Small ruminant drug use for the cow vet

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Abstract

With the rapid increase in numbers and popularity of small ruminants in North America, there is a need for ambulatory practitioners to provide for their care. With the economics of small ruminant practice not being near those of bovine practice, combined with extremely limited drugs for sheep and goats, there is an opportunity for creative solutions regarding bovine therapies for caprine and ovine patients. In this review the role of the small ruminant as a food animal will be discussed along with extralabel drug usage for food animal species. Analgesic drugs will be discussed for utility in ambulatory practice settings. Use of approved and extralabel antimicrobials will be investigated for control and prevention of infectious disease. Sedation practices will be mentioned, along with additional resources to guide the bovine veterinarian with small ruminant treatment decisions.

Key words: goat, sheep, pain, cephalosporin, extralabel

Introduction

Navigating drug selection for sheep, goats and other small ruminants can be challenging, time consuming, and difficult to tell fact from fiction. With increasing popularity as both production and companion animals, sometimes with "enthusiastic" owners, there is a need for veterinarians to provide services that involve drug therapies to these minor food animal species. An evidence-based and regulatory-compliant approach is necessary as few drugs are labeled for small ruminants in the United States, as "creative solutions" are often necessary when treating sheep and goats in the field. This review will cover the regulatory environment, as well as common pain medications, antimicrobials and sedatives for small ruminant use, focusing on drugs available and commonly used by ambulatory cattle practitioners.

Regulatory considerations

Despite what the client's intentions are, it is important to note that sheep and goats are minor species, they are minor **food animal** species in the U.S. Whether the animal may be in a companion or pet role is irrelevant from a legal perspective when choosing drugs. If a drug is outlined as illegal for food animal use in the U.S., it is illegal to be used in a sheep or goat. There are 2 main ways to be caught with respect to impermissible drug use in a food animal. The primary way is by the presence of a violative residue at slaughter, which is less likely with small ruminants compared to cattle because large amounts of sheep and goats are slaughtered in a private manner in the U.S. The second way that a violation could be discovered is through a complaint or litigation against a practitioner. This is something to be considered when working with pet, companion, or sanctuary food animal species, as while there is a very low likelihood these animals will enter the food chain, the additional intrinsic value of a companion animal to an animal owner could result in a higher likelihood of complaints for perceived issues with veterinary care. Most malpractice coverage does not have to cover the insured for an "illegal act" and public employees may be barred from breaking the law by grounds of their employment.

The use of drugs in food animal species in the United States is regulated by the U.S. Food and Drug Administration (FDA). The FDA's background in this matter has a historical foundation that starts with the Pure Food and Drugs Act (1906), updated by the Federal Food, Drug, and Cosmetic Act (1938), and further clarified by the Animal Medicinal Drug Use Clarification Act (AMDUCA, 1994). These acts provide the framework for insuring a safe food supply as well as clarifications for veterinary drug use.

AMDUCA clarified the prohibited status of several classes of drugs with respect to prohibited and restricted usage in food animals. They are divided into Groups I, II, and III as listed in Table 1.

Table 1: Prohibited and restricted drugs for food animals in the United States.

GROUP I: Drugs with no allowable extra-label uses in any food-producing animal species	GROUP II: Drugs with restricted extra-label uses in food-producing animal species	GROUP III: Drugs with special restrictions for grade "A" dairy operations
Chloramphenicol	Adamantane & neuraminidase Inhibitors	Non-medical grade Dimethylsulfoxide (DMSO)
Clenbuterol	Cephalosporins	Dipyrone
Diethylstilbesterol (DES)	Gentian violet	Colloidal silver
Fluoroquinolone-class antibiotics	Indexed drugs	
Glycopeptides	Phenylbutazone	
Medicated feeds	Sulfonamide-class antibiotics	
Nitroimidazoles		
Nitrofurans		

Extralabel drug decision making

When dealing with limited options of labelled drugs for small ruminant species, extralabel drug usage is a common occurrence practice. AMDUCA can serve to guide practitioners in this decision-making process. The American Veterinary Medical Association (AVMA) hosts an interactive AMDUCA app on the website **(https://zingtree.com/deploy/tree.php?z=embed&tree_id=673679905)** that can guide practitioners step-by-step through the decision-making process. Alternatively, the AMDUCA algorithm can be summarized as a series of 4 questions as follows:

