinical changes in cardiorespiratory function (Nishimura et al., 2017). The degree of sedation produced by the administration of acepromazine and buprenorphine compared to acepromazine combined with morphine is similar in sheep (Musk and Wilkes, 2018). These preanesthetic combinations did not produce observable adverse effects and were sufficient for restraint prior to anesthesia induction (Musk and Wilkes, 2018).

C. Benzodiazepines

Diazepam and midazolam are the most commonly used benzodiazepines in small ruminants due to their anxiolytic, anticonvulsant, and central muscle relaxant effects (Lin et al., 2012). These drugs have minimal cardiopulmonary depressant effects and may be used as alternatives to α_2-agonists for sedation and restraint in small ruminants and calves. Diazepam is frequently used for sedation and to decrease anxiety in high-risk animals and can be combined with ketamine to improve muscle relaxation during anesthesia (Gray and McDonell, 1986b). As a tissue irritant, diazepam should only be administered intravenously, while midazolam can be administered both IV and IM as it is water-soluble and nonirritating to tissues (Valverde and Doherty, 2008). In conscious sheep and goats, rapid IV administration of low doses of benzodiazepines may cause an initial excitement phase (Valverde and Doherty, 2008). Diazepam dosed at 0.2–0.5 mg/kg given slowly IV provides a short period of sedation and recumbency (Valverde and Doherty, 2008). The degree and duration of sedation produced may be enhanced when benzodiazepines are combined with an opioid, such as butorphanol or morphine. The effects of benzodiazepines can be reversed using flumazenil, but typically there is no need for a reversal of these agents (Valverde and Doherty, 2008).

D. Opioids

When administered alone as premedication, opioids do not produce reliable sedation and may cause unwanted behavioral changes in ruminants, such as agitation and chewing (Valverde and Doherty, 2008). However, when combined with other premedicant drugs, opioids may provide preemptive, multimodal analgesia, improved quality of sedation, as well as a reduction in the required anesthetic induction and maintenance doses. Adverse effects of ataxia and dysphoria have been reported following high doses of IV administration of butorphanol (0.1–0.2 mg/kg) in sheep (Waterman et al., 1991). To avoid these adverse effects, lower doses of butorphanol (0.02–0.05 mg/kg) should be used. Methadone (0.5 mg/kg), morphine (0.5 mg/kg), or tramadol (5 mg/kg) administered intravenously with acepromazine (0.05 mg/kg) were shown to produce sedation in sheep without clinically relevant cardiorespiratory changes (Nishimura et al., 2017). Acepromazine (0.03 mg/kg) administered with buprenorphine (0.02 mg/kg) or morphine (0.3 mg/kg) given IM as a premedication combination produced similar sedation in sheep without observed adverse effects (Musk and Wilkes, 2018). In comparison to conscious ruminants, opioids administered to anesthetized ruminants are less likely to cause excitement and are more beneficial due to their potent analgesic effects (Valverde and Doherty, 2008).

V. Anesthesia

A. Anesthetic induction

1. Barbiturates

Ultrashort-acting barbiturates, such as methohexital, are commonly used for rapid induction of anesthesia, followed by maintenance of anesthesia with inhalant anesthetics. Methohexital sodium (3−5 mg/kg IV) is a nonsulfur-containing, ultrashort-acting oxybarbiturate used to induce anesthesia and facilitate endotracheal intubation in sheep, calves, and goats (Carney et al., 2009b; Collan, 1970; Thurmon, 1986).

In comparison to the use of ketamine-combinations for anesthesia induction in sheep and calves, the authors (JI, RW) prefer methohexital as it produces significantly less salivary secretions, allowing for easier endotracheal intubation without the need to suction the oropharynx for improved visualization. In the authors' experience, rapid administration of methohexital often results in apnea, or a decreased respiratory rate, therefore necessitating prompt intubation and mechanical ventilation. Thiamylal (8−14 mg/kg IV) or thiopental (10−16 mg/kg IV) are thiobarbiturates previously used for induction of anesthesia; however, they are no longer available in the United States (Ewing, 1990). Because barbiturates are highly alkaline, they should be administered through a preplaced intravenous catheter to avoid tissue necrosis due to perivascular leakage of the agent (Swindle et al., 2002).

2. Propofol

Propofol (4−6 mg/kg IV) is commonly used for a smooth, rapid induction and/or maintenance of general anesthesia in sheep, goats, and calves (Alves et al., 2003; Carroll and Hartsfield, 1996; Prassinos et al., 2005; Reid et al., 1993; Riebold, 2015; Valverde and Doherty, 2008; Waterman, 1988). Because it is highly lipophilic, propofol distributes from blood to tissues and crosses the blood-brain barrier very rapidly, facilitating quick anesthesia induction with short-lasting effects (Cagnardi et al., 2009). Following induction, propofol may be administered as a constant rate infusion (0.5 mg/kg/minute IV) in sheep to produce light anesthesia (Lin et al., 1997). Calves induced with propofol (5 mg/kg IV) and maintained by continuous infusion of propofol (0.6−0.8 mg/kg/minute IV) developed no clinically significant hemodynamic changes (Deschk et al., 2016). In goats, the median minimum infusion rate of propofol required to prevent purposeful movement of the extremities in response to a noxious stimulus was determined to be 0.45 mg/kg/minute (Ferreira et al., 2016). In this study, no significant cardiopulmonary changes were observed, but clinically relevant hypoxemia was consistently present in the goats at 2 minutes following anesthesia induction (Ferreira et al., 2016). Apnea induced by propofol has been correlated more closely with dose rather than the rate of administration (Prassinos et al., 2005).

