The ABC’S OF ANTHELMINTIC USE IN SMALL RUMINANTS AND CAMELIDS

Lisa H. Williamson, DVM, MS, DACVIM
University of Georgia College of Veterinary Medicine
Athens, Georgia 30602, USA

Introduction
This presentation will review sensible anthelmintic use in small ruminants and camelids. Excellent dosing charts for goats, sheep and camelids can be downloaded free of charge at the website www.wormx.info.

Anthelmintics
The three classes of anthelmintics commonly used in small ruminants and camelids are (1) the benzimidazole class, (2) the imidazothiazole/tetrahydropyrimidine (membrane depolarizing) class, and (3) the macrocyclic lactone class. A new anthelmintic class, referred to as the amino-acetonitrile derivatives, is not yet labeled for use in the United States. Small ruminant veterinarians and producers must comply with Food and Drug Regulations withdrawal times for meat and milk. From a legal standpoint, a veterinarian-client-patient relationship needs to exist when using anthelmintics in an extra-label manner, which is often necessary, because so few drugs are labeled for small ruminant use. The Food Animal Residue Avoidance Databank can be accessed at www.farad.org. Questions regarding extra-label use are directed to usfarad@gmail.com. The site is updated regularly, so the withdrawal times listed in this document reflect information available at the time it was prepared. It is important to use the correct dose of anthelmintic, as under-dosing contributes to development of anthelmintic resistance. Iowa State University’s PHAST laboratory will test milk for drug residues; they can be contacted at (https://vetmed.iastate.edu/vdl/laboratories/phast).

Benzimidazole Class
Members of this class include albendazole (Valbazen®), fenbendazole (Panacur®, Safe-Guard®), oxibendazole (Anthelcide®) and oxfendazole (Synanthic®). These anthelmintics are often referred to as the “white dewormers” because of their appearance. Benzimidazoles kill nematodes by disrupting cellular energy metabolism. This class of anthelmintics generally has a wide margin of safety. The efficacy of a benzimidazole can be improved by fasting the animal 12 hours prior to treatment. Fasting slows gastrointestinal transit time, thereby allowing more contact time with the medication. Also, delivery of medication close to the pharynx (over the tongue) promotes better contact with the gastrointestinal tract. Syringes with adapters that facilitate delivery of an anthelmintic in the back of the oral cavity should be used when dosing small ruminants. Delivery deep into the oral cavity does avoid closure of the esophageal groove, so the medication enters the rumen rather than the abomasum, facilitating longer contact time of the drug with the gastrointestinal tract. To avoid
flooding the pharynx, medication should be delivered slowly and steadily so the animal has time to swallow during administration.

The efficacy of benzimidazoles in enhanced by repeating the treatment in 12-24 hours because contact time with the drug is increased. Animals can be fed between the first and the subsequent doses of the benzimidazole treatment. Fenbendazole is not as potent as albendazole, but it has a higher margin of safety. For this reason, it is the best benzimidazole to use for multiple day dosing protocols. The multiple day treatment strategy is often used to manage tapeworms and susceptible Nematodirus sp. However, the resistance level to the benzimidazoles is so high in *Haemonchus contortus* and *Trichostrongylus colubriformis* in the southeastern United States that multiple day dosing is now of very limited benefit to manage these particular nematodes in sheep, goats, and camels.²,³

Fenbendazole is labeled for sheep at 5 mg/kg orally; meat withdrawal time is 6 days and milk withdrawal is not reported. Fenbendazole is used extra-label in goats at 10 mg/kg orally, and has a 16-day meat withdrawal and 4-day milk withdrawal time. Add an extra day of withdrawal time for each additional day of treatment. Albendazole is the most potent member of the benzimidazole class. It should not be used in the first 30 days of pregnancy because it is teratogenic.² Albendazole is approved for sheep at 7.5 mg/kg orally, with a 7-day meat withdrawal time and no milk withdrawal. If used at a higher dose, use a 7-day milk withdrawal. Extra-label use of albendazole in goats at 20 mg/kg orally calls for a 9-day meat withdrawal and 7-day milk withdrawal time (FARAD). In camelids, a 20 mg/kg oral dose is recommended for fenbendazole and albendazole. Consecutive day dosing of albendazole (>20 mg/kg) can cause fatality in camelids (particularly crias), so use fenbendazole in situations when multiple-day dosing is necessary.⁴

**Imidazothiazole/tetrahydropyrimidine Class**

Members of this class include levamisole (Tramisol®, Prohibit®), morantel tartrate (Rumatel®), and pyrantel pamoate (Strongid®). Levamisole is an imidazothiazole drug that kills nematodes by depolarizing nicotinic neuromuscular junctions. It also acts as a cholinergic agonist in mammals, which is the reason for its narrow therapeutic index. To avoid toxicity, animals should be dosed according to weight. Further, the levamisole powder needs to be dosed according to the dilution method used. The package label lists several different dilutions, which can lead to confusion and dosing error. The oral route is associated with less toxicity than the injectable route. The dose should be delivered deep into the oral cavity, but there is no benefit to fasting animals prior to administration of levamisole. Signs of toxicity can occur within an hour of receiving a 2X (or greater) dose of levamisole.⁵ Symptoms include hyper-excitability, salivation, trembling, ataxia, urination, defecation, collapse and death. Atropine sulfate (0.6 mg/kg SQ) can alleviate side effects if given promptly.

