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ORIGINAL RESEARCH

Evidence of Ivermectin Resistance by *Parascaris equorum* on a Texas Horse Farm

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ABSTRACT

By collecting fecal samples every 2 weeks beginning at 2 months of age, 32 foals from a single Texas farm were monitored. The foals were administered ivermectin paste at the time of the first collection and again monthly. When foals had *Parascaris* egg counts higher 2 weeks after ivermectin treatment than at treatment, they were administered pyrantel pamoate at the manufacturer's recommended dose (6.6 mg/kg) or at twice the recommended dose (13.2 mg/ kg) when tapeworm eggs were also detected. An elevation or only minimal reduction (less than 75%) in *Parascaris* egg counts was seen 2 weeks after ivermectin treatment until the foals were 8 months of age, at which time there was an 85% reduction in fecal egg count after treatment. When pyrantel was administered at the manufacturer's recommended dose, a 42% to 84% reduction in egg counts occurred, but at 13.2 mg/kg there was a 98% to 100% reduction in fecal egg counts 2 weeks posttreatment. However, pyrantel failed to control strongylate egg counts even at the elevated dose, whereas ivermectin reduced strongylate fecal egg counts by greater than 99%, determined 2 weeks posttreatment. Pyrantel, but not ivermectin, lowered *Parascaris* egg counts. Ivermectin, but not pyrantel, lowered strongyle egg counts 2 weeks post administration. A single drug for all ages of horses approach to parasite control requires rethinking. Combinations of drugs or more careful evaluation of anthelmintics in foals may be necessary for continued parasite control.

Keywords: Foal parasites; *Parascaris equorum*; Ivermectin; Pyrantel

INTRODUCTION

Perceptions by practicing veterinarians and several recent publications indicated the failure of ivermectin to adequately control *Parascaris equorum* in foals.[1-3] The evidence presented in these papers indicated a lower efficacy than those seen in evaluations of ivermectin in various formulations against *Parascaris* previously reported.[4-11] In earlier publications, it appeared that a few worms survived in the host or were acquired soon after treatment. As a result, there have been continuing questions as to the effectiveness of ivermectin against *Parascaris*.[12] With the widespread popularity of ivermectin, which is a safe, effective broad-spectrum anthelmintic, the product has been used as the sole or predominant anthelmintic on many horse-rearing properties for a number of years. Because of the success of this drug and other anthelmintics, only limited evaluation of the efficacy of anthelmintics used in foals in recent years has been published.

With the movement of mares and foals to and from different breeding facilities, infections acquired on a farm in one area of the country could easily be spread to other regions within a few years. If any worms that were transported within the horse were resistant to anthelmintics, they could establish in the new environment. The selection of resistant worms is enhanced by the removal of susceptible worms from the population by effective anthelmintics, which leaves the resistant worms with only other resistant worms with which to mate.[13] The fecundity of *Parascaris equorum* and the long-term survival of infective eggs in the environment further increases the likelihood that, if resistance is present, it will become clinically relevant.

The disease caused by *P. equorum* is manifest clinically as nasal discharge and ill thrift or by elevated fecal egg counts.[13] As a part of other studies on a farm in 2003, observations were made that indicated the possibility of ivermectin-resistant *Parascaris*. This study was designed to look at the dynamics of parasite infection on the breeding farm without changing management of the foals, with the exception of collecting fecal samples approximately every 2 weeks.