3. Ketamine

Ketamine, a dissociative anesthetic agent, is frequently used as an induction agent in ruminants. When used as a sole agent, ketamine increases muscle tone, peripheral reflexes are maintained, and even at the highest dose, ketamine is not a complete anesthetic (Valverde and Doherty, 2008). It is therefore not recommended to be used as the sole agent for induction or short-term anesthesia. Instead, ketamine is often administered following premedication with acepromazine or α2-agonist such as xylazine or dexmedetomidine. Ketamine may be coadministered with a benzodiazepine such as midazolam for greater analgesia, sedation, and muscle relaxation during anesthesia (Lin et al., 2012). Because ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, its use often results in an apneustic breathing pattern, but may produce dose-dependent apnea during inspiration (Valverde and Doherty, 2008). Analgesia is also produced as a result of the effects of ketamine on the NMDA receptor (Himmelseher et al., 2005). However, the degree and duration of analgesia produced from ketamine utilized as a single agent are typically insufficient in effectively managing postoperative pain. As opposed to other anesthetics that cause cardiovascular depression, ketamine stimulates the sympathetic nervous system, leading to increased heart rate and arterial blood pressure (Lin et al., 2012). When ketamine is combined with an α_2-agonist, the cardiovascular stimulation induced by ketamine is offset by the cardiovascular depressive effects of the α_2-agonist. Small ruminants have been effectively induced or undergone a short duration of anesthesia with combinations of ketamine and xylazine, medetomidine, or dexmedetomidine (Caulkett et al., 1996; Coetzee et al., 2010; Gogoi et al., 2003; Kästner et al., 2001a; Lin et al., 1997; Raekallio et al., 1991; Singh et al., 2010; Swindle et al., 2002; Valverde and Doherty, 2008; Özkan et al., 2010). It is not recommended to use a combination of ketamine (2 mg/kg IV or 4 mg/kg IM) and xylazine (0.05−0.1 mg/kg IV or IM) for short-term anesthesia in clinically unhealthy ruminants with potential underlying cardiopulmonary disease due to the adverse effects on cardiopulmonary function associated with the large dose of xylazine (Abrahamsen, 2013). These IV and IM combinations should only be used in clinically healthy ruminants (Abrahamsen, 2013).

As an alternative to a ketamine-α_2-agonist combination, ketamine can be administered with diazepam or midazolam for induction of anesthesia with very minimal cardiopulmonary depression. Muscle relaxation provided by the benzodiazepines negates the muscle rigidity produced by ketamine. Equal volumes of ketamine (100 mg/mL) and diazepam (5 mg/mL) administered intravenously at 1 mL/18–22 kg will provide up to 20 minutes of surgical analgesia in small ruminants (Abrahamsen, 2013). Alternatively, ketamine (4 mg/kg) and midazolam (0.4 mg/kg) have been used to induce anesthesia in goats (Stegmann, 1998). In healthy small ruminants, anesthesia induction is commonly accomplished using a combination of ketamine (5 mg/kg IV), diazepam (0.3–0.5 mg/kg IV), and xylazine (0.03 mg/kg IM) (Valverde and Doherty, 2008). Xylazine is administered first to induce mild sedation and provide a more controlled induction, followed by IV administration of ketamine-diazepam, given to effect, to facilitate intubation (Valverde and Doherty, 2008).

4. Tiletamine-zolazepam

Telazol (tiletamine-zolazepam) is similar to ketamine-diazepam as a dissociative NMDA-antagonist (tiletamine) that is combined with a GABA-agonist benzodiazepine (zolazepam) (Valverde and Doherty, 2008). Telazol yields greater analgesic effects and muscle relaxation in comparison to ketamine (Valverde and Doherty, 2008). However, the degree and duration of analgesia provided by Telazol alone or ketamine alone, administered as single agents, are insufficient for adequately managing postoperative pain. Neither agent should be used for the sole purpose of providing analgesia. While it provides a rapid and smooth induction in ruminants, it often results in cardiovascular stimulation, hypoventilation, and hypothermia, necessitating oxygen and ventilatory support (Valverde and Doherty, 2008). A combination of Telazol (13.2 mg/kg IV) and xylazine (0.11 mg/kg IV) produced better muscle relaxation and a longer duration of anesthesia than Telazol alone (13.2 mg/kg IV) in sheep with a smooth and gradual recovery (Lin et al., 1993a).

VI. Maintenance of anesthesia

A. Endotracheal intubation of small ruminants and calves

Following the induction of anesthesia, it is crucial to intubate the airway of small ruminants as quickly as possible to prevent aspiration of salivary secretions and ruminal contents. Small ruminants and calves must be sufficiently anesthetized before trying to pass an endotracheal tube. The small ruminant should be positioned in sternal recumbency with the head and neck extended to allow for direct visualization of the larynx (Fig. 20.1). Depending on the size of the animal, the laryngoscope blade should be between 20 and 40 cm in length for small and larger animals, respectively, in order to reach the larynx (Valverde and Doherty, 2008). In comparison to goats, sheep have a slightly larger airway and typically require an endotracheal tube with an internal diameter of 8.5–14 mm (Valverde and Doherty, 2008). Calves typically require endotracheal tubes 11–14 mm in size (Valverde and Doherty, 2008). It is recommended to use the largest tube possible in order to prevent airway secretions and ruminal contents from entering the larynx (Valverde and Doherty, 2008). Use of a stylet is recommended in order to stiffen the tube to allow for easier passage through the larynx. Once placed, the cuff of the tube should be immediately inflated and the tube secured prior to moving or repositioning the animal (Valverde and Doherty, 2008). Alternatively, small ruminants can be intubated blindly in either sternal or lateral recumbency by an experienced individual (Valverde and Doherty, 2008).

FIGURE 20.1 Endotracheal intubation of an adult sheet after induction of anesthesia with methohexital. Positioning of the anesthetized animal in sternal recumbency with the head and neck extended by an assistant permits visualization of the epiglottis and tracheal opening and aids rapid intubation. Larger animals may be positioned on the floor or a table.