- Question 1: Does a drug labeled for food animals exist which fulfills all of the following: species, indication, in the needed dosage form, and concentration to be clinically effective?
  Yes: Use the labeled drug
  No: Proceed to Question 2
- Question 2: Is there an approved food animal drug that could be used in an extralabel fashion?
  Yes: Use that product
  No: Proceed to Question 3
- Question 3: Is there a non-food animal or human drug for extralabel use?
  Yes: Proceed to Question 4
- Question 4: Is there enough info to determine a withdraw recommendation?
  Yes: Proceed with the use of the drug identified in Question 3
  No: Do not use

When using this algorithm, it is important to have a working knowledge of the prohibited and restricted drugs as listed in Table 1. A common situation that is encountered is the lack of approved medications for the treatment of pain in small ruminants, as such all pain management is currently extralabel.

Pain management

As of the writing of this manuscript, there are currently no medications approved for the treatment of pain in any small ruminant species in the U.S. As such, all analgesic therapy is extralabel, with zero tolerance expected for levels in edible tissues. Commonly used extralabel analgesic drugs for sheep and goats in the United States include NSAIDs, opioids and gabapentin.

The non-steroidal anti-inflammatory drug (NSAID) class of compounds provides analgesia indirectly by decreasing the inflammatory response to tissue injury. Damage to tissue results in the production of inflammatory mediators such as kinins and prostaglandins that activate primary afferent neurons and result in pain. By blocking the cyclooxegenase (COX) pathway, NSAIDs prevent the formation of prostaglandins and other signals.[1] As such, the analgesic potency of the NSAIDs can be increased by preemptive employment before surgery or potentially painful management procedures.

NSAIDs have several benefits when compared to other classes such as opioids and α_2 adrenergic agonists. First, they do not result in sedation of the patient, a side-effect of the other 2 classes of drugs. Second, they provide a longer duration of analgesia and a slower plasma half-life. They are generally considered most effective against pain of low-to-moderate intensity and originating from the somatic or integumentary systems. The general side effects of this class of drugs includes gastrointestinal ulceration and nephropathy (especially in patients that are hypovolemic or dehydrated).[2] While NSAID drugs may be helpful in the management of chronic pain, the clinician should consider these side effects in developing treatment plans and should monitor for complications when long-term therapy is necessary.

In cases where patients present with severe dehydration, fluid therapy to restore perfusion and glomerular filtration rate may be warranted prior to the initiation of NSAID therapy due to its propensity to cause renal insult. Flunixin meglumine and meloxicam are commonly used NSAIDs for sheep and goats. Gabapentin was originally developed as an anticonvulsant, and it has since been appreciated to have effects for central and neuropathic pain. It has been used by itself, as well as an adjunct to NSAID therapy in sheep and goats. One of the adverse effects of the prostaglandin inhibition by the NSAIDs can potentially be abomasal ulceration. Often presenting with vague signs such as dark, tarry stool, or bruxism, clinicians can mitigate this risk by decreasing the NSAID dose to the lowest amount and lowest frequency necessary to gather an effect. If ulcers are suspected, treatment with a proton pump inhibitor, such as pantoprazole or esomeprazole can be considered.[3-5] Pantoprazole by injection 0.5 mg/lb IV; 0.5 to 1 mg/lb SC, q 24 hr, x 3 days, has been demonstrated to reduce abomasal acid secretion in alpacas, and calves.[6,7] The author has unpublished data supporting pantoprazole and esomeprazole use in sheep and goats as well. At the current time it is thought that oral administration of these drugs will not be effective in the mature ruminant.

