

Facts and fiction regarding anthelmintic efficacies in cattle; an updated assessment

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Abstract

Very few label claims for cattle anthelmintic efficacies are factual under all circumstances. This is because: 1) no new class of anthelmintic has been commercialized in the USA since the mid 1980s; 2) worm populations are forced into selection for resistance every time a bovine is treated; 3) some resistant female worms can void >2000 eggs per day; and 4) rarely are anthelmintics given at the farm level wherein sustainable effectiveness is safeguarded. Given the above, it is not shocking that most label claims of effectiveness and persistence for ALL anthelmintics (endectocides, flukicides, and nematocides) are currently overstated. Lack of excellent nematocidal efficacies has been either accepted as normal or overlooked by cattle people, a state of affairs made possible by the fact that bovine nematodiasis is largely a subclinical condition. Lack of anthelmintic efficacy is not connected to suboptimal animal performance. Routinely, there is no “real world” quantification of the detriment caused by post-treatment worm burdens; an observation primarily reserved for research projects. The efficiency of the cattle industry (beef and dairy) and the per-animal productivity in the US have been on a steady rise for decades, due in large part to advances in nutrition, genetics, husbandry, and disease control. Unfortunately, the trend in effective chemical control for parasites over the same period has been in the opposite direction. Advances are sorely needed in both chemical and non-chemical (husbandry, vaccine, biological, nutraceutical, genetic) parasite controls. In this paper, a few observations will be made on anthelmintic efficacies, and the impact of ineffective nematocidal control.

Key words: bovine, parasites, anthelmintics, efficacy

Résumé

Sur les étiquettes des anthelminthiques chez les bovins, peu de mentions concernant l'efficacité sont fondées sur des évidences. Ceci est dû à : 1) aucune nouvelle classe d'anthelminthique n'a été commercialisée aux États-Unis depuis les années 1980, 2) les populations de vers sont soumis à la sélection pour la résistance chaque fois qu'un bovin est traité, 3) quelques femelles résistantes peuvent produire plus de 2000 œufs par jour, 4) il est rare que les anthelminthiques soient utilisés dans une ferme qui favorise le maintien

de l'efficacité. Par conséquent, il n'est pas surprenant que la plupart des mentions d'efficacité et de persistance sur les étiquettes pour tous les anthelminthiques (endectocides, douvicides et nématocides) soient présentement surestimées. Le peu d'efficacité des nématocides est vu comme étant soit normal ou soit négligé par les gens qui travaillent avec les bovins d'autant plus que l'infection des bovins par les nématodes est le plus souvent sous-clinique. Le manque d'efficacité des anthelminthiques n'est pas associé à une performance animale sous-optimale. De façon routinière, il n'y a pas de quantification dans la vraie vie des dommages causés par la charge parasitaire suite au traitement, une observation qui est surtout associée aux projets de recherche. Le rendement de l'industrie du bétail (laitier et de boucherie) et la productivité par animal aux États-Unis sont en hausse constante depuis des décennies en grande partie en raison d'avancées en nutrition, en génétique, en pratique d'élevage et en contrôle des maladies. Toutefois, la tendance pour le contrôle chimique efficace des parasites durant la même période va dans la direction opposée. Il y a un besoin pressant d'avancées dans le contrôle chimique et non-chimique (pratique d'élevage, vaccination, biologique, alimentaire et génétique) des parasites. Dans cet article, quelques observations seront faites sur l'efficacité des anthelminthiques et de l'impact d'un contrôle inadéquat des nématodes.

Introduction

First, an acknowledgement that the authors totally recognize that parasitisms of cattle by lice, horn flies, stable flies, face flies, and liver flukes are extremely important and at times without effective treatment strategies or products. Generally, the above parasitisms are restricted by geography, topography, season of year, and production type. They are isolated, but extremely impactful relative to animal health and economics, and definitely in need of more investigation and innovation (drugs). The current paper unfortunately only addresses nematode infections: a parasitism of all grazing cattle, regardless of season, geography, or topography. For several years now, treatment of cattle in the USA with a single active anthelmintic should not have been termed “treating for worms”, but rather “providing a partial and temporary reduction of worm numbers”. Given how commonly we document reduced anthelmintic efficacies in the USA, it was curious to read the following in a recent paper, “Therefore,

it is surprising, and of some concern, that there appear to be products on the market in New Zealand which don't work to expected levels in a good proportion of tests".¹⁰ For a vast number of reasons (resistance, lack of initial drug efficacy, deficiencies related to formulation and administration), nematocides commonly do not "work to expected levels" in the US. Given that fact, we need to focus on best-case scenarios for nematode control in our cattle.