B. Inhalant anesthetics

The most commonly used inhalant anesthetics to maintain general anesthesia in ruminants are isoflurane and sevoflurane. Halothane and methoxyflurane are older anesthetics that are no longer available in most countries (Flecknell et al., 2015). The minimum alveolar concentration (MAC) values of inhalants that are currently used in ruminants are presented in Table 20.4. The advantage of using inhalant anesthetics is the ability to quickly adjust anesthetic depth with a rapid and smooth anesthetic recovery (Flecknell et al., 2015). The disadvantage of using

TABLE 20.4 Minimum alveolar concentration (MAC) values (%) of commonly used inhalants in ruminants.

Inhalant	Cattle	Sheep	Goat
Isoflurane	1.27	1.19–1.53	1.14–1.43
Sevoflurane	N/A	3.3	2.33
Desflurane	N/A	9.81	N/A

Note: *N/A*, not available.
Sources: Vlaverde and Doherty, (2008), Columbano et al. (2018a, 2018b)

inhalant anesthetics is the significant cardiovascular depression associated with these agents. All inhalant anesthetics produce decreases in stroke volume, cardiac output, blood pressure, tidal volume, respiratory rate, minute volume, and increases in $PaCO_2$ that are dose-dependent (Lin et al., 2012; Valverde and Doherty, 2008). Isoflurane and sevoflurane produce vasodilation, which results in decreased arterial blood pressure (Hikasa et al., 1998).

Inhalant anesthetics do not possess analgesic properties. Preanesthetic medications, as well as preemptive and intraoperative analgesics, often lower the MAC and the amount of inhalant required to maintain a surgical plane of anesthesia (Flecknell et al., 2015; Valverde and Doherty, 2008). Administration of a propofol CRI has been shown to significantly reduce the isoflurane MAC in a dose-dependent manner in goats without significant cardiovascular effects (Dzikiti et al., 2011). Tiletamine-zolazepam used as a premedicant or induction agent, as well as acepromazine administered as a premedicant, have been shown to reduce the isoflurane MAC or concentration required to maintain anesthesia in goats (Doherty et al., 2002a, 2002b).

Because sevoflurane and desflurane are less soluble in blood than isoflurane, their ability to induce and alter the depth of anesthesia is more rapid in comparison to that of isoflurane. Similarly, ruminants recover more quickly following sevoflurane and desflurane anesthesia (Flecknell et al., 2015). The use of sevoflurane for anesthesia maintenance of ruminants in a research setting may be limited due to its high cost and higher MAC necessary to reach a surgical plane of anesthesia.

C. Total and partial intravenous anesthesia

A combination of injectable anesthetic, sedative, and tranquilizer drugs can be administered intravenously via intermittent boluses or, preferably, as a continuous rate infusion for the maintenance of general anesthesia. Use of total intravenous anesthesia (TIVA) may be advantageous in a research environment when inhalant agents cannot be used, such as during MRI imaging studies. The use of a "double drip" consisting of ketamine (1 mg/mL) and guaifenesin (50 mg/mL) is commonly used to induce and maintain a stable plane of anesthesia in small ruminants (Abrahamsen, 2013). Guaifenesin provides muscle relaxation as well as some sedation (Valverde and Doherty, 2008). The induction of anesthesia with double drip is achieved by infusing 1.7–2.2 mL/kg, followed by maintenance of anesthesia with a continued infusion rate of 2.6 mL/kg/hour (Abrahamsen, 2013). It is recommended not to exceed 60–90 minutes of continuous guaifenesin administration, as a residual accumulation of guaifenesin may result in adverse effects such as muscle weakness and prolonged anesthetic recovery. Use of an opioid, such as butorphanol (0.05–0.1 mg/kg IV or IM) or morphine (0.05–0.1 mg/kg IV or IM), can be considered to provide enhanced analgesia when a CRI of double drip is used for maintenance of anesthesia (Abrahamsen, 2013).

Alternatively, a continuous intravenous infusion of guaifenesin (50 mg/mL), ketamine (1–2 mg/mL), and xylazine (0.1 mg/mL), commonly known as "triple drip," can be used to induce and maintain anesthesia in healthy ruminants (Abrahamsen, 2013; Lin et al., 1993a, 1993b). While the addition of xylazine provides further analgesic effects, adverse effects include cardiopulmonary depression. An initial administration rate of 1–1.5 mL/kg of triple drip is required to induce anesthesia, followed by a maintenance rate of 2.6 mL/kg/hour without significant depression of the cardiopulmonary systems (Abrahamsen, 2013).

The effects of a propofol (12 mg/kg/hour) and fentanyl (0.02 mg/kg/hour) TIVA versus a propofol (12 mg/kg/hour) and midazolam (0.3 mg/kg/hour) TIVA were compared in spontaneously-breathing goats receiving supplemental oxygen (Dzikiti et al., 2010). Cardiopulmonary function was well maintained with both TIVA combinations, and the median propofol dose for maintenance was less with the propofol-fentanyl combination (12 mg/kg/hour) compared to propofol-midazolam (18 mg/kg/hour) (Dzikiti et al., 2010). Anesthetic recovery following propofol-fentanyl was not consistently smooth (Dzikiti et al., 2010).

Partial intravenous anesthesia (PIVA) uses a combination of inhalants and injectable anesthetics. Anesthetic, analgesic, and sedative drugs delivered by constant rate infusion can enhance analgesia and reduce the MAC of the inhalant, subsequently reducing cardiopulmonary depression (Valverde and Doherty, 2008). In goats, a low dose ketamine CRI (25–50 μg/kg/minute) with or without lidocaine (100 μg/kg/minute) produced a 30% reduction in the MAC of isoflurane (Doherty et al., 2007; Queiroz-Castro et al., 2006). Lidocaine infused at 50 μg/kg/minute reduced the isoflurane requirement by approximately 17% in calves undergoing umbilical surgery (Vesal et al., 2011).

