Tutorial Article

A review of the use of moxidectin in horses

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Summary

Moxidectin has broad-spectrum anti-nematodal and anti-arthropodal activities in the horse but is not effective against tapeworms or flukes. Moxidectin and ivermectin have the same efficacy against internal, adult parasites of horses. Moxidectin, however, is highly effective in eliminating encysted and hypobiotic larval stages of cyathostomins, whereas ivermectin is not. Treatment of horses with moxidectin results in an egg-reappearance period (ERP) of 15–24 weeks. Because of its long ERP, moxidectin is labelled to be used at 12 week intervals. Moxidectin may provide protection against infection by ingested cyathostomin larvae for 2–3 weeks after it is administered.

The larvicidal activity of moxidectin has often been compared to that of fenbendazole administered at either 7.5 or 10 mg/kg bwt for 5 consecutive days. The efficacy of fenbendazole, when administered daily for 5 consecutive days at 7.5 or 10 mg/kg bwt, against all stages of cyathostomins is often less than that of moxidectin because resistance of cyathostomins to benzimidazoles is prevalent worldwide, and the 5 day course of fenbendazole does not overcome this resistance. There are now reports of resistance of ascarids to moxidectin. Overt resistance of cyathostomins and a shortened egg re-emergence period after treatment with moxidectin have been reported. Rapid removal of manure by natural fauna can significantly reduce larval nematode concentrations and thereby reduce intervals of anthelmintic treatment. Of the macrocyclic lactones, moxidectin has the least deleterious effect on faecal fauna.

Introduction

Moxidectin is a macrocyclic lactone that was first introduced to the equine market in 1997 (Quest)[1]. Macrocyclic lactones, which are produced naturally from soil-dwelling *Streptomyces* microorganisms, are divided into 2 classes of anti-parasitic drugs, the avermectins and the milbemycins. The first macrocyclic lactone introduced to the equine market was the avermectin, ivermectin, which was introduced in 1981. That drug revolutionised control of endoparasites and ectoparasites in many different species because of its relative safety and efficacy against most economically important parasitic diseases. Since the introduction of ivermectin, other macrocyclic lactones have been introduced, including albamectin, eprinomectin, doramectin, selamectin, moxidectin and milbemycin A3/A4. Ivermectin, albamectin and moxidectin are marketed for use in horses.

Mode of action

Macrocyclic lactones kill parasites by paralysing muscles of their pharynx and body wall by interfering with neurotransmission. They were originally thought to be γ-aminobutyric acid (GABA) receptor agonists that blocked hyperpolarisation of membranes of nematode somatic muscle by opening GABA-gated chloride channels (Holden-Dye and Walker 1990). Because mammalian hosts, which are not affected by macrocyclic lactones, are known to have peripheral GABA receptors on autonomic ganglia and gastrointestinal neurons, this hypothesis was not supportable (Martin *et al.* 2002). The macrocyclic lactones probably act by binding to and opening glutamate-gated chloride channels found only in neurons and myocytes of invertebrates, allowing chloride to influx into these cells to cause neuromuscular paralysis and death (Cully *et al.* 1994).

Efficacy of moxidectin in horses

The macrocyclic lactones have broad-spectrum anti-nematodal and anti-arthropodal activities. They are not effective against tapeworms or flukes because these helminths lack high-affinity binding sites for the macrocyclic lactones (Neal 2002). Labelled indications for moxidectin include control of adult and larval stages of large strongyles, small strongyles or

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cyathostomins, ascarids, stomach bots, adult hair worms (*Trichostrongylus axei*), and large mouth stomach worms (*Habronema muscae*). The omission of a statement of efficacy against some equine parasites on the label claim for moxidectin is most likely because of a decline in prevalence or economic importance of these parasites rather than because of a lack of efficacy (Monahan and Klei 2002). With few exceptions, moxidectin and ivermectin, when administered at the manufacturers' recommended doses, have the same efficacy against internal, adult parasites (Monahan and Klei 2002). There are significant differences, however, in the efficacy of these 2 drugs against the larval stages of cyathostomins. Moxidectin is highly effective in eliminating larval stages of cyathostomins (Bairden *et al.* 2006), whereas ivermectin is ineffective (Xiao *et al.* 1994).