The Texas horse farm, one on which approximately 30 Quarter Horse foals are raised each year, was investigated during 2004 and early 2005 to determine the effectiveness of ivermectin and pyrantel against *Parascaris equorum* and other gastrointestinal parasites. Ivermectin has been the primary anthelmintic used on the farm since 1984. Adult horses were treated every 60 days and foals monthly beginning at 2 months of age. Beginning in 2002, pyrantel pamoate (13.2 mg/kg) was rotated into

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0737-0806/$ - see front matter

doi:10.1016/j.jevs.2006.12.002

Table 1. *Parascaris equorum* fecal egg counts (FEC) collected at the time of treatment (T) or approximately 2 weeks post-treatment (A) with ivermectin at 0.2 mg/kg

	Age (days)											
	62		93		122		154		209		245	
	FEC T	FEC A	FEC T	FEC A	FEC T	FEC A	FEC T	FEC A	FEC T	FEC A	FEC T	FEC A
Mean	0	3	611	1,272	1,135	1,308	689	194	241	179	310	47
Range	0	(0–57)	(0–3,100)	(0–5,150)	(0–5,300)	(0–8,250)	(0–2,450)	(0–1,450)	(0–1,450)	(0–600)	(0–1,850)	(0–600)
Pos/exam	0/32	3/32	23/26	25/26	19/21	17/20	12/19	15/19	12/18	16/18	15/17	9/17
% Reduction		−100		−108		−15.2		71.8		25.7		84.8
Significance		NS		$P < .05$		NS		$P < .05$		NS		NS

NOTE. The age in days of the foal at the time of treatment is indicated. Significance is based on exact paired *t*-test comparing individual before and after counts ($P < .05$).

the autumn and winter treatments; and used alternately with ivermectin. Only foals born during 2004 were used in this study.

MATERIALS AND METHODS

Thirty-two foals, born between January 25 and June 9, 2004, were evaluated in this study. When each foal was approximately 2 months of age, a fecal sample was taken and the foal treated with ivermectin paste on that day. A weight tape was used to estimate the foal's weight, and the dose of paste was administered at the next highest mark on the dispensing syringe. Each foal was then sampled every 2 weeks until weaning and then sampled weekly to monthly thereafter until sold or moved to another location. Ivermectin was administered monthly after the initial treatment. Because of the number of foals used in the study, an attempt was made to sample and treat half of the foals each week. Further treatments with either ivermectin or pyrantel pamoate were done based on elevated egg counts for *Parascaris*, strongylids or tapeworms. When several foals in an age cohort had elevated *Parascaris* or strongylate egg counts, the entire cohort was administered an anthelmintic in 2 weeks, at the time of sampling. The dose used for ivermectin followed the manufacturer's recommendation of 0.2 mg/kg. Pyrantel pamoate was administered at 6.6 mg/kg, the manufacturer's recommended dose, or at 13.2 mg/kg for control of *Anoplocephala perfoliata*.[15-17] Two gropus of foals were treated with pyrantel at 144 or 148 days of age, the first group (148 days) had only *Parascaris*, and strongylate eggs. The second group (144 days) also had *Anoplocephala* eggs in the feces 2 weeks before the administration of 13.2 mg/kg pyrantel.

The number of fecal eggs per gram was determined by the modified McMaster method with a sensitivity of 50 eggs/g,[18] if no *Parascaris* eggs were detected by the McMaster method, a 5-g Wisconsin double centrifugation test was run on the sample, with a sensitivity of 0.2 eggs per gram of feces.[19] The fecal sample, collected the day of treatment, was considered the pre-treatment sample and the sample collected approximately 14 days later was the post-treatment sample, which was compared to the sample collected at the time of treatment. Except for the initial observation period, if a foal had no detectable *Parascaris* eggs at the time of treatment and no eggs at the time of the first post-treatment evaluation, the data were not included in the Tables.

Fecal egg count (FEC) reduction was calculated by the following formula using the arithmetic mean fecal egg count on each age group sampled. Samples were obtained from foals at approximately 2, 3, 4, 5, 7, and 8 months of age and compared with samples obtained 2 weeks later.

$$\frac{\text{FEC day of treatment} - \text{FEC 14 days post treatment}}{\text{FEC day of treatment}} \times 100$$

An exact paired *t*-test for differences of means before and after treatment was used to compare egg counts.

