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Clinical field efficacy and safety of pyrantel pamoate paste (19.13% w/w pyrantel base) against *Anoplocephala* spp. in naturally infected horses

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Abstract

Clinical field trials were conducted at five geographical locations in the USA (Oklahoma, Wisconsin, Tennessee, Virginia and Idaho) to evaluate the efficacy and safety of pyrantel pamoate paste (19.13%, w/w, pyrantel base) administered at the recommended dosage of 13.2 mg pyrantel base/kg (6.0 mg pyrantel base/lb) body weight (b.w.) against tapeworm infections of *Anoplocephala* spp. in naturally infected horses. Horses at each study site were allocated by restricted randomization based on the cestode status (positive or negative) of pre-treatment fecal egg counts to complete sets of four animals each or incomplete sets of fewer than four animals. Within sets comprising of two to four horses, one animal was randomly allocated to receive placebo vehicle paste and the remaining horse(s) received pyrantel pamoate paste administered orally at a minimum dosage of 13.2 mg pyrantel base/kg b.w. on Test Day (TD) 0. Single animal sets received pyrantel pamoate paste. Fecal samples of horses were collected and examined for equine tapeworm (*Anoplocephala* spp.) eggs a minimum of four times (once or thrice between TD −28 and −14, twice between TD −14 and −7, and once on TD 0) prior to treatment on TD 0. Fecal samples of horses that were positive for cestode infection pre-treatment were examined for cestode eggs on TD 7, 8, 9, 14, 15 and 16. Cestode-negative pre-treatment horses were not sampled again after treatment. A total of 241 horses (141 mares, 16 stallions and 84 geldings; 6 months–30 yrs of age; 173–646 kg; 13 recognized breeds and various crossbreds) were evaluated. The prevalence of *Anoplocephala* spp. determined by pre-treatment fecal examination ranged from 38.3% in Idaho to 68.1% in Tennessee with an overall prevalence of 52.3%. Ninety cestode-positive and 88 cestode-negative horses were treated with pyrantel pamoate paste, 36 cestode-positive and 27 cestode-negative horses were treated with placebo vehicle paste. Overall, 178 horses were

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treated with pyrantel pamoate paste, and 63 horses were treated with placebo paste. Of the 178 horses treated with pyrantel pamoate paste, no drug related, adverse clinical or neurological health events were observed. No doses of pyrantel pamoate paste were refused or lost during dosing. At each post-treatment time sampling interval, significantly fewer cestode eggs ($P < 0.0115$) were passed by cestode-positive horses treated with pyrantel pamoate paste compared to cestode-positive horses that received placebo paste. Efficacy of the pyrantel pamoate paste treatment ranged from 92 to 96% from TD 7 to TD 16 with an overall efficacy of 95%. The results of these trials demonstrated that pyrantel pamoate paste (19.13%, w/w, pyrantel base) administered orally at a dosage of 13.2 mg pyrantel base/kg b.w. is highly efficacious (95%) against *Anoplocephala* spp. and safe for use in horses with no adverse clinical or neurological health events observed under field use conditions.

Keywords: Pyrantel pamoate; Efficacy; Safety; Cestode; *Anoplocephala* spp.; Equine; Horse; Prevalence

1. Introduction

Three species of anoplocephalid (Cestoda: Anoplocephalidae) tapeworms (*Anoplocephala perfoliata*, *Anoplocephala magna*, and *Anoplocephaloides* (*Paranoplocephala*) *mamillana*) are found in horses in the USA (French and Chapman, 1992). Of these equine cestode species, *A. perfoliata* is the most prevalent (Chapman et al., 2002). A seroprevalence survey of horses in the USA reported that the overall national prevalence of antibodies to *A. perfoliata* was 54.2% (Reinemeyer et al., 2003). Equine exposure to *A. perfoliata* ranged from 12.7% along the Pacific coast to a high of 95.8% in the upper Midwest. Previous reports on the prevalence of tapeworm infection in horses at necropsy in the USA ranged from 13 to 64% (Hass, 1979; Slocombe, 1979; Reinemeyer et al., 1984; Torbert et al., 1986; Lyons et al., 1983, 1989, 1997; Benton and Lyons, 1994), while the prevalence based on fecal examinations ranged from 3 to 53% (Lyons et al., 1983, 1984; Beroza et al., 1986). Detection of tapeworm infection by fecal examination is problematic because of low sensitivity (Slocombe, 1979; French et al., 1994; Williamson et al., 1998; Lyons et al., 2000), poor correlation between the number of eggs and number of tapeworms present (Proudman and Edwards, 1992; Nilsson et al., 1995; Meana et al., 1998), and intermittent shedding of proglottids rather than continuous production of individual eggs as in nematode infections (Drudge and Lyons, 1986).

At the recommended nematocidal dosage of 6.6 mg pyrantel base/kg b.w., pyrantel pamoate has shown partial cestocidal activity against *A. perfoliata* (Lyons et al., 1974). Lyons et al. (1989) reported 67–100% (average 88%) efficacy with a paste formulation and 58–100% (average 75%) with a suspension when both were administered at 6.6 mg pyrantel base/kg b.w. The combined average removal of *A. perfoliata* for both formulations was 87%. In contrast, Slocombe (1979) reported that this dosage only caused destrobilation of gravid segments and did not dislodge the scolex of individual cestodes. Evaluation of the nematocidal dose by a modified critical test method (Lyons et al., 1997) yielded variable drug activity ranging from 0 to 100% (average 70%).