Control of large strongyles

Moxidectin provides good control of the large strongyles, *Strongylus vulgaris*, *S. equinus* and *S. edentatus*, including their larval stages (Monahan *et al.* 1995a). Heavy use of ivermectin since its introduction in 1981 and the management practice of administering anthelmintics at 6–8 week intervals to prevent maturation of the parasite (and therefore pasture contamination with nematode eggs) have largely eliminated large strongyles from equine populations in developed countries (Monahan 2000; Kaplan *et al.* 2004). Elimination of large strongyles has shifted the primary goal of programmes to control equine parasites from control of large strongyles to control of cyathostomins (Monahan 2000; Tarigo-Martinie 2001; Kaplan *et al.* 2004).

Control of cyathostomins

An anthelmintic programme that decreases faecal counts of parasite eggs to <200 eggs/g within the equine population decreases the incidence of colic (Uhlinger 1990). Because the major goal of an equine, anthelmintic programme is to control contamination of pasture with cyathostomin eggs, the efficacy of moxidectin against cyathostomins is of particular interest. Moxidectin is highly efficacious in controlling cyathostomins not only because of its activity against adult, egg-producing cyathostomins, but also because of its activity against encysted and hypobiotic larval stages.

Of the 3 classes of equine anthelmintics, the macrocyclic lactones have the longest egg-reappearance period (ERP). The ERP refers to the period of 0 eggs/g of faeces to a resumption of significant shedding of eggs in the faeces. Although the definition of what is significant shedding of eggs differs among researchers, the ERP for moxidectin is most often reported to range from 15–24 weeks, whereas the ERP for ivermectin is reported to range from 8–14 weeks (Taylor and Kenney 1995; Jacobs *et al.* 1995; Demeulenaere *et al.* 1997). The macrocyclic lactones are lipophilic and are, therefore, excreted in bile and eliminated in faeces (Zulalian *et al.* 1994). Moxidectin's long ERP can probably be accounted for by its larvicidal activity on encysted stages and its prolonged excretion in the faeces, which results from its prolonged plasma bioavailability (Pérez *et al.* 2001). Moxidectin may provide protection against infection by ingested cyathostomin larvae for 2–3 weeks after it is administered (Vercruysse *et al.* 1998). Because of its long ERP moxidectin is labelled to be used at 12 week intervals.

Knowledge of the life-cycle of cyathostomins is important in understanding the controversy concerning the efficacy of moxidectin against the encysted larval stages. Cyathostomin eggs on pasture develop into infective third-stage (L3) larvae that, after being ingested by a horse, become encysted in the mucosa of the large intestine. This population of larvae, which comprises the bulk of encysted larvae, are known as early L3s (i.e. EL3s). They eventually develop into late L3s (i.e. LL3s) and finally into L4s, which emerge into the intestinal lumen where they develop into adults (L5s) and then into egg-laying adults. Administration of an anthelmintic eliminates lumenal stages (L4 and adult) of the cyasthosomes, and stimulates encysted larvae to progress to the more mature L4 stage. This reservoir of EL3s is important in the epidemiology of cyathostomosis because maturation of EL3s to adult worms can result in massive contamination of pasture with parasite eggs. Intestinal disease is associated with mucosal damage caused by emergence of L4 larvae or by the inflammation associated with encysted larval stages (Monahan 2000). Parasite control strategies should be targeted at eliminating the EL3 stage (Bairden *et al.* 2001).

Early studies regarding the efficacy of moxidectin against larval stages of cyathostomins reported efficacies against LL3s and L4s that ranged from 50–87% and insignificant activity against EL3s (Xiao *et al.* 1994; Monahan *et al.* 1995a, 1996). Authors of these reports pointed out, however, that the results of these studies were obtained by examining the alimentary tract of horses only 2 weeks after the horses were treated, and that this time was insufficient to allow elimination of mucosal larvae (Monahan and Klei 2002). Studies at necropsy 5 weeks after treatment also found moxidectin to be ineffective against EL3s (Eysker *et al.* 1997), but death of LL3s and L4s may have prompted EL3s to mature to LL3s and L4s, thereby obscuring evidence of moxidectin's efficacy against the EL3 larvae (Monahan and Klei 2002). More recent studies indicate that moxidectin is highly efficacious in eliminating EL3s as well as other larval stages (Bairden *et al.* 2001, 2006; Reinmeyer 2003). Bairden *et al.* (2001) reported that moxidectin administered to ponies resulted in 100% reduction of adult and lumenal L4s, a 90.8% reduction in EL3s and a 99.9% reduction in other developing stages. They suggested that moxidectin has direct activity against EL3s or that it destroys later stages stimulating EL3s to mature to later, susceptible stages that are killed by residual anthelmintic.

