Newer Anthelmintic and Anti-Protozoan Agents

Dwight G. Bennett, *D.V.M., Ph.D.*
Professor of Veterinary Parasitology and Large Animal Clinics
Department of Large Animal Clinics
School of Veterinary Medicine
Purdue University
West Lafayette, Indiana 47906

This discussion will be limited to a consideration of those compounds having therapeutic or prophylactic value against important gastrointestinal helminths and protozoa, liver flukes and lungworms. Only compounds possessing some obvious advantages will be covered.

Much of this presentation will be a matter of opinion. My opinion is based sometimes upon facts garnered from a review of the literature, sometimes upon personal experience, and occasionally upon more nebulous factors. I shall strive to keep the latter to a minimum.

At the onset, I would like to call your attention to a paper by Dr. N. F. Baker in the November, 1971, issue of *The Bovine Practitioner* on anthelmintics in cattle. That paper contains many useful ideas and much valuable information, and I know it has influenced my thinking.

Evaluation of Drugs Effective Against Helminth Parasites

Before presenting an evaluation of various anthelmintic agents, it is important to pose the question, "How do you evaluate an anthelmintic?" There are several ways. Pre-treatment and post-treatment egg counts have the limitations of failing to distinguish the more pathogenic from the less pathogenic parasites, of often being misleading because of differences in fecundity between species of nematodes, of being markedly reduced by diarrhea which dilutes the feces, and of failing to detect the highly pathogenic larval parasites. Evaluations based upon comparative performance between treated and untreated cattle are attractive because the reason for using an anthelmintic in the first place is to improve performance. However, the results are dependent upon the parasite burden. Trials with cattle heavily parasitized with the more pathogenic parasites will make anthelmintics look much better than trials with cattle lightly parasitized with the less pathogenic parasites. For reasons already mentioned, it may be very difficult to estimate the level of parasitism involved, and impossible to determine the species of the predominant parasites.

The only reliable methods of evaluating anthelmintics are controlled and critical experiments. In controlled experiments anthelmintic efficacy is based upon comparative parasite counts at necropsy between treated and untreated cattle. In critical experiments efficacy is based upon comparisons between numbers of parasites passed in an animal's feces for a period of five to seven days following treatment and numbers remaining in his body at necropsy. All evaluations presented here are based upon controlled or critical experiments.

Important Helminth Parasites

Because different anthelmintics are effective against different parasites, it is useful in evaluating anthelmintics to consider the relative importance of the parasites of cattle. Based upon their pathogenicity and the frequency with which they infect cattle in North America, I have ranked the gastrointestinal nematode parasites in decreasing order of importance as follows: 1. *Ostertagia*; 2. *Trichostrongylus* (small intestinal); 3. *Trichostrongylus* (abomasal); 4. *Cooperia*; 5. *Bunostomum*; 6. *Haemonchus*; 7. *Oesophagostomum*. The relative importance of the parasites will vary from place to place, and many would disagree with my ranking, but I believe it will generally hold considering the continent as a whole. You will notice that some parasites, such as *Nematodirus* and *Trichuris*, were not deemed worthy of consideration in cattle.

In addition to the gastrointestinal nematodes, the lungworm, *Dictyocaulus vivaparus* may be important under some circumstances. The common liver fluke, *Fasciola hepatica* assumes real importance in some areas, notably the Gulf and Pacific coasts.

Some veterinarians and farmers believe the tapeworms, *Moniezia expansa* and *M. benedini* to be important parasites of cattle, but I have never seen the data to convince me. Because they are so large and they and their segments are so readily visible, tapeworms tend to be associated with effects caused by other factors.

The Anthelmintics

Let us move now to a consideration of the anthelmintics currently useful in cattle. We shall evaluate these on the basis of efficacy, ease of administration, cost and safety.

In evaluating efficacy we shall rank an anthelmintic's usefulness against a given parasite as excellent,

meaning that it has consistently removed 90 to 100% in critical or controlled experiments; or good, meaning that it has consistently removed at least 80%. If an anthelmintic will not remove at least 80% of a given parasite's number from the body, it is not considered useful against that parasite.