The opioid class of compounds is a broad group of drugs, all of which have been demonstrated to bind to opioid receptors in the nervous system. These drugs are sub-classified by their action as agonist, agonist-antagonist, or antagonist of one of several opioid receptors that have been identified. Common opioid receptors include mu (μ), delta (δ) and kappa (χ). Mu receptor actions typically result in analgesia and sedation, whereas kappa receptor activation can lead to central analgesia.[8] Like the α_2- adrenergic agonist, stimulation of the opioid receptors results in stimulation of the G-coupled protein pathways and the ultimate hyperpolarization of post-synaptic neurons. These compounds are generally believed to provide potent visceral analgesia. The majority of opioids are considered controlled substances and are regulated by the Drug Enforcement Agency (U.S.). They require special licenses and additional records to possess, order and prescribe and need to be stored in an approved manner (commonly double-locked, with an inventory record).[8,9] As a general class of drugs, the opioids have the potential to induce some degree of sedation, respiratory depression, decreased GI motility and decreased appetite. In some cases, they can induce a hyperexcitable state that will mask their sedative properties.[10] They do have potent analgesic activity, with some degree of variation in potency noticeable between the different specific compounds. Morphine, butorphanol and fentanyl are examples of opioids commonly used in small ruminants. Table 2 lists dosage, route, mechanism, frequency, as well as other considerations for several commonly used analgesic drugs for small ruminants.

Table 2: Commonly used extralabel analgesic drugs for sheep and goats in the United States.

Product	Dose	Route	Mechanism	Frequency	Note/adverse effects
Flunixin meglumine	0.5 to 1 mg/lb (1.1 to 2.2 mg/kg)	IV; SC (goats)	NSAID	q 24 hr, ~3 days maximum	Abomasal ulceration; Hydration status
Meloxicam	0.25 to 0.45 mg/lb (0.5 to 1.0 mg/kg)	PO	NSAID	q 24 hr	Abomasal ulceration
Transdermal flunixin	Not recommended due to low bioavailability in goats				
Gabapentin	2.5 to 7.5 mg/lb (5 to 15 mg/kg)	PO	Neuropathic and central pain	q 8-12 hr	Sedation
Morphine	0.025 to 0.05 mg/lb (0.05 to 0.1 mg/kg)	IV; IM/SC	Opioid: μ agonist	q 4-6 hours	Ileus
Butorphanol	0.05 to 0.1 mg/lb (0.1 to 0.2 mg/kg)	IV; IM/SC	Opioid: μ antagonist to partial agonist; k agonist	q 4-6 hours	Efficacy
Fentanyl	1.1 μg /lb/hr (2.5 μg/kg/hr)	Transdermal patch	Opioid: μ agonist, k antagonist	q 72-96 hr	Adverse effects, diversion
Buprenorphine	0.01 mg/kg	IV	Opioid: Partial μ and k agonist, δ antagonist	q 6 hr	Not as effective at FTP
Tramadol	2.0 mg/kg	PO	Opioid: Weak μ agonist; inhibitor of serotonin reuptake	N/A-Not recommended	N/A-Not recommended

Antimicrobials

The first step in antimicrobial selection for sheep and goats is to consider what antimicrobials are currently approved and labeled for the species by the FDA. Familiarity with the few antimicrobials labelled for sheep and goat use can help prevent inappropriate drug selection. Table 3 lists the approved antimicrobials for sheep with example products, label indications and additional notes. Table 4 lists the approved antimicrobials and for goats with example products, label indications and additional notes.

When considering extralabel drug usage in small ruminants with respect to antimicrobials it is essential to know what drugs are prohibited and/or restricted for food animal use by AMDUCA. Table 5 lists antimicrobials prohibited or banned by AMDUCA. Safety can be argued as a reason to select an extralabel drug and an example of when this could be considered is prescribing tulathromycin instead of tilmicosin if there are safety concerns surrounding the owner or nature of the animal, as a self-injection of tilmicosin by a person can be fatal.

Of particular interest in the 3rd generation cephalosporins (ceftiofur). In 2012 the 3rd Generation Cephalosporin Order of Prohibition went into effect. This law stated that for major food animal species (cattle, pigs, chickens and turkeys) that drugs of this class could be used extralabel, but in a precise fashion.[11] Dose, route, frequency and duration all has to be the same as labeled, with the only difference being indication. Minor species such as sheep and goats were exempt from this prohibition, however, a common misconception is that this is essentially a "blank check" to use ceftiofur in any manner in these species. AMDUCA still applies, as such it would be hard to justify an unlabeled formulation of ceftiofur such as Excede® for a small ruminant when a labelled formulation of ceftiofur exists for both sheep and goats (Naxcel®, Ceftiflex®).

