CHOOSING THE RIGHT DRUG FOR WORM CONTROL

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INTRODUCTION

Effective anthelmintics are currently an endangered commodity, as multi-drug anthelmintic resistance is steadily worsening around the world in all livestock species, particularly in small ruminants.[1,2,3]Anthelmintic resistance is a worldwide phenomenon, and it is rapidly progressing in both severity and prevalence.[1,2,3]Professionals who provide guidance for the appropriate use of anthelminticsin small ruminants need a good understanding of diagnostic tests that determine what types of worms are in present in a producer's animals, methods for determining anthelmintic efficacy, advantages and disadvantages of various anthelmintics, and how to most effectively deliverappropriate treatments at proper doses. Further, specific regulations regarding use of anthelminticsin food producing animals vary among countries, and these guidelines must be taken into consideration to ensure food safety. For example, in the United States, many anthelmintics are used in an extra label fashion in small ruminants, necessitating a valid veterinarian-client-patient relationship.[2]

Small ruminants are hosts to a vast array of trichostrongyle nematodes including *Haemonchus contortus*, *Teladorsagia circumcincta*,*Trichostrongylus colubriformis*, *Cooperia* spp, *Nematodirus* spp, *Oesophagostomum* spp, and *Bunostomum* spp.[4]*Haemonchus contortus* is the most dangerousnematode, as blood feeding by fourth stage larvae and adult worms in the abomasum can lead to severe morbidity and fatal anemia in the host. The loss of anthelmintic efficacy in *H. contortus* populations has, in particular, compromised the ability of producers and veterinarians to manage this wormin herds and flocks with high infection intensity.[1,2]Consequently, determining which drugs are most effective against the target parasite(s) is one of the most important factor when choosing the right treatment. These guidelines are discussed in detail in other presentations. The focus of this presentation will be reviewing the types of anthelmintics used in small ruminants, and appropriate use of the drugs.

ANTHELMINTIC CLASSES

The 3main 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. Recently 2 new classes reached the global marketplace for use in sheep:the amino-acetonitrile derivative (AAD) class, and the spiroindoles.[2]

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 anthelminitics generally has a wide margin of safety. Albendazole is not recommended for use in the first 30 days of pregnancy, however.[2] Efficacy of the benzimidazolescan be improved by fasting the animal 12-24 hours prior to treatment.Fasting slows gastrointestinal transit time, thereby allowing more contact time with the medication. The duration of benzimidazole exposure has a marked effect on efficacy in that a longer exposure time is associated with greater nematode-killing capacity. As a result, giving a second full dose of fenbendazole 12 hours after the first dose will increase it's lethality when resistance is starting to emerge.[5]However, consecutive day dosing will not achieve much benefit when the level of resistance tobenzimidazoles is alreadyhigh. Benzimidazole resistance is currently highly prevalent in *Haemonchuscontortus* and *Trichostrongyluscolubriformis* isolated from sheep and goats in the southern and mid-Atlantic regions of the United States, and elsewhere.[1,2,6,7]

Imidazothiazole/tetrahydropyrimidine Class

Members of this class commonly used in livestock include levamisole (Tramisol®, Prohibit®), and morantel tartrate (Rumatel®, Positive Pellet® Goat Dewormer). Morantel and levamisole are both cholinergic agonists, but levamisole is the more potent drug. Levamisole is available as an injectable and oral product. The injectable form offers no advantage over the oral form when treating worms, and the injectable form is more likely to induce an adverse reaction when overdosed. To avoid toxicity, animals need to be weighed prior to dosing,and animals should not be fasted prior to administration of levamisole. Sheep are drenched at 8 mg/kg orally whereas goats receive a 12 mg/kg oral dose. In goats, an overdose (24 mg/kg oral dose) can result in hyper-excitability within 60 minutes of administration.[8]

Other symptoms of over-dosing include excessive salivation, trembling, ataxia, urination, defecation, collapse and death. Atropine sulfate (0.6 mg/kg SQ) can alleviate side effects if given promptly. Resistance to levamisole is low to moderate in sheep and goats living in the southern and mid-Atlantic areas of the United States.[2,6]Levamisole and moranteldo not persist in tissues, so withdrawal times are short.