VII. Anesthesia monitoring

Ruminants should be monitored continuously during anesthesia. Many research facilities have the capability to measure pulse rate, cardiac rhythm, invasive or noninvasive blood pressure, end-tidal CO_2, and O_2 saturation. The depth of anesthesia can be assessed via clinical evaluation and physiological indicators. The palpebral reflex gradually wanes as the depth of anesthesia increases and becomes absent or sluggish once a surgical plane of anesthesia has been reached (Valverde and Doherty, 2008). While eye position is often used to assess anesthetic depth in other species, it is not a reliable indicator of anesthetic depth in sheep and goats (Riebold, 2015). Upon induction, the eye is centrally located and then rotates ventrally as the anesthetic plane deepens (Abrahamsen, 2009a; Riebold, 2015). Upon reaching a surgical plane of anesthesia, the eye will move back to a central location and will return toward the ventral position at deep planes of anesthesia (Abrahamsen, 2009a; Riebold, 2015). Motor movement either spontaneously or resulting from surgical stimulation is a clear indicator of an inadequate plane of anesthesia (Valverde and Doherty, 2008). Physiologic indicators, such as changes in heart rate, blood pressure, and respiratory rate, may be used in conjunction with assessment of the palpebral reflex and jaw tone to evaluate the anesthetic plane.

Cardiovascular monitoring should include the use of an ECG for continuous assessment of heart rate and rhythm, as well as the measurement of arterial pressure. Direct blood pressure measurement via a catheter placed in a peripheral artery is the most accurate. The medial auricular branch of the rostral auricular artery, the saphenous artery, or the common digital artery can be catheterized in small ruminants (Flecknell et al., 2015; Riebold, 2015). The common digital artery courses between the dewclaws of the forelimbs and is easily accessible (Fig. 20.2).

Noninvasive blood pressure measurement is inaccurate in sheep, goats, and calves (Aarnes et al., 2014; Izer and Wilson, 2020; Trim et al., 2013). A jugular catheter can be used to measure central venous pressure (normal range is 5−10 cm H_2O, 3−7 mmHg), and cardiac output may be monitored during anesthesia if necessary for the research protocol (Riebold, 2015).

The use of capnography and pulse oximeters to monitor end-tidal CO_2 levels and O_2 saturation is essential to ensure adequate ventilation and gas exchange (Lin et al., 2012). Capnography is advantageous in that it provides a breath-by-breath analysis of changes in $EtCO_2$, while pulse oximetry provides a continuous approximation of oxygen saturation (Valverde and Doherty, 2008). The lingual artery of the tongue and the auricular artery of the ear are common sites for probe placement in sheep and goats (Lin et al., 2012). Most research facilities have point-of-care blood analyzers available, which are the most accurate means of determining the partial pressures of oxygen and carbon dioxide in the animal's blood (Valverde and Doherty, 2008).

VIII. Intraoperative support

A. Hypotension

A balanced electrolyte solution should be administered intravenously at 5−10 mL/kg/hour to support hydration during anesthesia (Lin et al., 2012). Perioperative intravenous fluid administration increases cardiac output and blood pressure with a subsequent increase in oxygen delivery to tissues (Valverde and Doherty, 2008).

FIGURE 20.2 Catheterization of the palmar common digital artery of a calf for direct blood pressure measurement. Insertion point of a 20 gauge catheter in the common digital artery. The artery is most superficial just proximal to a point midway between the dewclaws of the forelimb. The artery courses in a slight lateral to medial direction.

Intraoperative hypotension is a common occurrence when anesthesia is maintained via inhalational anesthetics. Hypotension may also result from hypovolemia and decreased vascular resistance (Valverde and Doherty, 2008). Normotension can be achieved by correcting volume deficits and decreasing the anesthetic plane if the ruminant becomes too deep under anesthesia (Valverde and Doherty, 2008).

B. Mechanical ventilation

In addition to hypotension, inhalant anesthetics produce dose-dependent respiratory depression. When ruminants are placed in lateral or dorsal recumbency, pressure from the weight of the abdominal viscera pushes the diaphragm further into the thoracic cavity, reducing the functional residual capacity of the lung (Lin, 2015). The weight of the abdominal viscera will also compress the great vessels, such as the vena cava, which can result in decreased venous return, cardiac output, arterial blood pressure, and tissue perfusion (Klein and Fisher, 1988). Furthermore, gas produced as a byproduct of fermentation continues to accumulate in the rumen, increasing intragastric pressure. The subsequent decrease in tidal volume, lung compliance, and minute ventilation leads to increased ventilation/perfusion mismatch with significant hypoventilation, hypoxemia, and respiratory acidosis (Lin, 2015).

Mechanical ventilatory support is often needed with anesthetized ruminants as respiratory rate and tidal volume decrease with deeper anesthetic planes (Abrahamsen, 2009a). Many anesthesia systems used in the research setting offer the choice of either pressure- or volume-controlled ventilation when conventional positive pressure ventilation is utilized (Davis and Musk, 2014). Positive pressure ventilation using a tidal volume of 10−15 mL/kg, a respiratory rate of 8−12 breaths/minute, and a peak pressure not to exceed 30 cm H_2O is recommended for anesthetized small ruminants (Carney et al., 2009b Valverde and Doherty, 2008). In the authors' experience, the use of 5−12 cm H_2O positive end-expiratory pressure (PEEP) aids in preventing pulmonary atelectasis during thoracic surgery. Application of 10 cm H_2O of PEEP significantly improved lung aeration and gas exchange in adult laterally recumbent sheep anesthetized via a continuous rate infusion of propofol (Staffieri et al., 2010). Tidal volume should be adjusted to produce inspiratory pressures sufficient to maintain an end-tidal CO_2 of 35−45 mm Hg. In pregnant anesthetized ewes, both volume-controlled ventilation and pressure-controlled ventilation have been shown to produce adequate oxygenation, but pressure-controlled ventilation gave superior oxygenation at a lower peak inspiratory pressure (Davis and Musk, 2014). Regardless of the ventilation mode selected, the use of capnography with spirometry, along with arterial blood gas analyses, is recommended to best assess the adequacy of ventilation and oxygenation.