The larvicidal activity of moxidectin has often been compared to that of fenbendazole administered at either 7.5 or 10 mg/kg bwt for 5 consecutive days, but comparisons were often between studies that used different experimental protocols and performed post treatment necropsies at different times using different techniques to count larvae. In one study, fenbendazole, when administered at 10 mg/kg

bwt daily for 5 consecutive days, had good efficacy against cyathostomin larvae; EL3s were reduced by 98% and LL3s and L4s were reduced by 96% (DiPietro *et al.* 1997). In another study, when fenbendazole was administered daily for 5 consecutive days at 7.5 mg/kg bwt, LL3s and LL4s were reduced by 99.4% and EL3s by 91.5% (Duncan *et al.* 1998). In subsequent studies (Chandler *et al.* 2000; Chandler and Love 2002; Lyons and Tolliver 2003), however, the efficacy of fenbendazole, when administered daily for 5 consecutive days at 7.5 or 10 mg/kg bwt, against all stages of cyathostomins was markedly less. Resistance of cyathostomins to benzimidazoles is prevalent worldwide (Tarigo-Martinie *et al.* 2001; Kaplan *et al.* 2004), and results of these studies indicate that a 5 day course of fenbendazole, administered at either 10 or 7.5 mg/kg bwt, does not overcome this resistance.

A recent study that compared the inflammatory consequences of larvicidal treatment of horses with either moxidectin or fenbendazole found that both drugs were efficacious against larval stages of cyathostomins, but mucosal inflammatory responses to dead or dying larvae differed markedly between the 2 groups (Steinbach *et al.* 2006). Larvae killed by moxidectin elicited minimal inflammation, whereas larvae killed by fenbendazole elicited severe inflammation causing damage to the large intestine. The reason for this difference between drugs in eliciting inflammation was not apparent.

Control of ascarids

Both ivermectin and moxidectin are highly efficacious against lumenal and larval stages of *Parascaris equorum* (Daurio and Leaning 1989; DiPietro *et al.* 1989; Monahan *et al.* 1995b). Practitioners should be aware, however, that 5 investigations, 4 from Europe (Boersema *et al.* 2002; Stoneham and Coles 2006; Schougaard and Nielsen 2007; von Samson-Himmelstjerna *et al.* 2007) and one from Canada (Slocombe *et al.* 2007), found macrocyclic lactone-resistant *Parascaris equorum* on horse farms.

Control of *Gastrophilus* spp.

Although moxidectin is efficacious against nematodes at a dose of 0.3 mg/kg bwt (Bello and Laningham 1994; Xaio *et al.* 1994; Monahan *et al.* 1995a) this dose is ineffective in eliminating stomach bot larvae. Moxidectin administered at the labelled dose of 0.4 mg/kg bwt has an efficacy against bot fly larvae greater than 90%, which is more than acceptable for controlling this parasite (Coles *et al.* 1998; Monahan and Klei 2002).

Ectoparasites

Recommendations concerning administration of macrocyclic lactones for treating horses for ectoparasites are based on efficacy reported for other species and on only a few studies performed using horses (Monahan and Klei 2002). The effects of avermectins in controlling ectoparasites are unpredictable, and administration of an avermectin is unlikely to completely eliminate ectoparasites because adequate control of infestations of ectoparasites requires almost 100% efficacy against all stages of the parasite (Vercruysse and Rew 2002). The milbemycins probably have the same poor efficacy against ectoparasites.

For cattle, only the injectable and pour-on formulations of macrocylic lactones seem to be effective against mange mites (Vercruysse and Rew 2002), and when horses with chorioptic mange are treated with oral ivermectin paste at either 0.1 mg/kg bwt daily for 7 days or at 0.2 mg/kg bwt, twice at 2 week intervals, mites are reduced in number but not eliminated (Little *et al.* 1995). Draught horses treated for chorioptic, sarcoptic or psoroptic mange with either ivermectin oral paste or moxidectin oral gel, however, had complete clinical and parasitological cure (Osman *et al.* 2006). In the experience of one of the authors (J.S.) chorioptic mange (clinical signs and recovery of the mite) persisted in a herd of draught horses despite routine anthelmintic treatment with orally administered moxidectin (J. Schumacher, unpublished data 2008).

