

BOVINE ANTHELMINTICS



BASICS

OVERVIEW

- There are three primary classes of anthelmintics available for use in treatment of helminth infections in cattle: (1) benzimidazoles (BZ), (2) imidazothiazoles/tetrahydropyrimidines (I/T, also referred to as membrane depolarizers), and (3) avermectin/milbemycins (AM, also referred to as macrocyclic lactones and macrolide endectocides).
- All three major anthelmintic classes are broad-spectrum nematocides, but effectiveness against other groups of parasites varies widely.
- Clorsulon is a narrow-spectrum flukicide that does not belong to any of the three primary drug classes (benzenesulfonamide).
- Cattle are typically infected with multiple species of helminth parasites that differ in their susceptibilities to different anthelmintic drugs.
- Cattle parasites are increasingly become resistant to anthelmintics, and this resistance is more common in some parasite species and to some drug classes than to others
- Some species of parasites are much more pathogenic than others and therefore are much more important to target in treatment.
- Virtually all cattle benefit from anthelmintic treatment. However the magnitude of benefit is related to the level of infection both individually and on a herd level, the timing of treatment in relation to the parasite transmission dynamics, and the management and forage grazing system.
- Using a combination of anthelmintics concurrently is recommended. This approach will increase species-specific efficacy, increase the spectrum of efficacy across multiple species, and decrease the rate at which resistance develops. Where combination products are not available commercially, each product should be given separately according to label instructions

CATEGORIES OF ANTHELMINTICS

- Nematocides
- Flukicides
- Cestocides
- Some compounds may be in more than one category and some may also have activity against non-helminth parasites.

CLASSES OF ANTHELMINTICS

- Specific anthelmintic agents that are used in cattle are described in *Table 1*.

Benzimidazoles (BZ)

- Benzimidazoles bind to β -tubulin, preventing polymerization of tubulin into microtubules. May involve several effector mechanisms at the cellular level.
- General features:
 - Very broad spectrum – have the broadest spectrum of activity across phyla/classes of parasites of any drug class
 - All products approved for cattle are both nematocides and cestocides (affect *Moniezia* spp.)
 - Some are flukicides (albendazole)
 - All are antiprotozoals (affect *Giardia* spp.)
 - Are ovicidal - worm eggs excreted within a few hours of BZ treatment become nonviable and will not hatch
 - Have larvicidal activity
 - Many BZ kill larval stages of nematodes as well as adults, but often at lower efficacy than for adults
 - Have efficacy against hypobiotic (arrested L₄ stage) larvae, but at lower efficacy than the avermectin/milbemycins
 - Increasing the duration of treatment (e.g., treat for multiple days) will increase efficacy against larval stages (and adults).
- Safety
 - Toxic dose is 10 to 100 times the therapeutic dose
 - Safe to use in debilitated animals
- Administration
 - Administered orally only
 - Feed premix, bolus, drench, paste, mineral/protein block, pellets, intraruminal injection
 - Compatible: can be mixed or administered concurrently with many other drugs, including flukicides, cestocides, insecticides, antibiotics, and vaccines
- Disadvantages:
 - Albendazole is teratogenic in mice; rare reports of teratogenicity in ruminants. The label warning with albendazole is to not use this drug in cows during the first 45 days of gestation.
 - Drug resistance: The development of resistance has rendered BZ useless for many major nematode parasites of small ruminants and horses; however resistance in cattle parasites has not yet become problematic in the USA.
- Metabolism and excretion
 - Rumen reservoir and gut recycling leads to prolonged gut levels of BZ in ruminants (but still for short duration, <24 hours)
 - Non-persistent, rapidly metabolized
 - Excreted in feces and urine
 - Improve efficacy by restricting feed intake for 24 hours before treatment
 - Increases digesta residence time by decreasing digesta transit rate
 - Increases drug availability and contact time of drug and parasite

Membrane Depolarizers

Membrane depolarizers are two chemically unrelated groups of drugs that have very similar mechanisms of action. Cholinergic (nicotinic) agonists act on nematode muscle cells, causing paralysis of worms.