Because ruminants continue to produce a large amount of saliva while anesthetized, they should be positioned in such a way to facilitate saliva egress by placing a pad or a rolled-up towel under the neck so the opening of the mouth is below the level of the larynx (Abrahamsen, 2013). Doing so, along with the use of a cuffed endotracheal tube, will help protect the airway of the anesthetized ruminant from saliva and rumen contents. Preemptive treatment with atropine to reduce salivation is not recommended, as atropine merely reduces the water content of the saliva, causing it to become more viscous and therefore more likely to obstruct the endotracheal tube (Weaver, 1971). Passage of an orogastric tube into the rumen with intermittent suctioning of the mouth will help decrease the risk of aspiration. The use of an orogastric tube also minimizes the occurrence of free-gas bloat and ruminal tympany. Proper positioning and provision of adequate padding are important to prevent muscle and nerve damage during anesthesia. A 5 cm-thick foam pad is recommended to prevent nerve paralysis in calves and small ruminants (Lin, 2015).

C. Thermal support

Hypothermia frequently results in a major reduction of anesthetic requirement, prolonged anesthetic recovery, and adverse effects on wound healing and blood coagulation (Hall and Clarke, 1983; Valverde and Doherty, 2008). Thermal support can be provided by the use of a circulating warm water blanket or other commercial warming pads such as electronically conductive fabric (HotDog® Patient Warmer, Eden Prairie, MN). Forced air warming systems, IV fluid line warming devices, and maintenance of a warm environmental temperature can also be used to support normothermia during anesthesia and recovery. Like other species, ruminants should not be placed directly on radiant heat sources to avoid burns and overheating (Valverde and Doherty, 2008).

IX. Analgesia

To ensure animal welfare and a high standard of care, it is imperative for small ruminants to be routinely assessed for pain and distress, regardless of the analgesic regimen selected (Izer et al., 2019). Opioids, α-2 adrenergic receptor agonists, nonsteroidal antiinflammatory drugs (NSAIDs), and local anesthetics, either administered as sole agents, or preferably, in combination, are the analgesics most frequently used in small ruminants and calves. These agents can be administered via IV, IM, epidural, local infiltration, and intraarticular routes (Valverde and Doherty, 2008). As with other species, the use of preemptive and multimodal analgesia is recommended to produce effective, balanced analgesia. The use of several classes of analgesics together prevents pain transmission at multiple levels and decreases the adverse effects of each drug since a lower dose of each agent is required (Lin, 2014). Doses of systemic analgesics are presented in Table 20.5.

TABLE 20.5 Common routes and doses for analgesic drugs and NSAIDs in small ruminants.

Variable	Dose	Route
Morphine	0.1–0.5 mg/kg	IM
	0.5–1 mg/kg	IV
Butorphanol	0.05–0.5 mg/kg	IM, IV, SQ
Buprenorphine	0.005–0.01 mg/kg	SQ
	0.005–0.1 mg/kg	IM, IV
Fentanyl	2.5–5 mcg/kg	IV
	50 mcg/hour	Transdermal
Xylazine	0.05–0.2	IM, IV
Detomidine	0.003–0.01	IM, IV
Medetomidine	0.005–0.01	IM, IV
Lidocaine	2.5 mg/kg	IV
	0.05–0.1 mg/kg/minute	CRI
Ketamine	0.4–1.2 mg/kg/hour	CRI
	0.25–0.5 mg/kg	IM
Trifusion		CRI
Ketamine	0.6 mg/kg/hour	
Butorphanol (or alternatively morphine)	0.022 mg/kg/hour	
	0.025 mg/kg/hour	
Lidocaine	1.2 mg/kg/hour	
Pentafusion		CRI
Ketamine	0.6 mg/kg/hour	
Butorphanol	0.022 mg/kg/hour	
Lidocaine	1.2 mg/kg/hour	
Dexmedetomidine (or alternatively, detomidine)	0.0005 mg/kg/hour	
	0.004 mg/kg/hour	
Acepromazine	0.0022 mg/kg/hour	
Aspirin	50–100 mg/kg	PO
Flunixin meglumine	1–2.2 mg/kg	PO
	1–2.5 mg/kg	SQ
	1 mg/kg	IV
Ketoprofen	2–3 mg/kg	IV, IM
Phenylbutazone	5–10 mg/kg	PO
Carprofen	2–4 mg/kg	PO, SQ, IV

Source. Valverde and Doherty (2008).

A. Regulatory considerations

The use of many anesthetic and analgesic drugs in small ruminants may constitute "extra-label" use. Currently, there are no analgesic drugs approved for the alleviation of pain in livestock in the US (Coetzee, 2013; Smith, 2013; Stock and Coetzee, 2015). Only one anesthetic drug, 2% lidocaine is approved for use in cattle in the United States and one NSAID, flunixin meglumine, is approved for use in livestock for the relief of pyrexia and inflammation, but not pain (Smith, 2013; Smith and Modric, 2013). The Animal Medicinal Drug Use Act of 1994 permits the extra-label use of drugs for the alleviation of pain and suffering if all criteria for the extra-label use of such compounds in food-producing animals are met. Specifically, the animal must be identified and steps taken to assure the animal does not enter the food chain. This regulatory requirement must be considered if there is the potential for return of ruminants used in research into the food supply through practices such as adoption, resale, or rendering.

B. Opioids

Commonly used opioids for pain management in small ruminants are buprenorphine, butorphanol, meperidine, and fentanyl. Morphine, a full μ receptor agonist, should be used with caution due to the potential adverse effects on the GI system, such as decreased GI motility and reduced fecal output (Flecknell et al., 2015). Morphine has also produced behavioral side effects as a result of CNS stimulation and has poor analgesic properties in sheep and goats (Flecknell et al., 2015; Lin et al., 2012). Meperidine is a synthetic opioid that produces mild sedation with an analgesic potency of only 10%−50% that of morphine (Lin, 2014).