We shall list the methods of administration available for each anthelmintic. In general, the more methods available, the more useful the anthelmintic. You, as bovine practitioners, can use your own judgement as to which methods are of most use to you. It seems to me that feed, paste and injectable preparations are most practical under most current circumstances.

Cost will vary from place to place and with the volume purchased; figures given here will be as close as I can come to an average price of each compound charged to a veterinarian in the midwestern United States.

The safety of each compound will be given as excellent, very good, good, fair or poor based upon a comparison of the maximum recommended therapeutic dose with the toxic dose. Excellent means the toxic dose is at least 10 times the therapeutic dose, and very good at least five times.

Phenothiazine. Efficacy: Excellent against *Haemonchus*, Abomasal *Trichostrongylus* and *Oesophagostomum*. In cattle efficacy against no other helminths has been consistent. Administration: Drench, Bolus. Cost: 4 cents/100 lbs. body weight. Safety: Fair to Poor.

One might question even considering phenothiozine's usefulness anymore as an anthelmintic for cattle. It's only real advantage is its low cost. It is not effective by our criteria against the two most important gastrointestinal helminths of cattle.

Thiabendozole (Thibenzole, Omnizole). Efficacy: Excellent against *Ostertagia*, Abomasal and Small intestinal *Trichostrongylus* and *Haemonchus*. Good against *Cooperia* and *Oesophagostomum*. Administration: Feed, Paste, Drench, Bolus. Cost: 16 to 26 cents/100 lbs. body weight. Safety: Excellent.

This is a truly excellent anthelmintic for cattle. Its major disadvantage is its high cost, particularly when we consider that in most cases the higher dosage rate is indicated.

L-Tetramisole (Tramisol, Ripercol, Levamisole, Levasol). Efficacy: Excellent against *Ostertagia*, small intestinal *Trichostrongylus*, *Cooperia*, *Haemonchus*, *Bunostomum* and *Oesophagostomum*. Good against *Dictyocaulus*. Administration: Injectable, Feed, Drench, Bolus. Cost: 14 cents/100 lbs. body weight. Safety: Very good.

Tetramisole as first marketed in other countries had essentially equal parts of the dextro and levo isomers. It has since been shown that the levo isomer has nearly all the anthelmintic activity and that the dextro isomer contributes only to the toxicity. Removing the dextro isomer, as is done with the product marketed in the United States, makes the compound twice as safe and fully as effective. It is an excellent anthelmintic, and is the only one available with any value against the cattle lungworm. It may not be given to female dairy cattle of breeding age, because residues in milk have not been established.

Haloxon (Loxon). Efficacy: Excellent against Abomasal and small intestinal *Trichostrongylus*, *Cooperia* and *Haemonchus*. Good against *Ostertagia*. Administration: Drench, Paste, Bolus. Cost: 16 cents/100 lbs. body weight. Safety: Very good.

This is an organophosphate. It is reasonably good in anthelmintic spectrum, although it has occasionally fallen beneath the good level against *Ostertagia*.

Coumaphos (Baymix). Efficacy: Excellent against *Cooperia* and *Haemonchus*. Good against *Ostertagia* and abomasol and small intestinal *Trichostrongylus*. Administration: Feed only (6 days). Safety: Fair.

Coumaphos is an organophosphate closely related to Haloxon. It has been used for some time as a systemic insecticide to kill flies breeding in feces at 1.25 to 2.0 mg/kg/day. It was of interest to know whether such doses had any anthelmintic effect. Experiments demonstrated the above efficacy after six days at 2.0 mg/kg. Single doses are entirely too toxic to use. I was unable to find the cost of such treatment.

Cambendazole. Efficacy: Excellent against *Ostertagia*, abomasal and small intestinal *Trichostrongylus*, *Cooperia*, *Haemonchus* and Oesophagostomum. Good against *Dictyocaulus*. Administration: Feed, Drench, Bolus. Cost: Unknown. Safety: Excellent.