Vercruysse and Rew (2002), in a review of the efficacy of macrocyclic lactone against cattle ectoparasites, cite studies that show that both single-host and multi-host ticks and lice of cattle are controlled by parenteral treatment with moxidectin. These ectoparasites of horses are also likely to be controlled by administration of moxidectin.

Parasite resistance

Of the 3 commonly used classes of equine anthelmintics, avermectins/milibemycins, benzimidazoles and pyrantel salts, cyathostomins are highly resistant to the the bendzimidazoles and the pyrantel salts (Kaplan 2002). Decreased activity of ivermectin (von Samson-Himmelstjerna *et al.* 2007; Lyons *et al.* 2008; Molento *et al.* 2008) and moxidectin (Trawford *et al.* 2005; Edward and Hoffman 2008) on cyathostomins has recently been reported. In those reports the egg reappearance period was much shorter than the manufacturers' recommended dosing interval and shorter than when these anthelmintics were first marketed. Resistance of cyathostomins to either ivermectin or moxidectin was reported in Brazilian horses (Molento *et al.* 2008). Because ivermectin has little effect on encysted larval stages of cyathostomins, which represent the majority of the cyathostomin gene pool, this pool of immature cyathostomins should be slow to develop resistance to ivermectin (Monahan and Klei 2002). Because moxidectin has a profound effect on immature stages of cyathostomins it should have a greater likelihood of selecting for resistance (Coles 2002; Earle *et al.* 2002). The use use of moxidectin in sheep was shown to be associated with a higher prevalence of resistance of *Ostertagia* spp. to macrocyclic lactones than was the use of ivermectin (Rendall *et al.* 2006). The reason for few reports of resistance of cyathostomins to moxidectin is not clear, but the absence of resistance may be because the prolonged ERP after treatment

with moxidectin reduces the number of anthelmintic treatments thus reducing the exposure of larvae to drug selection (Monahan and Klei 2002). It has been pointed out, however, that resistance of cyathostomins to macrocyclic lactones is unlikely to be noted until it has become flagrant because parasite resistance is seldom investigated (Pritchard 2002). One of the authors (J.S.) has administered moxidectin (at 12 week intervals) as the sole anthelmintic to a herd of 200 horses for 5 years. When the efficacy of moxidectin in this herd was recently investigated, cyathostomin resistance was not found (J. Schumacher, unpublished data 2008).

Some researchers have suggested that use of moxidectin be restricted to young horses (i.e. 1–6 years of age), which are more likely to benefit from the larvicidal activity of moxidectin and which have a shorter ERP, and that older horses be treated with ivermectin (Monahan and Klei 2002). This type of programme would reduce the likelihood of cyathostomins becoming resistant to moxidectin because a large part of the cyathostomin genome in the horse herd would not receive selection pressure. Decreased selection pressure would make the establishment of a gene resistant to moxidectin less likely.

Another suggestion for delaying cyathostomin resistance to moxidectin is to base the interval between anthelmintic treatments on faecal egg counts rather than the manufacturer's recommended dosing interval because, in many cases, faecal egg counts remain low for longer periods (Martin-Downum *et al.* 2001). Expanding the period of time between treatments may reduce selection pressure for resistance (DiPietro *et al.* 1997). Suggestions for when to repeat anthelmintic treatments have been reviewed (Martin-Downum *et al.* 2001). These include: 1) when egg counts rise to 10% of Day 0 concentrations (Borgsteede *et al.* 1993); 2) when 50% of horses have a mean EPG of >200 (Taylor and Kenney 1995); and 3) when the mean egg count of all horses is >100 EPG (Boersema *et al.* 1998). Unfortunately, for large horse herds, quantitative faecal egg count monitoring is unlikely to be adopted for practical and economic reasons (Abbott *et al.* 2004).