The Helminths

A listing of the parasitic helminths most commonly found in North American cattle, and a discussion relative to their specific epidemiologies and considerations can be accessed elsewhere²¹ and is not revisited here. However, a few nematodes do warrant being singled out in this paper, as they very much dictate the overall success of any control measures employed for nematode infections. These nematodes are *Nematodirus helvetianus*, *Oesophagostomum radiatum*, *Cooperia oncophora*, *C. punctata*, *Ostertagia ostertagi*, and *Haemonchus placei*.

N. helvetianus is the "thread-necked worm". Its incidence is primarily restricted to animals 2 years of age and younger, and is generally more of a concern in replacement dairy animals as opposed to beef animals. This nematode has the distinction of being the most persistent on pasture due to protection of the larvae by the egg, and has been cited as embarking on a new epidemiologic pattern due to global warming.⁷ *Nematodirus* infections are non-responsive to ivermectin¹⁸ or doramectin,^{17,20} but for the most part effectively removed by eprinomectin,¹⁹ moxidectin,²⁴ and the benzimidazoles.¹⁸

O. radiatum is the nodular worm, a name it gets from the nodules that are formed around the fourth stage larvae during nematode development in the submucosa of the small intestine prior to re-location of the adult worms to the large intestine. This worm is flagged here because we consistently see it in appreciable numbers at necropsy and in coproculture on animals of all ages, regardless of recent treatment with benzimidazole or macrocyclic lactone (unpublished data).

The cooperiads (*C. oncophora* and *punctata*) have never been labeled with a catchy common name. They are found in animals of all ages, but infections that occur at significant magnitudes are restricted to younger animals (< 3 years). These infections can be extremely debilitating with intense inflammatory and immunologic responses at the level of the small intestine.¹ The cooperiads are the nematodes most often cited for resistance to the avermectins, and in 1 instance, this resistance has been associated with increased pathogenicity.¹⁴

O. ostertagi is the brown stomach worm, and is common in great numbers in animals of all ages. *Ostertagia* infections, relative to "treatability", must be considered both from the standpoint of anthelmintic resistance and stage of development/arrestment. Generally, benzimidazoles marginally re-

move adult *Ostertagia*, but do not effectively remove arrested (IEL₄) *Ostertagia* when treatment is at routine levels.²² The macrocyclic lactones were initially highly effective against all stages of *Ostertagia*, but ML-resistant isolates of the brown stomach worm are being detected.⁵ Recently (2016), while searching for a ML-resistant isolate of *O. ostertagi*, we found 3 animals with ML-resistant ostertagiasis at the first stocker operation we went to (unpublished data). Given the ubiquity and pathogenicity of this nematode in cattle in temperate zones, and our unabated reliance on ML treatments, the occurrence of ML resistance in *Ostertagia* populations is particularly concerning.

H. placei is the barber pole worm, so named because of the appearance each fecund female nematode presents with its white ovary twisted around its blood-filled intestine. The small ruminant species of *Haemonchus* (*H. contortus*) is the parasite-scourge of the sheep and goat industries, a level of significance this genus does not hold in the cattle industry. However, it is extremely prevalent and in high numbers in the southern tier of the US, infections that most certainly confer significant detriment to cattle. Unfortunately, *H. placei* infections are becoming common in more northern latitudes (personal observation), a northern migration that is coinciding with global warming,⁷ and species-level acquisition of anthelmintic resistance.