Fentanyl, a full μ receptor agonist, has a potency that is 75−100 times that of morphine and can be administered either parenterally or transdermally in small ruminants (Lin et al., 2012). Intravenous administration of fentanyl produces analgesia within 5 minutes and lasts for approximately 20 minutes (Lin et al., 2012). Intravenous administration of fentanyl in nonanesthetized farm animals has been associated with adverse effects including pica, hyperexcitability, ataxia, nystagmus, sedation, bradycardia, and respiratory depression (Carroll et al., 1999; George, 2003). With a half-life of 3 hours following IV administration in sheep, fentanyl is an effective peri-operative analgesia with minimal effects on GI function and rumen motility (Ahern et al., 2010; Flecknell et al., 2015). When placed 12 hours prior to general anesthesia, transdermal fentanyl patches (50 μg/hour) produced stable blood fentanyl concentrations for 40 hours in adult ewes (Ahern et al., 2010). For sheep undergoing orthopedic surgery, a preemptive fentanyl patch should be placed 24−36 hours prior to surgery, and 2 μg/kg/hour is an effective minimum therapeutic dose rate (Christou et al., 2015). Studies have shown high interindividual variability in absorption rates with the use of transdermal fentanyl patches in pregnant sheep models (Heikkinen et al., 2015; Musk et al., 2017a). Sheep displayed significant interanimal variation in plasma fentanyl concentrations after transdermal fentanyl solution dosing as well as adverse effects such as severe sedation, stereotypic pacing and head pressing, and drug-induced urinary retention necessitating naloxone reversal (Jen et al., 2017).

Buprenorphine hydrochloride, a partial μ agonist, has an analgesic potency that is 25 times that of morphine and is an effective analgesic in small ruminants and calves. In comparison to other species, it has a shorter duration of action in ruminants and requires more frequent dosing at 4−6 hours (Ahern et al., 2009; Swindle et al., 2002). Analgesia onset is approximately 45 minutes after IM administration (0.005−0.01 mg/kg) and lasts for 240 minutes (Lin et al., 2012). Reported adverse effects in sheep following buprenorphine administration include rapid and frequent head movements, propulsive walking, chewing, and heightened sensitivity to visual and auditory stimuli (Nolan et al., 1987). Buprenorphine (0.01 mg/kg IM) administered every 6 hours to goats after orthopedic surgery produced satisfactory analgesia (Lin, 2014). Others have reported agitation, rumen stasis, and increased plasma concentrations of cortisol and vasopressin following buprenorphine treatment (0.02 mg/kg IV or IM) in goats (Ingvast-Larsson et al., 2007). Therefore, buprenorphine should be used with caution in this species.

A sustained-release formulation of buprenorphine is now commercially available which has the advantage of minimizing restraint-induced stress associated with repeated injections and decreasing the probability of end-of-dose breakthrough pain (Walkowiak and Graham, 2015). A single dose of sustained-release (SR) buprenorphine (0.27 mg/kg IM or SQ) produced steady plasma concentrations and continuous analgesia assessed via thermal nociception for 72 hours without clinical adverse effects in a pilot study of adult sheep (Walkowiak and Graham, 2015). Another study found a long-lasting potential analgesic plasma level of buprenorphine following a single SQ dose of 0.1 mg/kg of SR buprenorphine in adult sheep starting 2 days after treatment, which lasted for 5 days (Zullian et al., 2016). These results were based on an effective analgesic plasma threshold determined in other species to be 0.1 ng/mL, but the authors acknowledge that a threshold specific to sheep has yet to be determined (Zullian et al., 2016).

Butorphanol is both a κ receptor agonist and a μ receptor antagonist. When dosed at 0.05−0.1 mg/kg IV, IM, or SQ every 4−6 hours, it can relieve mild to moderate pain in small ruminants (Abrahamsen, 2009b). When administered as a sole agent, it can produce light sedation in small ruminants (Lin et al., 2012). Adverse effects, including ataxia and excitement, have been reported with IV administration of butorphanol in sheep and goats (Doherty et al., 2002a; Waterman et al., 1991). Butorphanol combined with a sedative or a tranquilizer can effectively produce standing sedation and analgesia for minor surgery in small ruminants (Lin et al., 2012).

C. Nonsteroidal antiinflammatory drugs

NSAIDs including flunixin meglumine, carprofen, meloxicam, ketoprofen, phenylbutazone, and aspirin have been used in ruminants for the relief of pain (Anderson and Edmondson, 2013; Lin, 2014; Plummer and Schleining, 2013; Swindle et al., 2002; Valverde and Doherty, 2008). Although not labeled for use as an analgesic, flunixin meglumine (1.1−2.2 mg/kg) is often used for pain management in ruminants. Dosing should be limited to a maximum of four doses to minimize the adverse effects of renal toxicity and gastric hemorrhage (Swindle et al., 2002). Carprofen administered to sheep at 0.7 mg/kg and 4 mg/kg IV had therapeutic plasma concentrations of the drug for a duration of at least 72 hours (George, 2003). When compared to phenylbutazone and aspirin, carprofen is more potent and has less potential to induce GI ulceration (Delatour et al., 1996). In addition to reaching therapeutic plasma concentrations, studies have demonstrated the efficacy of NSAIDs in reducing pain-associated behaviors and physiological responses to painful husbandry procedures in sheep and calves (Colditz et al., 2009; Faulkner and Weary, 2000; Paull et al., 2007, 2009).

Meloxicam has provided effective analgesia to calves following castration and dehorning and has reportedly produced significant analgesic effects in pain models of sheep (Colditz et al., 2019; Heinrich et al., 2010; Marini et al., 2015; Theurer et al., 2012; Todd et al., 2010). An initial study of the use of sustained-release meloxicam in sheep following SQ administration demonstrated higher plasma levels of the drug than from the standard formulation throughout the initial 24 hours period (Dunbar et al., 2019). There was variability in plasma levels of sustained-release meloxicam thereafter, and presumed therapeutic levels of 400 ng/mL were not sustained for the full 72 hours across all animals in this preliminary investigation (Dunbar et al., 2019). Additional studies are needed to fully characterize the use of sustained-release meloxicam in sheep.