There is conflicting evidence as to whether or not resistance to one type of macrocyclic lactone confers resistance to others. This evidence concerns parasites of species other than the horse (Craig *et al.* 1992; Pankavich *et al.* 1992; Conder *et al.* 1993), but a recent report cites a horse that developed resistance of cyathostomins to ivermectin and also had a greatly shortened egg reappearance period when administered moxidectin (Edward and Hoffman 2008). Because no new class of anthelmintic drugs is likely to be marketed in the near future, increasing incidences of resistance of cyathostomins to macrocyclic lactones is a serious threat to the horse industry. Methods for detecting and reversing resistance to macrocyclic lactones, however, are being devised (Wolstenholme *et al.* 2004). There is also a recent report of the discovery of a new class of anthelmintics, known as amino-acetonitrile derivatives, which have potent activity against animal parasites (Kaminsky *et al.* 2008).

Toxicity of moxidectin

Moxidectin has been demonstrated to be safe for most horses, including breeding mares, stallions and even young foals, when administered at up to 3 times the recommended dose of 0.4 mg/kg bwt (Rulli 1996). Since its release, however, numerous, adverse drug reactions associated with administration of moxidectin have been reported (Hampshire *et al.* 2004). Most of these reactions have been associated with over dosage, either by gross over-estimation of weight by owners or from slippage of a faulty syringe locking mechanism, which has since been replaced by an improved lock (Johnson *et al.* 1999; Khan *et al.* 2002; Hampshire *et al.* 2004; Müller *et al.* 2005).

Because moxidectin is very lipophilic (100 times more so than ivermectin; Hayes 1994), it becomes highly concentrated in the serum when it is administered to horses with little body fat, such as foals or debilitated horses. When the concentration of moxidectin in the serum is high, moxidectin is able to cross the blood-brain barrier. The less developed blood-brain barrier of neonates may make them more susceptible to overdoses of moxidectin (Johnson *et al.* 1999; Müller *et al.* 2005). Once it is in the central nervous system, a macrocyclic lactone stimulates the synaptic secretion of the inhibitory neurotransmitter, GABA. By binding at the receptor site, GABA causes influx of chloride ions into neurons, causing the neurons to become hyperpolarised, which in turn, causes diminution in neuronal activity, resulting in sedation of the horse and relaxation of the horse's skeletal muscles (Enna and Gallagher 1983).

In one clinical study, signs displayed by foals with moxidectin toxicity included dyspnoea, depression, ataxia, weakness, coma and seizures (Johnson *et al.* 1999; Khan *et al.* 2002; Hampshire *et al.* 2004; Müller *et al.* 2005). Clinical signs were seen 2–22 h after moxidectin was administered. Most affected foals survived with supportive care that included fluid therapy and administration of drugs to control seizures and to regulate temperature. Administration of sarmazenil (0.04 mg/kg bwt i.v. every 2 h for 6 treatments), a benzodiazepine antagonist that decreases chloride conductance at GABA receptor sites, may have elicited the rapid improvement seen in a foal suffering from moxidectin toxicity (Müller *et al.* 2005).

Effect of moxidectin on faecal fauna

Widespread use of parasiticides to control internal and external parasites has raised concerns that their residues adversely affect pasture ecology (Herd 1995; Lumaret and Errouissi 2002; Floate *et al.* 2005). Insects, particularly dung beetles, have an important role in dispersal of manure and are essential for long-term maintenance of hygiene and productivity of pastures. Accumulated manure harbours parasites, is a breeding site for flies and can drastically reduce the available grazing area. Rapid removal of manure by natural fauna can significantly reduce larval nematode concentrations and thereby reduce anthelmintic treatment intervals (Abbott *et al.* 2004).

The macrocyclic lactones, which are primarily excreted through the faeces, are toxic to faecal fauna. Of these drugs moxidectin appears to be far less toxic than any of the avermectins, including ivermectin. When horses are treated with ivermectin dispersal of manure is markedly delayed (Herd *et al.* 1993). It has been recommended that ivermectin-treated horses be kept off pasture for 3 days post treatment when manure is most toxic (Herd *et al.* 1993). Moxidectin, however, is unlikely to have a deleterious effect on manure fauna (Herd 1995; Kadiri *et al.* 1999; Lumaret and Errouissi 2002; Floate *et al.* 2005).

Manufacturer's address

[1]Fort Dodge Animal Health, Fort Dodge, Iowa, USA.

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