Choosing an extralabel antimicrobial

Before a drug can be administered in an extralabel fashion in the U.S. a valid veterinarian-patient-client relationship must exist. Resources regarding this relationship for small ruminants are available at the American Association of Small Ruminant Practitioners (AASRP) website. According to AMDUCA convenience and cost are not factors for extralabel drug selection. Extralabel use will require some form of evidence prior to administration and this evidence could be an academic paper, textbook, or medical record of a similarly managed case. Culture and susceptibility reports compared to levels and durations reached in the pharmacokinetic literature can be a good starting point. Table 6 lists several common extralabel antibiotics used in small ruminants, as well as the species and indication, with references.

Table 3: Approved antimicrobials for sheep in the United States

Drug (Examples)	Label Indication	Note
Ceftiofur Sodium (Naxcel®, Ceftiflex®)	Respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida*	Zero-day withdrawal if used according to label. Other forms of ceftiofur (Excede®, Excenel RTU EZ®, are not labelled for small ruminants)
Procaine Penicillin G (various formulations)	Bacterial pneumonia caused by *Pasteurella multocida*	Label dosage (3,000 IU/lb) may not be clinically effective
Tilmicosin (Micotil® 300)	Ovine respiratory disease associated with *Mannheimia haemolytica*	Safety concerns when handling
Neomycin (various formulations)	For the treatment and control of colibacillosis (bacterial enteritis) caused by *Escherichia coli* susceptible to neomycin sulfate	Administered orally, by feed (VFD), or in water
Chlortetracycline (various formulations)	As an aid in reducing the incidence of vibrionic abortion caused by *Campylobacter fetus* infection	Type A medicated feed
Decoquinate (Deccox®)	Use for the prevention of coccidiosis caused by *Eimeria ovinoidalis*, *E. crandallis*, *E. parva*, and *E. bakuensis*	Type A medicated feed, not for use in sheep producing milk for human consumption
Lasolacid (various forumulations)	Use for the prevention of coccidiosis caused by *Eimeria ovina*, *E. crandallis*, *E. ovinoidalis* (*E. ninakohlyakimovae*), *E. parva*, and *E. intricata*	Type A medicated feed for use in all classes of sheep
Tetracycline ointment (Terramycin®)	For prophylaxis and local treatment of superficial ocular infections due to oxytetracycline- and polymyxin B-sensitive organisms	Topical formulation, also contains polymyxin B

Table 4: Approved antimicrobials for goats in the United States

Drug (Examples)	Label Indication	Note
Ceftiofur Sodium (Naxcel®, Ceftiflex®)	Respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida*	Zero-day withdrawal if used according to label. Other forms of ceftiofur (Excede®, Excenel RTU EZ®, are not labelled for small ruminants)
Neomycin (various formulations)	For the treatment and control of colibacillosis (bacterial enteritis) caused by *Escherichia coli* susceptible to neomycin sulfate	Administered orally, by feed (VFD), or in water
Monensin (various formulations)	Use for prevention of coccidiosis caused by *Eimeria crandallis*, *Eimeria christenseni*, and *Eimeria ninakohlyakimovae* in adult non-lactating goats	Type A medicated feed
Decoquinate (Deccox®)	Use for the prevention of coccidiosis caused by *Eimeria christensen* and *E. ninakohlyakimovae*, for adult non-lactating goats	Type A medicated feed
Tetracycline ointment	Not currently available	Topical formulation

Table 5: Restricted antimicrobials for food animals in the United States.

GROUP I: Antimicrobials with no allowable extra-label uses in any food-producing animal species	GROUP II: Antimicrobials with restricted extra-label uses in food-producing animal species
Chloramphenicol	3rd Generation Cephalosporins
Medicated feeds	Sulfonamide-class antibiotics
Fluoroquinolone-class antibiotics	
Nitroimidazoles	
Glycopeptides	
Nitrofurans	

Table 6: Several commonly used extralabel antibiotics in small ruminants.