This compound is closely related to thiabendazole, and is just about to be placed on the market. I have been unable to find out its cost, but otherwise it appears to be an excellent anthelmintic for cattle.

Obviously there are several highly safe and effective anthelmintics available for cattle. Hopefully with the information given here and elsewhere, it should not be difficult to select an antinematodal drug for nearly any situation in cattle.

The only helminth of major importance in cattle in the United States which will not be removed in a satisfactory manner by any of the compounds already covered is the common liver fluke, *Fasciola hepatica*. This parasite may be very troublesome in the Gulf and Pacific Coast regions of the United States. In recent years several highly effective treatments have been developed. These include rafoxanide, oxyclozanide, clinoxonide and menichlopholan. Unfortunately none of these compounds is available in the United States, because pharmaceutical manufacturers do not feel that they can sell enough of these compounds to recover the cost of development and clearance. The best fasciolicide currently available in the United States is still hexachorethane.

Anticoccidials

Coccidiosis is a self-limiting disease, and for this reason many ineffective remedies have received undue credit for recovery of affected calves. The perti-

nent facts are that no available compound will reverse the life cycle of the coccidia once it has proceeded beyond the first generation of schizogony and that clinical illness does not develop at least until the second generation of schizogony or later in the life cycle. This means that treatment must be instituted before illness develops or, much better, before exposure even occurs if there is to be a chance of stopping the progression of the disease. Oral sulfonamides may help stop secondary bacterial invaders and fluid therapy will help combat dehydration.

Two compounds, Amprolium and Monensin Sodium, are effective in preventing bovine coccidiosis if calves are started on continous low levels prior to exposure.

Anthelmintic Failure

Occasionally there are reports of anthelmintics failing to remove nematodes against which they previously have been shown to be effective. While drug resistance to phenothiazine, thiabendazole and cambendazole has been reported in nematode parasites of sheep, no cases have been reported in cattle helminths. Many cases in which drug resistance is suspected because of high egg counts or numbers of parasites at necropsy following treatment are actually due to the maturation of inhibited larvae. In several species of nematodes larval stages may be inhibited in their development when large numbers of adult parasites are already present. Removal of the adults with an anthelmintic allows the inhibited larvae, which have been waiting safely in the mucosal glands, to develop quickly to adulthood. This is why repetition of treatment is recommended in two weeks in cases of heavy parasitism.

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Toxicology - Pinpointing the Toxic Agent

Roger A. Yeary, *D.V.M.*
Department of Veterinary Physiology and Pharmacology
The Ohio State University
Columbus, Ohio 43210

While fundamental to all diagnostic problems the importance of a thorough history and examination of surrounding environment are essential to clinical toxicology. Comparatively few plants or chemicals produce pathognomonic signs or lesions. It seems to be impudent to speak of the approach to anamnesis to bovine practitioners who practice the art daily. But it is appropriate to emphasize the context in which accidental intoxication may occur. It is important to determine not only what chemicals, including drugs and feed additives, are in use but also to determine what substances are stored on the farm, to inspect the storage areas and to determine the method of disposal of unused chemicals and other trash.

The first discovery of aflatoxins was made in tracing back the events that led to massive deaths of turkey poults in England in 1961. The trail led to mold-contaminated peanut meal and had a significant impact on research and knowledge of mycotoxins. The history should not be limited to recent occurrences for it is possible to have intoxication resulting from events that took place months previously. Such events may include: application of pesticides on both crop and non-crop lands, painting of buildings, fences, bridges, pipeline construction, well drilling and perhaps such events that took place on adjacent property.

Human error in preparing or administering chemical substances may not be known but should not be discounted. A classical example of such an error is illustrated by the following report from the New Zealand Vet. J. 19, (March 1971): because of an error in preparation of sodium selenite solution 376 of 557 Aberdeen Angus calves weighing approximately