The Anthelmintics

Currently available in the US are the benzimidazoles, the macrocyclic lactones, and an imidazothiazole. The benzimidazoles can be subdivided into 2 subgroups, the nematocide-only chemicals (fenbendazole and oxfendazole) and the nematocide/adulticidal flukicide chemical (albendazole). There is an immense void of information relative to the current efficacies of these products in cattle. Certainly, there is not the extent of resistance to this class of compound in cattle as there is in small ruminants or horses, but the genetic foundation for that resistance is definitely in place in US cattle.⁴ Anthelmintic resistance notwithstanding, the major gap in the benzimidazole spectrum of activity is with arrested *O. ostertagi*, significant populations of which occur during the winter in the northern tier of the US, and during the summer in the southern tier. In a control study conducted nearly a decade ago, oxfendazole was significantly more efficacious than fenbendazole against arrested *Ostertagia*.²²

The macrocyclic lactones available in the US for nematode control are ivermectin (pioneer and generic), doramectin, eprinomectin, and moxidectin. Relative to molecular structure and associated properties, each of these is significantly different from each other. Specific to overall effectiveness against nematodes however, these molecules can be grouped as avermectins (ivermectin, doramectin, and eprinomectin) and milbemycin (moxidectin). Due to lipophilicity and overall bioavailability in the host (persistent presence at the nematode), efflux molecule (multidrug

resistance ATP-binding cassette protein) efficiency by the parasite, attachment site abundance, specificity, and affinity in the parasite, and metabolic degradation by the parasite, moxidectin is rendered more effective than the avermectins, before and after ML resistance has been developed.^{8,11,12,13,15,25}

The 1 imidazothiazole available in the US is levamisole. Once the second-generation benzimidazoles and the MLs became available (early 1980's), use of levamisole was greatly curtailed. Amongst its less than desirable characteristics, levamisole has a relatively small therapeutic index and a very limited spectrum of activity.¹⁶ Fortunately, it was (still?) effective against the cooperiads and *Haemonchus*, 2 of the most prevalent ML-resistant nematodes, and hence can be used today for partially addressing anthelmintic resistance.

In addition to the anthelmintics themselves, there is the factor of formulation when anthelmintic usage is considered. Currently available in the US for cattle are feed (granule and block) and oral (suspension and solution) formulations of benzimidazoles, and injectable (therapeutic and long acting) as well as topical formulations of the MLs. Judging from usage, the topical formulation is the most popular amongst producers. Factors contributing to the overwhelming popularity of topicals include ease of application, minimal animal restraint, minimal facility requirements, minimal applicator expertise, and the additional bonus of activity against lice and horn flies. Unfortunately, there is a considerable downside to the use of a topical. It has been our observation that pouring an animal lends itself to cursory attention afforded to accurate product measure and application. Additionally, wastage via runoff is common. Lack of precise animal treatment with pour-ons is coupled with the inherent lack of optimal and consistent bioavailability of MLs in the animal after administration.⁹

As mentioned above, there are currently available generic and pioneer preparations of ivermectin, as well as therapeutic versus long-acting formulations of MLs (eprinomectin). At our research facilities, the generic ivermectins have never performed as well as the pioneer.²³ Regarding the extended-release formulation of eprinomectin, we have found it to be effective when the populations of ML-resistant nematodes are low (replacement heifers on cow-calf facilities), but very ineffective when used in stocker calves that are characteristically carrying and ingesting nematodes selected over the years for ML-resistance.²⁶ Relative to the stocker calf study, and as indicated by a fecal egg count reduction (FECR) test at its conclusion, both ivermectin and doramectin injectables proved < 80% effective in the majority of the calves, but injectable moxidectin was > 90% effective in the majority of the calves (unpublished data).²⁷

Dealing with Resistance

Anthelmintic resistance is to be expected when dealing with cattle nematodes, with parasitisms at the replacement/stocker level presenting the greatest incidence and abundance of resistant nematodes.²⁴ Relative to chemical inter-

vention, resistance can be addressed with: 1) introduction of chemicals with unique modes of action, 2) increasing the dosage rates of what we are currently using, and 3) combining current anthelmintics so that the individual drug inefficiencies are canceled by the combination. The first possibility has not occurred as of yet in the US, despite the fact that several new molecules have been made available for ruminants in other countries (e.g. abamectin, monepantel, and dequantel). The second solution, increasing the dose rate, might very well be happening on a site-by-site basis, especially with benzimidazoles and generic MLs, but published/sponsored research in this area is lacking. The third scenario of combining drugs of different modes of action is occurring at feed yard and stocker operations with current products, mostly an ML combined with a benzimidazole (personal observation). Hopefully in the near future, there will be progress at the junction of our country's pharmaceutical companies and government regulatory agencies to get a single formulation, combination product proven and cleared.