D. Ketamine

At subanesthetic and anesthetic doses, ketamine inhibits NMDA receptors and stimulates μ receptors to produce strong analgesic effects (Lin, 2014). There is increased acceptance of using low-dose ketamine either to manage acute or chronic pain in humans and animals (Chiz, 2007; Gorlin et al., 2016; Muir, 2010). In humans, subanesthetic doses (0.3 mg/kg or less IV) blunt central pain sensitization with negligible physiologic effects (Gorlin et al., 2016). Perioperative low-dose ketamine enhances analgesia and reduces opioid requirements in the postoperative period following a variety of surgical procedures in humans (Gorlin et al., 2016). Low-dose ketamine has been safely used for short- and long-term pain management in healthy conscious horses via continuous rate infusion at 1.5 mg/kg/hour, with excitability effects noted when plasma concentrations exceeded 0.280 mg/mL (Lankveld et al., 2006). Ketamine (0.6 mg/kg/hour) is useful as an adjunct to other perioperative analgesics to provide pain control and decrease the concentration of inhalant anesthetic required in dogs and cats (Bednarski, 2015). Similarly, ketamine (1.5 mg/kg IV loading dose followed by 50 μg/kg/minute) combined with lidocaine (2.5 mg/kg IV loading dose followed by 100 μg/kg/minute) resulted in a substantial reduction in the concentration of isoflurane required to maintain general anesthesia in goats (Doherty et al., 2007). Subanesthetic infusions of ketamine (20 μg/kg/minute) reduced postoperative pain following rumenotomy in goats; however, the low-dose ketamine infusion did not provide sufficient analgesia intraoperatively in the ketamine-diazepam anesthetized goats (Udegbunam et al., 2019). There is a potential for using low-dose ketamine for analgesia in sheep. Long-lasting analgesic effects have been reported in sheep undergoing orthopedic procedures (Guedes et al., 2006). Ketamine in combination with drugs active at other receptor sites, i.e., α2-adrenergic agonists is recommended for the control of severe pain in sheep (Lizarraga and Chambers, 2012). Ketamine combined with lidocaine and butorphanol (“trifusion”) has been used by the authors to effectively manage postoperative pain following thoracotomy in sheep and calves, as discussed below.

E. Multimodal analgesic continuous rate infusions

Administration of analgesic combinations via continuous infusion allows low doses of analgesics to be used to maintain steady-state plasma concentrations and avoid breakthrough pain associated with peak and trough fluctuations of drug effects that occur with repeated injections (Lin, 2014). A continuous rate infusion of an opioid (butorphanol 0.022 mg/kg/hour or morphine 0.025 mg/kg/hour), lidocaine (1.2 mg/kg/hour), and ketamine (0.6 mg/kg/hour), commonly referred to as “trifusion,” is effective in providing long-lasting analgesia in sheep and goats (Lin, 2014). The solution is prepared by adding 20 mg butorphanol, 1200 mg lidocaine, and 600 mg ketamine to a 1 L bag of 0.9% NaCl for final drug concentrations of 0.02 mg/mL butorphanol, 1.2 mg/mL lidocaine and 0.6 mg/mL ketamine. Before initiating the CRI, a loading dose of butorphanol (0.05−0.1 mg/kg IV or IM) should be administered to small ruminants to immediately increase the plasma concentration of the drug (Lin, 2014). A loading dose of lidocaine (1 mg/kg IV) may be administered slowly to prevent adverse cardiovascular and CNS effects (Lin, 2014); however, in the author's experience, is not necessary prior to initiating the CRI.

Detomidine (0.004 mg/kg/hour) and acepromazine (0.0022 mg/kg/hour) have been added to trifusion, creating a five-drug combination known as "pentafusion" (Abrahamsen, 2009b). The authors use a lower concentration of dexmedetomidine (0.0005 mg/kg/hour), which minimizes behavioral or GI side effects, to successfully alleviate postoperative pain in sheep and calves following thoracotomy and sternotomy. It is the authors' practice to administer dexmedetomidine and acepromazine as individual CRIs separate from the trifusion combination to allow for a gradual decrease and discontinuation of one analgesic at a time as the immediate postoperative period progresses and the need for severe pain management diminishes.

F. Local and regional anesthesia

Local anesthetics such as lidocaine, bupivacaine, and others can be used as sole agents for minor procedures or as supplements to anesthetic or analgesic regimens. Infusion of lidocaine alone or in combination with ketamine during surgery has an anesthetic-sparing effect, improving anesthetic stability (Raske et al., 2010; Vesal et al., 2011). When combined with other analgesics in a constant rate infusion, lidocaine acts in an additive or synergistic effect for the management of severe acute pain in the postoperative period (Abrahamsen, 2009b; Lin and Walz, 2014).

Local anesthetics injected or infiltrated subcutaneously (i.e., ring block) can be effectively used in the awake animal for minor procedures such as laceration repair. Intravenous regional anesthesia achieved by injection of local anesthetics in the vein of a distal limb after compression of the venous drainage, the eponymously named "Bier block", will effectively anesthetize the region of the limb below the point of venous occlusion (Edmondson, 2016; Campoy and Read, 2015). The technique is often used in the field for surgery on the foot, but one of the authors (RW) has used the technique for minor surgery of the distal limb in calves. The technique is well described and illustrated in the cited references.

Local anesthesia of specific nerves and administration of analgesics by the epidural route has long been used in the clinical management of various conditions in ruminants. These can be easily adopted to supplement the anesthesia and analgesia of ruminants in the biomedical research setting. Detailed description of the various techniques is beyond the scope of this chapter, and the reader is referred to any of the comprehensive veterinary anesthesia texts such as *Lumb and Jones Veterinary Anesthesia and Analgesia* (Grimm et al., 2015) and *Farm Animal Anesthesia* (Lin and Walz, 2014).

