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Resistance to avermectin/milbemycin anthelmintics in equine cyathostomins – Current situation

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ABSTRACT

Avermectins and milbemycins (AM) are potent compounds against all major nematode parasites, but their continuous usage has led to the development of widespread resistance in many of the important species of ruminant and equine parasites. The exception to this has been the cyathostomins, where AM resistance was recently first reported only after decades of drug exposure. Data from a Brazilian study suggests that AM resistance has developed in cyathostomins and reports of shortened egg reappearance periods after ivermectin treatment have been published recently from USA and Germany. Thus, AM resistance in cyathostomins is an emerging worldwide concern, but there is only limited amount data on the extent of this problem. To limit the development and spread of AM-resistant cyathostomins the equine industry must implement new strategies for worm control, and the veterinary parasitology community must develop and validate improved protocols for detecting anthelmintic resistance in the field.

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1. Introduction

Cyathostomins are the most prevalent parasites affecting horses and can be found in virtually all grazing horses worldwide (Torbert et al., 1986; Silva et al., 1999; Lichtenfels et al., 2001). Early third stage larvae (EL_3) of these parasites undergo encystment as a part of the life cycle, and numbers of encysted larvae often reach more than 200 thousand in clinically healthy horses (Bucknell et al., 1995; Barbosa et al., 2001; Martins et al., 2001; Pook et al., 2002). When the encysted larvae emerge and enter the lumen, inflammatory changes occur in the large intestinal wall. When this occurs in very high numbers, larvae are capable of causing serious illness with signs of weight loss, diarrhea, anaemia, hypoalbuminemia and colic episodes (Love et al., 1999; Peregrine et al., 2006).

Most horse-owners almost everywhere, have easy access to relatively inexpensive commercially available anthelmintics without restrictions, thus there is a major concern regarding over usage and the high selection pressures placed on parasite populations for resistance (Sangster, 1999; Kaplan, 2002; Molento, 2005). With increasing levels of resistance to benzimidazoles and pyrantel being reported worldwide (reviewed by Kaplan, 2002, 2004), equine parasite control now relies heavily on the avermectin/milbemycin (AM; also referred to as macrocyclic lactones) drug class. Over the past couple of decades, parasitologists have recommended changing parasite control regimens from the intensive interval-dose treatment regime into a more sustainable approach, which has a secondary goal of also preserving the effective lifespan of the drugs (Duncan and Love, 1991; Gomez and Georgi, 1991; Lloyd et al., 2000; Kaplan, 2002; Kaplan et al., 2004). Despite this, most equine establishments continue to rely

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on continuous prophylactic usage of anthelmintic compounds at frequent intervals (NAHMS, 1998; Biggin et al., 1999; Pascoe et al., 1999; Lloyd et al., 2000; Earle et al., 2002; Matthee et al., 2002).

The various anthelmintic drugs of the AM class share common structural features, featuring a complex macrocyclic ring structure (Shoop et al., 1995; McKellar and Benchaoui, 1996). Though there are a large number of different AM drugs marketed for various host animals, only ivermectin (IVM) and moxidectin (MOX) are sold for horses in most of the world. Ivermectin is a chemically modified avermectin (AVM) compound with a disaccharide linked to the macrocyclic ring structure. Moxidectin, lacks this sugar group, and is classified as a milbemycin. When administered at the recommended label doses to horses, both drugs have similar absorption profiles, but MOX has a four-fold greater mean plasma residence time, and almost three-fold greater area under concentration–time curve than does IVM (Pérez et al., 1999). Thus the pharmacokinetic profiles of the commercial preparations of these two drugs are significantly different, and these differences may have important implications for the development of resistance (Sangster, 1999).

Both IVM and MOX exhibit similar, but not identical efficacies against a large spectrum of equine parasites; including >99% removal of luminal cyathostomins (reviewed by Monahan and Klei, 2002). One major difference in the efficacy profile between IVM and MOX, is that MOX kills encysted and hypobiotic cyathostomin larvae with moderate to high efficacy, whereas IVM has virtually no effect against these stages (Monahan and Klei, 2002). In a very detailed review evaluating the factors surrounding the potential for the development of AM resistance in cyathostomins, Sangster (1999), concluded that resistance to the AM drug class was inevitable, and predicted emergence of AM resistance in cyathostomins in the near-term. We are now more than ten years later, and rather surprisingly, AM resistance in cyathostomins is still not a widespread problem. However, several recent reports suggest evidence of developing AM resistant cyathostomins in a number of countries, which include the UK (Trawford et al., 2005), Germany (von Samson-Himmelstjerna et al., 2007), USA (Lyons et al., 2008), Italy (Traversa et al., 2007, 2009) and Brazil (Molento et al., 2008).