For an assortment of reasons, the use of anthelmintic combinations as a means of addressing and perhaps delaying anthelmintic resistance in cattle has been conducted (with publication) overseas. In a study conducted with feedlot cattle in Argentina,⁶ fecal egg count reductions (FECR) and weight gains were obtained for control cattle, and those given ivermectin alone, ricobendazole (albendazole sulphoxide) alone, or a combination of ricobendazole with levamisole. All parasitisms were subclinical, but a stepwise increase in animal performance was coincident with the increase in FECR percentage (Figure 1), with control < ivermectin < ricobendazole < levamisole with ricobendazole. Strongyle genera cited as predominate in this study were *Cooperia* and *Haemonchus*.

In another study conducted in Argentina,² cattle with mixed infections were used in a FECR study with control, ivermectin, ricobendazole, and ricobendazole with ivermectin treatment groups (Table 1). Judging from fecal egg count reductions noted at 15 days post-treatment, the combination proved superior to either single-treatment, with FECR

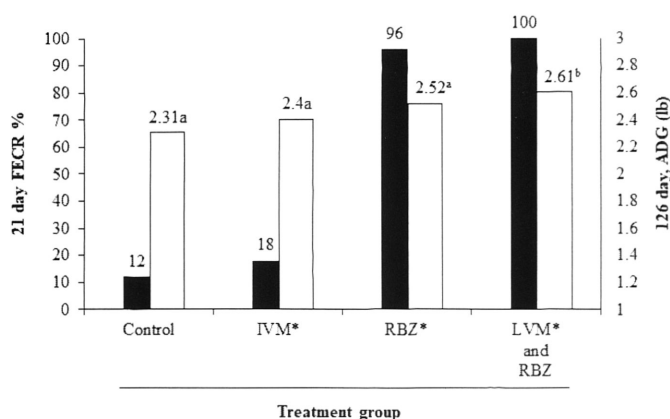


Figure 1. Fecal egg count reductions and corresponding average daily gain for cattle in feedlot in Argentina (Fazio et al, 2014).

Table 1. Strongyle eggs excreted per day, per animal for the first 15 days post-treatment for control animals and those treated with ivermectin (IVM) alone (0.2 mg/kg); ricobendazole (RBZ) alone (3.75 mg/kg) or the combination of ivermectin and ricobendazole (IVM + RBZ) (Canton et al, 2017).

Treatment group	Total	Calculated as:			
		Cooperia	Haemonchus	Ostertagia	Oesophagostomum
Control	2,128,993	1,703,194	340,639	42,580	42,580
IVM	1,061,811	276,070	785,740	0	0
RBZ	134,784	22,913	8,087	103,784	0
RBZ & IVM	41,984	30,228	0	11,756	0

percentages of 50.1 (ivermectin), 93.7 (ricobendazole), and 98.0 (ricobendazole with ivermectin). Additional data made possible from composite coproculture results showed that treatment with ivermectin alone appeared to be effective against *Ostertagia* and *Oesophagostomum* infections, partially effective against *Cooperia*, but seemingly stimulatory in regard to *Haemonchus*; a compensatory response by *Haemonchus* in the face of anthelmintic treatment that has been demonstrated previously.²³ When given alone, ricobendazole appeared effective against *Cooperia* and *Haemonchus*, but fecundities by *Ostertagia* appeared to increase after treatment; an observation the authors cautioned against, given the low and perhaps misleading larval counts for *Ostertagia* across all treatment groups. As stated above, the combination was most efficacious in reducing total fecal egg counts, but provided no improvement over ricobendazole alone in the reduction of *Cooperia* fecundities, or over ivermectin alone in the reduction of *Ostertagia* fecundities. It is apparent from these findings that combining anthelmintics of different modes of action and spectra of activities might not provide for complete nematocidal activity.