- **Imidazothiazoles (Levamisole)**
- General features:

- Broad-spectrum nematocide but no effect on any other groups of parasites
- Not effective against hypobiotic (arrested) *Ostertagia* larvae in cattle
- Very short acting
- Inexpensive
- May modulate the immune system: potentiate T-cells, and stimulate phagocytosis in monocytes
- Safety:
 - Toxicity appears at 3 to 5 times the therapeutic dose
 - Safe in pregnant animals but low therapeutic index
 - Use with care in debilitated and/or dehydrated animals
 - Overdose resembles organophosphate poisoning
 - May cause transient ataxia, salivation/muzzle foaming, muscle fasciculations
 - May potentiate organophosphate toxicity, especially in Brahman cattle
- Administration:
 - Oral and injectable, topical no longer marketed
- Disadvantages:
 - Not as safe as BZ or AM anthelmintics
 - Spectrum is narrower than for BZ or AM anthelmintics
- Advantages (of Levamisole)
 - Highly effective against avermectin/milbemycin-resistant *Cooperia* spp.
 - No known resistance in cattle parasites in USA
 - Inexpensive
 - Relatively short meat withholding period
- **Tetrahydropyrimidines (Morantel Tartrate)**
- General features
 - Broad-spectrum nematocide
 - Approved for use in lactating animals
 - Not effective against hypobiotic (arrested) larvae in cattle
- Safety
 - Very safe and gentle
 - No contraindications for debility, pregnancy, age, concurrent drugs
- Administration
 - Oral administration only, available only as feed premix
 - Dose = 10 mg/kg, supplied as 88 gm/lb premix; feed 0.1 lb of premix (0.44 g of morantel tartrate) per 100 lb body weight
- Disadvantages (Morantel)
 - Only available as a feed premix; unequal consumption likely leads to some animals ingesting a sub-therapeutic dose
 - Nematocide only - spectrum is narrower than for BZ or AM anthelmintics
- Advantages (Morantel)
 - Effective against avermectin/milbemycin-resistant *Cooperia* spp.
 - No known resistance in cattle parasites in USA
 - Approved for use in dairy cattle; 0 days milk withholding period
 - If fed in milking parlor then consumption can be monitored to ensure full dose is consumed

Avermectins/Milbemycins (Macrocyclic Lactones, Macrolide Endectocides)

- These drugs bind to glutamate-gated chloride channels, causing hyperpolarization of cells. This leads to inhibition of pharyngeal pumping and starvation of parasites, as well as paralysis.
- General features:
 - Derivatives of naturally occurring antibiotic-like compounds secreted by soil-dwelling bacteria of the genus *Streptomyces*. This is presumably a defense against bacteria feeding soil nematodes.
 - Broad spectrum: Effective against most nematodes and arthropod parasites
 - Excellent efficacy (>99%) against both adult and larval stages of virtually all trichostrongyle parasites, including arrested (hypobiotic) larvae ,
 - *Cooperia oncophora* is the dose-limiting parasite species, and efficacy against *Nematodirus* spp. is often less than that for most other worm species,
 - Though all members of the class have excellent broad-spectrum efficacy, avermectins are more potent than milbemycins against arthropod parasites and milbemycins (moxidectin) are more potent than avermectins against nematode parasites
 - Are lipophilic and provide residual activity against reinfection for variable periods of time depending on the drug and the species of parasite. However, once worms start becoming drug-resistant this residual activity is lost before the drug fails against adult stages.
- Administration
 - All have same dosage: 0.2 mg/kg if given SC or PO; 0.5 mg/kg as pour-on; the only exception is long-acting eprinomectin at 1.0 mg/kg
 - Formulations of Macrolide Endectocides: injectable and pour-on; in the USA there are no oral formulations available for cattle, though published research has shown that the oral route is the most efficacious
- Metabolism and excretion
 - Little metabolism of drug; most drug is excreted unchanged in feces
 - Lipophilic; persist in fatty tissue; long half-lives
 - Have persistent activity: kills incoming larvae for several weeks after treatment. Period of residual activity differs for each worm species and also differs depending upon route of administration and drug; see package label of individual products for details
 - Persistent activity claims are based on studies using drug-sensitive strains; residual activity will be reduced and then lost as worms become resistant to the drugs
- Disadvantages:
 - Some concerns of ecotoxicity from killing of arthropods in the feces, though evidence suggests this is not a significant problem
 - Drug resistance – magnitude of this problem in the USA is currently unknown, though evidence suggests the level and spectrum of resistance is worse than is generally recognized. In other major cattle producing countries of the world where studies have been performed, high prevalences of resistance have been reported, particularly in *Cooperia* spp. and *Haemonchus* spp.
 - Drug resistance in *Ostertagia* is reported in the USA and elsewhere, but does not yet seem to be a serious problem at present. If resistance in *Ostertagia* were to increase in prevalence, this would become a serious problem to the cattle industry.

