

Extending the Efficacy of Anthelmintics

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Anthelmintics, commonly referred to as “dewormers” and “drenches” are compounds used to kill gastrointestinal parasites (worms) without harming the host. Effective anthelmintics are a precious commodity, as decades of nonselective use (whole herd treatment using calendar based intervals) have promoted drug resistance in worm populations. It is important that producers use anthelmintics judiciously with the goal of not only optimizing productivity of their livestock, but also with the goal of preserving efficacy of the anthelmintics.

The first step to using anthelmintics wisely is to know the basics about these drugs. The three classes of anthelmintics commonly used in small ruminants are (1) the benzimidazole class, (2) the imidothiazole/ tetrahydropyrimidine (membrane depolarizing) class, and (3) the macrocyclic lactone class. A new anthelmintic class, referred to as the amino-acetonitrile derivatives, was recently introduced in several other Countries, but is not yet labeled for use in the United States. Small ruminants are food animals, so veterinarians and producers must be mindful of Food and Drug Regulations withdrawal times for meat and milk. A veterinarian-client-patient relationship must exist when using anthelmintics in an extra-label manner, which is often necessary, because so few anthelmintics are labeled for small ruminants. Information concerning label and extra-label use can be accessed through the Food Animal Residue Avoidance Databank at www.farad.org. Questions regarding extra-label use can be 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.

Benzimidazole Class: members of this class include albendazole (Valbazen®), fenbendazole (Panacur®, Safe-Guard®), oxbendazole (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. Medication should be delivered slowly and steadily. Delivery deep into the oral cavity does avoid closure of the esophageal groove, so the medication enters the rumen rather than the abomasum, facilitating greater contact time of the drug in the gastrointestinal tract. A unique feature of the benzimidazole is that the duration of exposure has a marked effect on efficacy.¹ Longer exposure times are associated with greater nematode-killing capacity. As a result, giving a second full dose of a benzimidazole such as fenbendazole 12 hours after the first dose, will increase lethality. A study conducted on goats with benzimidazole resistant *Haemonchus contortus* showed that two consecutive-day doses of fenbendazole reduced the fecal egg count (FEC) by 92%, whereas a single dose had only achieved a 50% fecal egg count reduction.² The goats and sheep can be fed between the first and second dose of benzimidazole. The benefit of multi-day dosing on nematode populations with emerging benzimidazole resistance is expected to be short-lived, because resistance will progress to total failure of benzimidazoles with repeated exposures. Currently, high level benzimidazole

resistance is prevalent in *Haemonchus contortus* and *Trichostrongylus colubriformis* isolated from sheep and goats in the southeastern United States.³ Veterinarians should **not** rely on the benzimidazoles for control of these worms unless prior susceptibility testing indicates that this class is efficacious.

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. 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. Albendazole is approved for sheep at 7.5 mg/kg orally, with a 7-day meat withdrawal time and no 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).

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. Therefore, animals need to be weighed and dosed carefully. The oral route is safer 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. Toxicity can occur with a $\geq 30\%$ overdose, and symptoms such as hyper-excitability, salivation, trembling, ataxia, urination, defecation, collapse and death can occur within a few hours after treatment. 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 are still sensitive to levamisole³, perhaps as a result of the infrequent use of this anthelmintic 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.

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 are also less toxic and therefore 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 time.

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 have a wide margin of safety in most situations. 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.⁴

Moxidectin is a more potent, lipophilic macrocyclic lactam than ivermectin, so it will kill ivermectin resistant nematodes for a while. However, side resistance will develop in ivermectin-resistant intestinal nematodes within 1-2 grazing seasons with nonselective use.⁵ Many *Haemonchus contortus* isolates from small ruminants are already ivermectin resistant, and moxidectin resistance is on the rise.³ 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. FARAD does not list a milk withdrawal time for dairy sheep. However, when contacted regarding this issue, FARAD gave the following response via email: “in regards to your question of sheep verses goat recommendations, for this drug (moxidectin) and dose, the withdrawal recommendation for goats could be used for dairy sheep as well” (FARAD personal communication, June 2013). Milk testing can be performed to determine if moxidectin levels are in an acceptable range: Iowa State University offers this service (<http://vetmed.iastate.edu/diagnostic-lab/cycads>). When using oral moxidectin in an extra-label fashion in goats, the dose is doubled to 0.4 mg/kg orally. FARAD assigned a meat withdrawal time of 17 days, and recently modified the caprine milk withdrawal time to 14 days (FARAD website, June 2013).

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.⁶ Pour-on products formulated for cattle are **not** recommended for small ruminant gastrointestinal nematode control, topically or orally. A few years ago, the American Consortium For Small Ruminant Parasite Control members recommended using subcutaneous moxidectin in goats, but this recommendation has been withdrawn for several reasons. Oral treatment is more likely to achieve higher concentration of drug in the worms, and FARAD recently issued a very long meat (132 days) withdrawal for subcutaneous moxidectin use in goats.⁶ Efficacy of ivermectin is enhanced by fasting the animals 12 hours prior to treatment, and by dosing deep into the oral cavity. There is no benefit to fasting animals prior to drenching with moxidectin.

Simultaneous use of anthelmintics from 2-3 different classes

Treatment of animals with 2-3 anthelmintics from different classes is advantageous when low-level resistance exists to the various drugs, because the additive effect enhances the killing effect on multi-drug resistant worms.^{7,8,9} This strategy delays progression of resistance 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.¹⁰ 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

The dose of each medication used in the anthelmintic combination should not be decreased. The medications should be administered sequentially, and should not be pre-mixed in the

same syringe. Meat and milk withdrawals should be assigned based on the medication used in the combination that has the longest withdrawal times.

Recommendations

1. Know what worms are in your herd or flock. Test (fecal egg count reduction test or larval developmental assay) every 2 years to determine which anthelmintics are effective.
2. Treat only the animals that need it based on low body condition scores, high FAMACHA scores, and prevailing circumstances (time of year, use and age of the animal, and condition of the rest of the herd or flock).
3. Weigh animals and use a treatment chart to ensure proper dosing. Recently updated dosing charts for sheep and goats are available on the web page (wormx.org).
4. Use oral anthelmintics, and use medications formulated for oral use.⁹
5. Dose deep into the oral cavity.
6. Remember that goats require a double dose for most anthelmintics. Levamisole is the exception to this rule: use a 1.5 times increase over the sheep dose in goats.
7. Withhold feed for 12 hours prior to treatment when using the benzimidazoles and ivermectin.
8. Use a combination of anthelmintics from several different classes when low-level multi-resistant worms are present.
9. DO NOT use long acting preparations as use of these products has been shown to reduce refugia and accelerate anthelmintic resistance.⁹
10. Store medications properly, and do not use them past their expiration date.

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