Delivery of local anesthetics directly to the wound is a common technique for providing additional analgesia postoperatively. Application of local anesthetics to the wound, so-called "splash blocks" are a simple method for providing additional analgesia in the immediate postoperative period. However, the duration of analgesia is short and unpredictable, being determined by the specific local anesthetic used, the rate of diffusion from the wound site, dilution by bodily fluids, etc. Continuous delivery of local anesthetic to the surgical wound through a diffusion ("soaker") catheter is a technique adopted from human medicine and widely used for supplemental analgesia following surgery in companion animals. The authors have routinely used wound catheters to deliver local anesthetics (lidocaine and bupivacaine) to thoracotomy incisions in calves and sheep. Following the closure of the thoracotomy incision, an 18 cm or 22.5 cm diffusion catheter (Mila International, Inc.) is placed along the suture line at the level of the ribs and intercostal muscles and the subcutaneous and skin are closed over the catheter (Fig. 20.3). Bupivacaine is administered every 4−6 hours using a dose extrapolated from the canine dosage (5 mL for lambs and 8 mL for adult sheep and calves). Assay of plasma bupivacaine levels have not detected concentrations associated with toxicity in sheep (unpublished data). Typically, the catheters are kept in place and local anesthetics are administered for 3−5 days postsurgery. Additional analgesia is administered if indicated. It is possible to administer local anesthetics through the diffusion catheter by CRI; however, experience with this administration route in dogs indicates periodic bolus administration provided superior drug concentrations at the wound site (Hansen et al., 2013). Delivery of local anesthetics to the surgical wound combined with systemic analgesics provides effective pain management for ruminants following surgeries involving thoracotomies (Izer et al., 2018, 2019).

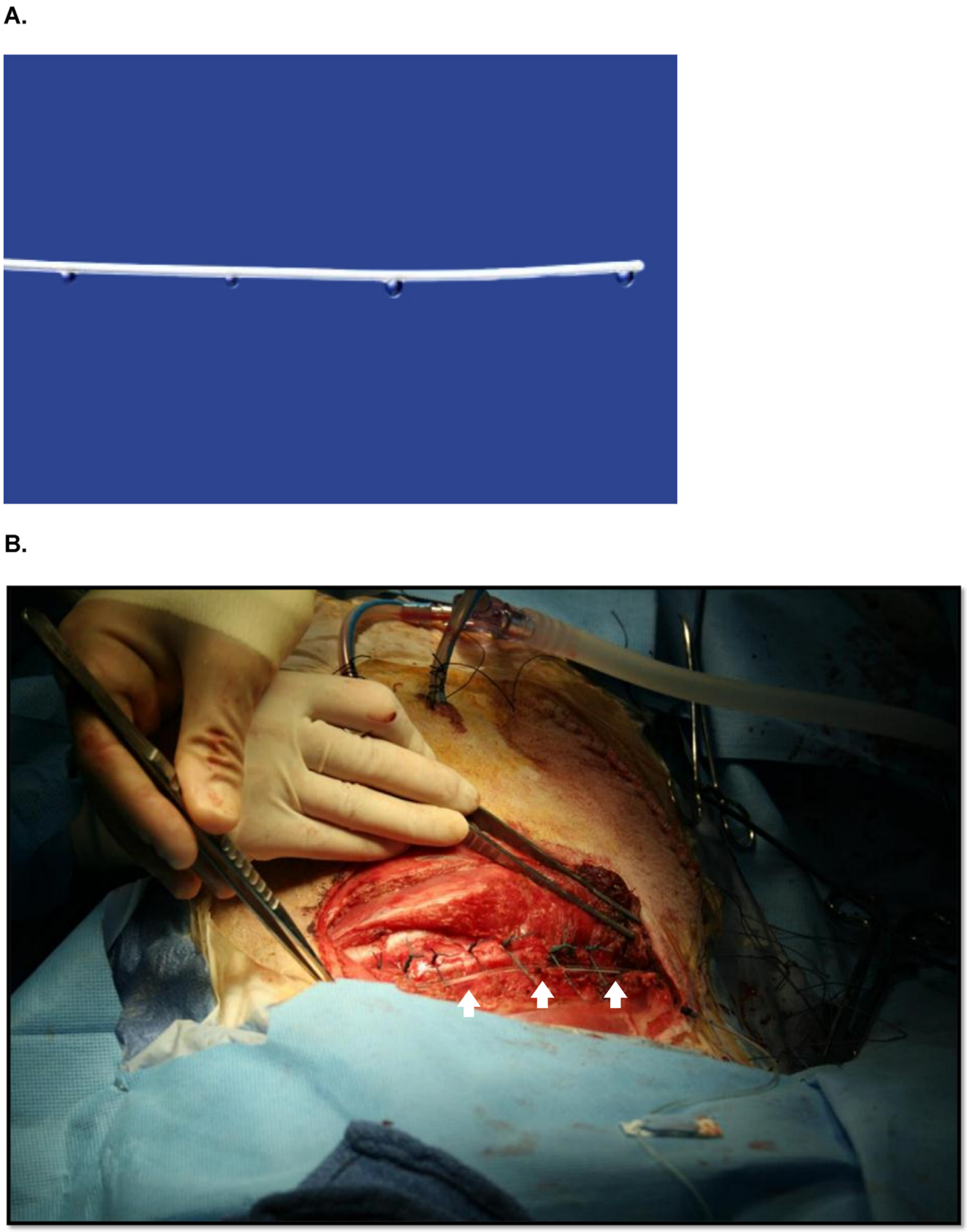

FIGURE 20.3 Placement of diffusion (“soaker”) catheter at thoracotomy incision for delivery of local anesthetic. (A) 22.5 cm diffusion catheter. (B) The catheter (*arrows*) is placed after closure of the chest incision and before closure of the subcutaneous layers and skin. *(A) Photo courtesy of Mila International.*

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