Antimicrobial	Species	Indication	Reference
Tulathromycin (Draxxin®)	Goats	Respiratory disease (2.5 mg/kg subcutaneously, once or repeated in 5 to 7 days)	12; 13
Tulathromycin (Draxxin®)	Sheep	Respiratory disease (2 to 5 mg/kg subcutaneously)	14
Florfenicol (Nuflor®)	Goats	Respiratory disease (20 mg/kg, intramuscularly)	15
Florfenicol (Nuflor®)	Sheep	Respiratory disease (20 mg/kg intramuscularly, or 40 mg/kg subcutaneously)	16
Oxytetracycline (Various formulations)	Goats	Respiratory disease, abortion, listeriosis (20 mg/kg, intramuscularly or subcutaneously)	17; 18
Oxytetracycline (Various formulations)	Sheep	Respiratory disease, abortion, foot rot, listeriosis (20 mg/kg, intramuscularly or subcutaneously)	19; 20; 18

For all of these drugs ample evidence exists for a withdrawal time to be generated by the Food Animal Residue Avoidance Databank (FARAD; **www.farad.org**). It should never be assumed that withdrawal recommendations for cattle are directly applicable to sheep and goats. Species-specific differences in metabolism can vary from large to small ruminants, as well as between small ruminants. Additionally, when a drug is used in a label fashion, the withdrawal time is based upon a tolerance, which is the maximum level of the drug or metabolite considered safe in animal tissues for human consumption. When drugs are used in an extralabel fashion there is no tolerance for residues, so the drug will most likely take longer to reach nondetectable levels. FARAD should be contacted frequently for extralabel withdrawal recommendations instead of "banking" withdrawal times for extended periods because they are frequently conducting research into residue determination that could yield extended withdrawal times.

Sedation

Clinicians should exercise caution with xylazine in sheep, as it has been associated with an increased risk of pulmonary embolism in the species. Acepromazine can be used for general sedation at doses of 0.05 to 0.01 mg/lb (0.01 to 0.02 mg/kg) intravenously, and higher doses can be considered for intramuscular or subcutaneous administration. Care should be taken with higher dosages as it can cause hypotension in some species. Midazolam can be used for short procedure sedation either by itself at 0.1 50 0.25 mg/lb (0.2-0.5 mg/kg) intravenously or intramuscularly, or combined with butorphanol (with 0.05 to 0.1 mg/lb [0.1 to 0.2 mg/kg] of butorphanol added).

The author has had success with sedation for short procedures with what has been described as "goat juice". To make this multimodal sedation cocktail, 1-part butorphanol (10 mg/mL) is combined with 1-part xylazine (100 mg/mL) and 10 parts ketamine (100 mg/mL). This sedation combo is administered at a dose of 0.1 mL per 20 lbs (~10 kgs) intravenously or intramuscularly. Intravenous administration will result in higher levels of sedation quickly, but may need topped off with an additional 25 to 50% dosage. Intramuscular administration will take longer to reach effect, but will last longer. Unlike similar combinations in cattle for standing sedation, small ruminants can to a recumbent position with this combination. If an animal has lingering sedative effects, they can be reversed with yohimbine.

Additional resources

Regardless of the role of the patient, the U.S. FDA recognizes sheep and goats as food animals. While they are minor species, from a legal perspective it does not matter what the animal's role is (companion vs production), a sheep or goat is considered a food animal based on species alone. AASRP recognizes sheep, goats, as well as farmed cervids as food animals and encourages provision of withdrawal times for therapies in these species.[21] As such, a withdrawal time should be provided to the owner and documented in the medical record, regardless of the animal's intention. The author has worked with multiple clients

and sanctuary organizations that would find the suggestion of the consumption of their companion sheep or goat offensive, and has provided a withdrawal recommendation in this format:

"While we recognize that <name> is a companion animal, we are legally obligated to provide you a withdrawal time of <XX> days."

This format can diffuse client emotion of the suggestion of the consumption of their animal, as well as to legally document that a withdrawal time was advised.

The AASRP has multiple resources available on its website **(www.aasrp.org)** to guide veterinarians on the small ruminant's status as a food animal in the United States, antimicrobial stewardship, clarifying a veterinarian-client-patient relationship, in addition to other materials. FARAD **(www.farad.org)** is also rapidly developing more and more resources to guide clinicians with extralabel drug selection.

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