Providing more caution regarding the combination of anthelmintics into 1 formulation in an attempt to address resistance, New Zealand researchers conducted a FECR test at 6 farms looking at oral abamectin alone, oral levamisole alone, and the 2 in combination as 1 oral and 2 topical formulations.¹⁰ Oral abamectin alone reduced *Cooperia* and *Ostertagia* egg counts by 69 to 100% and 88 to 100%, respectively. Oral levamisole alone reduced *Cooperia* and *Ostertagia* egg counts by 99 to 100% and 13 to 99%, respectively. A combination oral formulation displayed a synergistic overlap with >97% fecal egg count reductions for both *Cooperia* and *Ostertagia*. Unfortunately, neither topical combination formulation consistently conferred a fecal egg count reduction of ≥ 90% for the 2 nematodes. The authors cited the poor pharmacokinetics of topical anthelmintics in general, as well as their own documentation of a decrease in the bioavailability of abamectin caused by the combination with levamisole in the topical formulations. Given what is known now about the poor and extremely variable bioavailability of anthelmintics delivered by topical formulations in comparison to oral or injectable formulations, and barring any innovation or technology that makes topicals more efficient relative to effective chemical bioavailability, it would

seem prudent that any new formulation, combination or not, would be an oral or an injectable.

Conclusion

At present we have, for the most part, animals that are doing better than ever before,³ but anthelmintics that are performing worse and worse. When anthelmintic resistance is verified, and practices are developed to kill all the worms, and not just the susceptible ones, treated animals correspondingly do better. Therefore, anthelmintic effectiveness should be determined on a farm-by-farm basis; a daunting task, but given the many factors that dictate the development and maintenance of resistance in a nematode population, an essential task. That leads us to the fecal egg count reduction test (FECRT); the only test that can be easily and economically accomplished on a massive scale. Our version of the FECRT “rules” have been published.²⁴ Regardless of the exact rules employed, the test should be conducted with attention to accuracy and quality both at the farm (weigh the animals, measure the product, fecal sample correctly) and in the laboratory. Overly simplified egg-per-gram-of-feces (EPG) trends that can ensue following animal treatment are presented in Figure 2. If the species/strain is highly susceptible to treatment, then the nematodes are killed and EPG levels decline to zero for that strain until animal re-infection. If the strain is a mixture of susceptible and resistant forms (the predominate population in animals today), then the EPG levels decrease

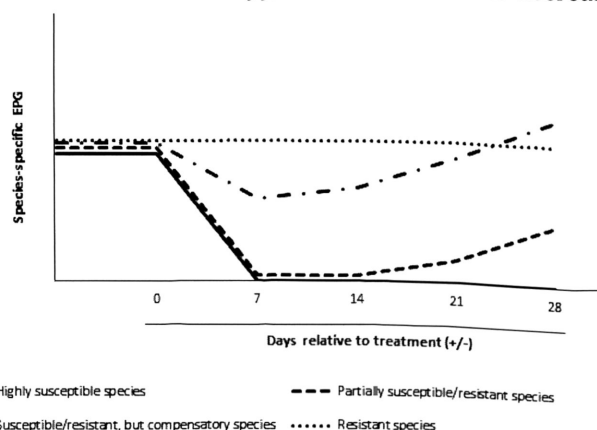


Figure 2. Eggs per gram trends that develop for species/strain-specific nematode burdens at and after therapeutic anthelmintic treatment.

temporarily in accordance with the balance of susceptible vs resistant forms. If the strain is overwhelmingly resistant, (e.g. cooperiads and *Haemonchus* in a great portion of younger cattle from the southern tier in the US), then EPG levels stay straight-lined or slightly, temporarily decline. If the strain shows a compensatory response with increased fecundity by surviving females (e.g. *Haemonchus*), then a decline is followed by elevated EPG levels. In order to find out what you have in your animals and on your farm, you have to do accurate fecal egg counts (pre-and post-treatment) followed by representative coproculture harvests and accurate L3 differentiations, the only way to match effective/ineffective anthelmintics with susceptible/resistant nematode species/strains. Once the species-specific efficacies of anthelmintics are established for a farm, then corrective measures can be put in place (different drug, different formulation, combination of drugs) to insure fewer worms and more pounds of cattle.

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