Table 2. *Parascaris equorum* fecal egg counts (FEC) collected at the time of treatment (T) or approximately 2 weeks post-treatment (A) with pyrantel pamoate at 6.6 mg/kg or pyrantel 2× at 13.2 mg/kg

	Pyrantel (age 112 days)		Pyrantel 2X (age 144 days)		Pyrantel (age 148 days)		Pyrantel 2X (age 265 days)	
Foal	**FEC T**	**FEC A**	**FEC T**	**FEC A**	**FEC T**	**FEC A**	**FEC T**	**FEC A**
Mean	2,642	1,528	1,460	23	486	77	101	0
Range	(1,200–3,650)	(0–5,800)	(8–3,700)	(0–250)	(1–1,700)	(0–700)	(7–650)	0
Pos/exam	6/6	4/6	11/11	2/11	10/10	5/10	7/7	0/7
% Reduction		42.4		98.4		84.1		100
Significance		NS		$P < .05$		NS		$P < .05$

NOTE. The age of the foal at the time of treatment is indicated. Significance is based on exact paired *t*-test comparing individual before and after counts ($P < 0.05$).

Table 3. Strongylate eggs recovered from foals at the time of treatment with ivermectin or pyrantel and a subsequent egg count two weeks (pyrantel 13.2 mg/kg or ivermectin 0.2 mg/kg) later

	Ivermectin	0.2 mg/kg	Pyrantel	13.22 mg/kg
Mean FEC	311.6	0.4	320.2	126.7
(Range)	(1.8–2,550)	(0–3.8)	(1.2–700)	(0–450)
Pos/exam	25/25	14/25	17/17	16/17
% Reduction		99.9		60.4
Significance		$P < .05$		$P < .05$

NOTE. Significance is based on exact paired *t*-test comparing individual before and after counts ($P < .05$).

Differences were considered nonsignificant (NS) if P was greater than .05.

RESULTS

Results of *Parascaris* fecal egg counts are presented in Tables 1 and 2. None of the foals had patent infections at the time of the first sampling, at 57 to 68 days of age, when ivermectin was administered. Three of these foals had patent infections 2 weeks post-treatment. By the time they were 3 months of age, 24 of 31 foals had patent *Parascaris* infections. At the second ivermectin treatment (approximately 3 months of age), a reduction in egg count was seen in foals, whereas most had an increase in egg counts. However, by the final ivermectin treatment, at an average of 245 days of age, there was an 85% reduction in the *Parascaris* FEC (Table 1).

The findings with pyrantel pamoate were as follows: The treatment at 112 days of age resulted in a 42.4% reduction in *Parascaris* egg count; 2 of the 6 foals did not have reduced egg counts. When treated at 148 days of age (6.6 mg/kg), the mean egg count 2 weeks later was reduced by 85%; however, 1 foal had an increased FEC. When pyrantel was administered at twice the manufacturer's recommended dose (13.2 mg/kg) the *Parascaris* FEC was lowered by 98% to 100% when administered at 144 or 265 days of age (Table 2).

Both drugs were compared for their effectiveness on strongylids (Table 3). This comparison was done when foals were administered one of the anthelmintics when there were relatively high egg counts at the time of treatment. The observations showed that ivermectin was effective in lowering the strongylate egg count by 99.9%. Although there was a statistically significant decrease in egg counts compared with levels at the time of treatment with pyrantel, at 13.2 mg/kg the reduction in egg counts was 60%.

Statistical evaluation of anthelmintics presented in Tables 1 to 3 indicated differences among groups comparing egg counts at the time of treatment and 2 weeks post-treatment. The differences were positive (the anthelmintic worked), negative (the anthelmintic utterly failed), or in between (the product worked but below the expected efficacy).