Macrocyclic Lactone Class

The macrocyclic lactone (ML) chemical class consists of the avermectins and milbemycins. Avermectins include ivermectin (Ivomec®), eprinomectin (Eprinex®), and doramectin (Dectomax®). Moxidectin, a mibemycin, is chemically very similar to the avermectins. 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). The anti-pararasitic effect of the macrocyclic lactones is mediated through selective binding to glutamate-gated chloride ion channels in the nervous system. 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. Efficacy of ivermectin is enhanced by fasting the animals 12 hours prior to treatment, and by dosing deep into the oral cavity. Sheep are dosed at 0.2 mg/kg orally, but ivermectin is used extra label in goats (0.4 mg/kg orally)in the United States.Moxidectin is a more potent, lipophilic macrocyclic lactone than ivermectin. Moxidectin is labeled for sheep at 0.2 mg/kg orally, but used extra label in goats at 0.4 mg/kg orally in the United States. Fasting prior to use is not recommended. Moxidectin will kill ivermectin resistant nematodes for a short duration of time, but ultimately side resistance will develop in ivermectin-resistant intestinal nematodes within 1-2 grazing seasons with nonselective use.[9]Moxidectin is highly persistent in tissues, and can prevent establishment of ivermectin sensitive *Haemonchuscontortus* for 35 days.[2]Most*Haemonchuscontortus* isolates from small ruminants in the southeastern and mid-Atlantic aspects of the United States are already ivermectin-resistant;moxidectin resistance is moderate, and on the rise.[2,6]

Although injectable products are available, ivermectin and moxidectin should only be administered orally for gastrointestinal nematode control. When oral and injectable routes were studied in lambs, oral administration of ivermectinresulted in higher concentrations of ivermectin within the *H. contortus*abomasal populations.[10]Similarly, when efficacy of an oral, topical and subcutaneous dose of moxidectin was studied, cattle receiving moxidectinorally had a significantly higher reduction in their fecal egg count post-treatment compared to cattle treated topically or subcutaneously.[11] When oral and subcutaneous moxidectinwas administered to camelids naturally infected with moxidectin-sensitive *Haemonchuscontortus*, a significantly higher fecal egg count reduction occurred in orally treated animals (Williamson, unpublished data). Pour-on products formulated for cattle are notrecommended for small ruminant gastrointestinal nematode control, topically or orally.

Amino-Acetonitrile Derivative (AAD) Class

Monepantel, a new amino-acetonitril derivative, was released as Zolvix® (Novartis Animal Health, Inc.) in New Zealand in 2009, and subsequently many other countries, for use in sheep. It is not yet available for use in the United States. It is the first new class of sheep drenches to be released since the 1980's. Monepantel paralyzes worms by binding to a specific receptor found only found in nematodes, so it has a high safety margin. Lending further evidence to the concept that "no drench is immortal", resistant *Teladorsagiacircumcincta* and *Trichostrongyluscolubriformis* populations were identified in goats treated repeatedly with Zolvix® within a few short years of it's release.[12]

Spiroindoles

Derquantel, developed in combination with abamectin, was introduced in 2010 as Startect® (Pfizer Animal Health) as a drench for sheep. Derquantel acts as an acetylcholine antagonist, causing flaccid paralysis and expulsion of parasites. The combination of derquantel and abamectinhas a synergistic effect on parasitic nicotinic acetylcholine receptors.[13]Startect® is unlikely to reach the United States market.[2]

PRINCIPLES OF SUSTAINABLEANTHELMINTIC USE

1. Give the right dose: weigh animals and use a treatment chart to ensure proper dosing. Goats require 2X the sheep does for most anthelmintics, asdrug bioavailability is lower in goats.[2]Levamisole, is used at a 1.5 X the sheep dose in goats.

2. Use ORAL anthelmintics for worm control! Dose deep into the oral cavity using a calibrated dispenser with a nozzle that can reach to the back of the throat. Administer the dose slowly and steadily. Delivery deep into the oral cavity avoids closure of the esophageal groove, so the medication goes into the rumen rather than the abomasum.This step facilitates longer contact time of the drug with the gastrointestinal tract, and improves drug efficacy.[2]

3. Withhold feed for 12-24 hours prior to treatment with benzimidazoles and/or ivermectin. This step is not recommended prior to treatment with moxidectin or levamisole.[2]Rumen volume remains relatively constant, so feed restriction slows the transit rate of ingesta, thereby increasing drug availability.[2]

4. Use a combination of anthelmintics from different classes when low-level resistance is evident.[14,15,16] Treatment with a high-efficacy combination of anthelmintic delays the progression of anthelmintic 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. 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.[14]The dose of each medication used in the combination drench should not be decreased, and medications are administered sequentially. Use meat and milk withdrawals for anthelmintic with longest withdrawal time in the combination.

5. Avoid the use of long acting preparations for worm control, as their use escalatesanthelmintic resistance.[16]Prolonged post-administration activity of these drugs suppresses establishment of susceptible larvae, providing an important reproductive advantage to resistant worms.

6. DO NOT treat all (or even most) of the animals, especially if treated animals are immediately moved to a pasture with very little refugia on it. Field trials have demonstrated that this practice assures that the pasture will be re-populated mainly with anthelmintic resistant worms.[16]

7. Use an anthelmintic /combo until treatment is no longer achieving a sufficient response. Do not randomly "rotate" among anthelmintic classes.[2,16]Evaluate treatment efficacy every 2-3 years by performing a fecal egg count reduction test, or an *in vitro* larval developmental assay.[2,17]

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