The aim of this review article is to give a current status and discussion of the evidence regarding the development of resistance in equine cyathostomin nematodes to the AM drug class.

2. Spectrum and efficacy of avermectin and milbemycin

Other authors have reviewed the pharmacology and modes of action of AM drugs (Wolstenholme and Rogers, 2005), and this will not be covered in the present article.

Ivermectin, a synthetic derivative, was the first AVM drug selected for commercial development with excellent potency against a wide spectrum of nematode parasites and with great safety (Fisher and Mrozik, 1989). Egerton et al. (1981) determined that IVM given at a dosage of 0.1 mg/kg would eliminate adult stages of most nematode parasites of the horse with at least 99% efficacy, including the large strongyles *Strongylus vulgaris*, *S. edentatus* and *S. equinus* and the cyathostomin species *Cyathostomum pateratum*, *C. catinatum*, *Cylicocyclus nassatus*, *C. leptostomus*, *Cyliostephanus minutus*, and *C. longibursatus*. Overall, the efficacy of a 0.1 mg/kg dose of IVM was >99% against all species of adult cyathostomins present in the horses tested; however, a dose of 0.5 mg/kg was need to achieve >90% efficacy against *C. goldi*. With regard to other equine parasites, a dosage of 0.1 mg/kg yielded 94–100% efficacy against immature stages of *Oxyuris equi*, *Parascaris equorum*, *Onchocerca cervicalis* and the arthropod parasites *Gasterophilus intestinalis* and *G. nasalis*. Based on the results of this study, it was suggested that a dose of 0.2 mg/kg would prove satisfactory in eliminating nearly all important parasites of the horse.

Moxidectin, a member of the milbemycin group, is produced by the chemical modification of a natural fermentation product from the actinomicete *Streptomyces cyanogriceus* spp. *noncyanogenus* (Carter et al., 1987; Zulalian et al., 1994; Hubert et al., 1995). The antiparasitic activity of MOX has been evaluated in horses in many studies, and results suggest a similar spectrum of efficacy to IVM (Monahan and Klei, 2002).

Both IVM and MOX are efficacious against the majority of adult cyathostomin species in controlled efficacy trials, suggesting that these compounds are equally effective against all luminal cyathostomin stages (Monahan and Klei, 2002). However, against the encysted larval stages, the two drugs demonstrate vast differences in efficacy. In a study comparing the efficacy of IVM and MOX, Xiao et al. (1994) reported that MOX demonstrated greater than 60% efficacy against encysted late third stage and fourth stage larvae, and greater than 99% efficacy against luminal fourth stages. In contrast, IVM demonstrated 99% efficacy against luminal fourth stage larvae, but essentially no efficacy against encysted stages. Other studies have found variable efficacies of MOX against late third stage larvae ranging from less than 50% (Monahan et al., 1996) to about 75% (Bauer et al., 1998), and even approaching 100% (Bairden et al., 2006). However, the early third stage larvae in the mucosa appear to remain unaffected by MOX treatment (Eysker et al., 1997).

The differences between IVM and MOX in their pharmacokinetics, and in their efficacy against the encysted stages likely are responsible for the differences observed for egg reappearance period (ERP). Though farm-related variability and difference in experimental design can affect the ERP reported in any given study, MOX consistently demonstrates a longer ERP, with ranges of 8–14 weeks for IVM and 15–24 weeks for MOX (Taylor and Kenny, 1995; Jacobs et al., 1995; Monahan and Klei, 2002).

3. Detecting AM resistance

Critical and controlled efficacy tests have been used in many research studies but are not applicable in the field because it requires euthanasia of horses. For AM drugs, no in vitro assays have yet been standardized for resistance diagnosis, though progress is being made on this front (Matthews, 2005; Matthews et al., 2012). Thus, the

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