DISCUSSION

The evidence is quite strong that *Parascaris* were not adequately removed by treatment with ivermectin paste. In fact, there was a significant rise in egg counts indicating maturation of worms already present in the intestine. However, the product was more effective in older foals. Several possible explanations may be made for this observation. One explanation is that the older foals may have been exposed to different populations of worms on the farm. During the first 2 months, the mares and foals were utilizing a pasture where daily observation of behavior of both mares and foals could easily be done. This observation was directed toward the mares exhibiting signs of estrus and general health of the foals. The pasture has been used for years by the same class of horses because of the ease of observation and movement of individual animals

to working facilities. Later, when the mares were bred, they were moved to other pastures, which have had other classes of horses grazing on them and the concentration of horses was less than in the breeding pasture. A second explanation could be that young horses do not metabolize ivermectin in a way that presents it to the worms as efficiently as in older horses. Certainly there is a shorter return to cyathostome egg production after treatment in young compared with older horses.[12,20] Whether this is attributable to pharmacological differences, to an immaturity that allows an increased survival rate of larvae, or an accelerated maturation of worms is not known.[21] A third possibility is that, as the foals are exposed to the parasite, presumably numerous times, the acquired immune response also may have effects on expelling adult worms damaged, but not killed, by the anthelmintic. The immune response against incoming worms is extremely effective, as *Parascaris* is seldom seen in older horses.

The variable efficacy seen by treatment with pyrantel at 6.6 mg/kg is consistent with observations elsewhere.[3] Pyrantel had been used at the facility sparingly in years preceding this trial primarily for treatment of *Anoplocephala;* however, some horses had been pastured at other farms and presumably had an opportunity to become infected by resistant worms. The resistant worms were then imported from other farms.[22] Neither ivermectin nor pyrantel at 6.6 mg/kg adequately controlled *Parascaris equorum* on this farm. Conversely, the effect of ivermectin against cyathostomes was excellent (Table 3), whereas pyrantel (even when administered at an elevated dose) failed to effectively reduce cyathostome egg counts to the level of 90% or more expected of modern anthelmintics. This study demonstrates an example in which resistance to one class of anthelmintic is seen with *Parascaris* and resistance of strongyles (cyathostomes) to another anthelmintic.

The reliance on a single anthelmintic for all ages of horses on a farm may not provide adequate helminth control. Foals must be evaluated and treated differently than adult horses. When resistance to one class of anthelmintic by one parasite and resistance to another drug by another parasite occurs on an individual farm, the concurrent use of anthelmintics from different drug classes at the same time may be considered. Certainly, the precedence of the concomitant use of macrolides and praziquantel to control both tapeworms and strongylids in horses is established. In small ruminants, the combination of anthelmintics in different drug classes is used to aid in the control of multiple resistant nematodes. This approach has been used to control worms resistant to individual anthelmintics without increasing toxicity.[23,24]

Control of helminth parasites in foals is not equivalent to that in adult horses, and a few geographically separate reports of resistance are probably not the exception but rather a common occurrence. The only way to establish whether clinically relevant resistance is present is to evaluate horses on that farm periodically (every few years) to determine the effectiveness of anthelmintics against clinically important parasites. The evaluation must be done by fecal egg reduction test, because there is no practical in vitro system to evaluate *Parascaris* eggs for resistance. Collecting samples at the time of treatment and again 2 weeks later is a reasonable period to establish whether the adult egg producers had been removed or are still present in the intestine. Evaluation of foals older than 3 months of age, even if they previously have been administered an anthelmintic seems most reasonable. A longer interval between treatment and reevaluation would indicate the removal or failure to remove egg-laying adults plus maturing worms in the intestine. The prepatent period of *Parascaris equorum* is as short as 10 weeks, with all but the first month of development in the intestine. Even if the anthelmintic is effective only against luminal parasites, reevaluation by egg counts is valid up to 6 weeks post-treatment. However, an intestine full of adult worms can produce millions of eggs per day, which suggests that a fecal egg count reduction determination should be done earlier post-treatment[14] so that remediation can be done to lessen environmental contamination. By the same token, if evaluated too early, the worms and eggs may not have been completely evacuated from the intestine. Evaluation of the effectiveness of the anthelmintic 2 weeks post-treatment should preclude this possible problem.

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