Approximately half of the *Haemonchus contortus* isolates from sheep and goats and approximately 3.4 of the isolates from camelids are sensitive to levamisole³. This finding
could be related to less frequent use as safer products came on the market. Levamisole is labeled for use in sheep at 8 mg/kg orally; it has a 3-day meat withdrawal and zero day milk withdrawal. Levamisole is used extra-label in goats at 12 mg/kg orally; FARAD recommends a 4-day meat withdrawal and a 3-day milk withdrawal. The 8 mg/kg oral dose is effective in camelids.

Morantel tartrate and pyrantel pamoate are tetrahydropyrimidine drugs that also act as cholinergic agonists, but they are less potent than levamisole. On the positive side, they have a wider margin of safety. Pfizer, Inc. indicates that goats can receive Rumatel®88 (morantel tartrate) at 10 times the recommended dose for 3 consecutive days without suffering any ill effects. Morantel tartrate is more effective in ruminants than pyrantel pamoate. Morantel tartrate is recommended in goats at a dose of 10 mg/kg, orally, with a 30-day meat withdrawal and a zero day milk withdrawal. Morantel tartrate is not highly effective against Haemonchus contortus, even isolates that test sensitive to levamisole, however (Williamson, unpublished data). It should not be used as a “stand alone” treatment in a heavily infected animal, but could be used in combination with other drug classes to boost overall treatment efficacy.

**Macrocyclic Lactone Class**

The macrocyclic lactone (ML) chemical class consists of the avermectins and milbemycins. Avermectins include ivermectin (Ivomec®), eprinomectin (Eprinex®), and doramectin (Dectomax®). The anti-parasitic effect is mediated through selective binding to glutamate-gated chloride ion channels. Despite the fact they are lipid soluble, the macrocyclic lactones do not readily cross the blood brain barrier in mammals. As a result, they generally have a wide margin of safety. Ivermectin is labeled for sheep at 0.2 mg orally with a meat withdrawal of 11 days and 21-day milk withdrawal (US FARAD, 2013). Ivermectin is used extra-label in goats at a dose of 0.4 mg/kg orally; FARAD recommends a meat withdrawal time of 14 days and a milk withdrawal of 9 days. Efficacy of ivermectin is enhanced by fasting the animals 12 hours prior to treatment, and by dosing deep into the oral cavity.

Moxidectin is a more potent, lipophilic macrocyclic lactone than ivermectin, so it will kill ivermectin resistant nematodes for a while. However, side resistance can develop in ivermectin-resistant intestinal nematodes within 1-2 grazing seasons with nonselective use. Many Haemonchus contortus isolates from small ruminants are already ivermectin-resistant, and moxidectin resistance is on the rise. Food animal moxidectin products include Cydectin® Oral Drench for Sheep (1 mg/ml), Cydectin® Pour-On for Cattle (5 mg/ml), and Cydectin® Injectable for Cattle (10 mg/ml). Moxidectin is labeled for sheep at 0.2 mg/kg orally; meat withdrawal time is 14 days. Although a milk withdrawal time for dairy sheep is not listed, when contacted regarding this issue, FARAD indicated that when using Cydectin® Oral Drench for Sheep at label dose, the milk withdrawal recommendation for dairy goats can also be used in dairy sheep (June 2013). Milk testing for moxidectin levels is available at Iowa State University (http://vetmed.iastate.edu/diagnostic-lab/cycads). Goats require a moxidectin

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dose of 0.4 mg/kg orally (2X the sheep and cattle dose). This extra-label use of moxidectin requires a meat withdrawal time of 17 days, and a milk withdrawal time of 14 days (FARAD website, June 2013). Recent research indicates that oral moxidectin dosing (0.4 mg/kg) is efficacious in cameldids (Williamson, unpublished data). Further, oral moxidectin treatment is more efficacious than subcutaneous treatments to reduce *Haemonchus contortus* burdens.