Drug	Class	Spectrum	Dosage (mg/kg)	How supplied	Meat withdrawal	Approved for use In dairy cattle*	Remarks
Clorsulon	Other	F	2.0	Injectable in combination with ivermectin	21 days	No	Used in combination with ivermectin in areas endemic for liver flukes
Ivermectin	AM	D,T,H,E	0.2 0.5	Injectable Pour-on	35 days 48 days	No No	Avermectin
Eprinomectin	AM	D,T,H,E	0.5 1.0	Pour-on Long-acting injectable	None 48 days	Yes No	Avermectin Has residual activity for 100-150 days depending on the species of parasite.
Doramectin	AM	D,T,H,E	0.2 0.5	Injectable pour-on	45 days 45 days	No No	Avermectin
Moxidectin	AM	D,T,H,E	0.2 0.5	Injectable Pour-on	21 days None	No Yes	Milbemycin
Levamisole	I/T	T,D	6 8	Oral (powder, bolus) Injectable	48 hours 7 days	No No	Toxic side effects: salivation, restlessness, and muscle fasciculations
Morantel	I/T	T	10	Feed premix	14 days	Yes	Good option for dairy when fed individually. Group feeding will result in sub-therapeutic consumption in some animals
Fenbendazole	BZ	T,D,C	5	Paste/suspension Mineral, pellets Protein feed block	8 days 13 days 16 days	Yes; no milk withdrawal for paste, suspension, pellets and mineral	10 mg/kg for <i>Trichuris</i> , <i>Moniezia</i> , arrested <i>Ostertagia</i> larvae
Oxfendazole	BZ	T,D,C	4.5	Suspension	7 days	No	
Albendazole	BZ	T,D,C,F	10	Paste/suspension	27 days	No	Don't use within 45 days of conception

Table 1: Anthelmintic agents available for use in cattle

- * Drugs not approved for use in dairy cattle should not be used in female dairy cattle 20 months of age or older
- C = Cestodes (*Moniezia* tapeworm)
- D = *Dictyocaulus viviparus* (lungworm)
- E = Ectoparasites (lice, mange mites, horn flies)
- F = *Fasciola hepatica*
- H = *Hypoderma* spp. (grubs)
- T = Trichostrongylid/Strongylid nematodes
- AM = Avermectin/Milbemycin
- BZ = Benzimidazole
- I/T = imidazothiazole/tetrahydropyrimidine

CONSIDERATIONS FOR TREATMENT AND CONTROL OF GASTROINTESTINAL NEMATODES IN CATTLE

- Parasite control programs must be tailored to individual operations since differences in climate, weather, type of cattle, grazing management, cattle/milk prices, etc., will impact decisions for what constitutes the optimal control program for a specific operation.
- Selection of drugs may be based on many factors, the most important of which are efficacy against the targeted species/stages, type of cattle, time of year, cost, and convenience.
- Drug resistance in nematode parasites of cattle is becoming a serious problem. Current concern is focused on *Cooperia* spp. and *Haemonchus* spp., but resistance in *Ostertagia* is reported. Should resistance in *Ostertagia* increase in prevalence, it would have a major impact on cattle health and productivity. Thus, it is advisable to implement practices that decrease the chances of resistance developing.
- Given the increasing prevalence of drug resistance being reported worldwide, testing of drugs for their effectiveness using the fecal egg count reduction test (FECRT) should be a routine practice on all properties. Drug choices should be based on the results of such testing.
- Proper timing of treatments differs greatly in the northern and southern regions of the United States.
- Drugs with residual activity are most useful when cattle are grazing pastures contaminated with infective nematode larvae.
- Total reliance of anthelmintics of parasite control is not recommended and will not be sustainable into the future, as drug resistance becomes a more serious problem. Anthelmintics must be thought of as part of a comprehensive parasite control program. Sound nutritional and pasture management must be included in the program.
- Appropriate meat withdrawal times must be followed for all anthelmintics administered to food-producing animals.
- Anthelmintics not labeled for use in dairy cattle should not be administered to dairy cattle of breeding age or older.



MISCELLANEOUS

SEE ALSO

- Liver Flukes
- Food Animal Residue Avoidance Databank (FARAD) (www.fiveminutevet.com/ruminant)
- Pharmacokinetics and Pharmacodynamics (www.fiveminutevet.com/ruminant)

ABBREVIATIONS

- BZ = benzimidazoles
- I/T = imidazothiazoles/tetrahydropyrimidines
- AM = avermectin/milbemycins
- FARAD = Food Animal Residue Avoidance Program
- FECRT = fecal egg count reduction test

SUGGESTED READING

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