Regardless of species, ivermectin and moxidectin should be administered orally rather than by any other route for gastrointestinal nematode control. When oral and injectable routes were studied in lambs, oral administration of ivermectin resulted in higher concentrations of ivermectin within the *H. contortus* abomasal populations.7 Pour-on products formulated for cattle are not recommended for small ruminant gastrointestinal nematode control, topically or orally.2 A few years ago, the American Consortium For Small Ruminant Parasite Control members recommended using subcutaneous moxidectin in goats, but this recommendation has now been withdrawn for reasons stated above. Further, FARAD issued a very long meat (132 days) withdrawal for subcutaneous moxidectin use in goats.

**Long-Acting Anthelmintics**

A long-acting injectable eprinomectin called LongRange® was recently introduced by Merial for use in cattle. The dosage cannot be readily extrapolated from cattle to small ruminants. For instance, a study conducted using LongRange® in alpacas showed that 5 times the cattle dose was necessary to achieve therapeutic concentrations for 120 days.8 Local reactions were common at injections sites, but were self limiting. The researchers concluded that LongRange® has potential for use as a meningeal worm preventative in alpacas, but there was no difference in fecal egg counts or in skin mites between controls and treated alpacas.8 Further, parasitologists do not recommend long-acting products for worm control, as they have been shown to significantly reduce refugia and accelerate anthelmintic resistance.9

**Simultaneous use of anthelmintics from 2-3 different classes**

Use of a combination of anthelmintics *at the same time* is now highly recommended. Treatment of animals with 2-3 anthelmintics from different classes is advantageous when low-level resistance exists to the various drugs (now commonplace), because the additive effect enhances the overall killing effect on worms.10,11 This strategy not only delays progression of resistance, there is new evidence that this approach actually can help reduce the level of resistance to the drugs used in the combination.10 The benefits are achieved through the “efficacy dilution principal”: the more effective the treatment, the less refugia needed to dilute the negative impact caused by resistant worms that survived treatment.12 For example, if the efficacy of treatment is 99.9%, then leaving 1% of the animals untreated is enough to produce an approximately 10 fold dilution of resistant eggs with drug-susceptible eggs (from untreated animals) on pasture. If the efficacy of treatment is reduced slightly to 95%, then at least 34% of the animals need to be left untreated to achieve the same degree of dilution.10 Another benefit of using a combination of anthelmintics is that it also improves the spectrum of activity. For
example, use of a white dewormer such as fenbendazole (in combination with moxidectin and/or levamisole) might add only marginal benefit to *Haemonchus* control, but would provide also treat tapeworms, whipworms, and possibly Nematodirus. The dose of each medication used in the anthelmintic combination should not be reduced. The medications should be administered sequentially, and should not be pre-mixed in the same syringe. Meat and milk withdrawal times are based on the medication used in the combination with the longest withdrawal time.

In contrast, using a different anthelmintic class in a rotational schedule is NOT recommended, as it does not slow resistance. Further, treatment is less likely to be effective than when combination therapy is used, and it is likely that some of the single treatments will be ineffective anyway.

**Selective Anthelmintic Use**

Treat *only* the animals that need it based on low body condition scores, high FAMACHA scores, fecal egg count testing, and prevailing circumstances (time of year, use and age of the animal, and condition of the rest of the herd or flock). The majority of the animals in most herds and flocks have low parasite burdens, and they will not gain much benefit from anthelmintic treatment. As a result, it makes sense to treat part of the herd or flock (targeted selective treatment) and leave the animals with minimal-to-no morbidity untreated to provide refugia. *The greater the unselected portion of parasites in the animals and environment (refugia), the slower anthelmintic resistance develops.* This concept is no longer just theory; painstaking studies have proven it is a real phenomenon.\(^\text{13}\)

One practice that should be avoided at all cost is treating all (or most) of the animals with anthelmintics, followed by moving the animals to a “safe” pasture that has very little parasite refugia on it.\(^\text{9}\) We used to recommend this “treat and move” strategy, but field studies have clearly demonstrated that this practice dramatically accelerates anthelmintic resistance.

Regular observation of physical parameters such as changes in body weight, body condition score, fecal consistency, condition of the wool or hair coat, and pallor of the conjunctiva are useful indicators of overall health, so the benefit of these observations extends well beyond worm control. Ocular membrane color is the basis of the FAMACHA\(^\circledR\) system. Sheep, goats, and camelids with paler ocular membranes in the face of moderate to high exposure to *Haemonchus contortus* in grazing systems are often carrying the heavy worm burdens internally.\(^\text{14,15,16}\) Anthelmintic treatment is targeted at animals showing morbidity attributable to parasitism. Inquiries about FAMACHA\(^\circledR\) cards can be directed to famacha@uga.edu. For more information on use of integrated parasite management, go to [http://www.acsrpc.org](http://www.acsrpc.org).

**References**