At the elevated (2×) dosage of 13.2 mg pyrantel base/kg b.w., pyrantel pamoate exhibited 93% efficacy in 30 horses infected with *A. perfoliata* (Lyons et al., 1986). Using smaller numbers of infected horses, Slocombe (1979) reported 97.8 and 100% efficacy against *A. perfoliata* with dosages of 13.2 (2×) and 19.8 (3×) mg pyrantel base/kg b.w., respectively. Further investigations by Slocombe (1995) and Höglund et al. (1998) demonstrated 96.6 and 94% efficacies against *A. perfoliata* at 13.2 mg pyrantel base/kg b.w., respectively. Thus, the dosage of 13.2 mg pyrantel base/kg b.w. via a double dose of the nematocidal single dosage has become a widely accepted target dosage for the treatment of *A. perfoliata* in horses (Slocombe, 1995).

Since no pyrantel pamoate paste had been approved for the treatment of equine tapeworms in the USA, federal approval of this new paste product required the development of a New Animal Drug Approval (NADA). This report describes the clinical field efficacy and safety studies of a pyrantel pamoate paste containing 19.13% (w/w) pyrantel base for the single oral treatment of horses infected with *A. perfoliata* at the recommended dosage of 13.2 mg pyrantel base/kg

b.w. The dosing syringe contains 7.20 g pyrantel base in 37.6 g paste with each milliliter containing 226 mg pyrantel base as pyrantel pamoate. This new formulation contains a 25% higher concentration of pyrantel base thus yielding 20.5% less paste volume than treating a horse with a double volume of the nematocidal formulation. The utility of the syringe allows for administration of dosages for the treatment of infections of both nematodes and tapeworm, *A. perfoliata*.

2. Materials and methods

2.1. Study sites and investigational animals

The studies were negative control, single treatment sets, multicenter, clinical efficacy and safety evaluations using a randomized block design. The experimental unit was the individual horse. A study site met the qualification criteria if a minimum of two but no more than 10 sets of four horses each showed evidence of cestode infection by the demonstration of tapeworm (*Anoplocephala* spp.) eggs in fecal samples collected between Test Days (TD) −28 and −15. Enrolled horses were privately owned, and horse owners were required to sign a consent form before enrolling their horse(s) in the study. The population of horses enrolled at each site was comprised of cestode-positive animals to evaluate efficacy and safety, and cestode-negative horses to generate additional data regarding safety of pyrantel pamoate paste. On TD −14 to −5, depending on the specific study site, enrolled horses were classified by infection status (positive (minimum of two fecal samples) or negative based on fecal samples collected anytime between TD −28 and −7) and randomly allocated within group status to complete sets of four animals each or incomplete sets of one to three horses each in order to include the total animal population at the site. Within complete sets, three horses were randomly allocated to treatment with pyrantel pamoate paste and one horse was randomly allocated to a placebo vehicle paste. Within incomplete sets of two or three horses, one horse was randomly allocated to receive placebo vehicle paste, while the remaining horse(s) was randomly assigned to receive the pyrantel pamoate paste. A single horse set was assigned to the pyrantel pamoate paste. Identification of acceptable study sites and test subjects began as early as TD −28. Once a study site qualified, all horses had been residents of the study site for a minimum of 14 days prior to treatment. Confinement and management conditions were according to local practice including husbandry, feed and ad libitum water and were identical for animals within sets during the conduct of the study. A physical examination was conducted by a veterinarian on TD −14 to confirm the general health of the enrolled animals.

2.2. Fecal examinations

Fecal samples were collected from candidate horses between TD −28 and −15, between TD −14 and −7, on TD 0 prior to treatment, and again on TD 7, 8, 9, 14, 15 and 16 post-treatment. All fecal samples were attributable to specific horses, either by observed defecation, manual rectal collection, or by confining individual animals in separate, cleaned stalls or enclosures. Horses that were cestode-negative at any pre-treatment collection were not sampled again after treatment. Fecal samples (10 g) were examined and cestode eggs counted using a modified Wisconsin double centrifugation/flotation technique (Cox and Todd, 1962). Briefly, 10 g of individual fecal samples were mixed thoroughly with 40 mL of tap water, pressed with a tongue depressor through two layers of cheesecloth, and the liquid fraction centrifuged at ∼1500 rpm for ∼5 min. The supernatant was discarded and the fecal sediment resuspended in concentrated sucrose solution (s.g. 1.275), which was added until a convex menicus formed on the top of each test tube. A coverslip was placed on top of the tube and the tubes were centrifuged again at ∼1500 rpm for ∼5 min. Each coverslip was transferred to a labeled microscope slide and examined for eggs of *Anoplocephala* spp. The calculated sensitivity of the procedure was one cestode egg per 10 g of feces.

2.3. Treatment and animal observations

A paste formulation containing 7.2 g of pyrantel base as pyrantel pamoate in an inert vehicle was provided in individual calibrated disposable syringes containing 37.6 g (31.8 mL) of paste (19.13%, w/w, pyrantel base; 226 mg pyrantel base/mL). Paste was

administered orally to each horse on TD 0 at a dosage of 13.2 mg pyrantel base/kg b.w. Body weights were measured on TD −14 with a calibrated weight/girth tape (Nasco, horse and pony height–weight tape, Fort Atkinson, Wisconsin 53538). The pre-filled product syringes were calibrated with four weight mark increments to deliver 1800 mg pyrantel base/136.4 kg b.w. per increment for the tapeworm dosage up to an animal weight of 545 kg b.w. per syringe. The commercial syringes (IVX Animal Health, Inc., A NADA 200–342) are also separately calibrated with eight weight mark increments to deliver 900 mg pyrantel base/136.4 kg b.w. per increment for the nematocidal dosage, thus allowing for the treatment of tapeworms and nematodes with a single syringe. The placebo paste contained 0 mg pyrantel base in an inert vehicle (same as pyrantel pamoate paste) and was administered at the same body weight volume as the pyrantel pamoate paste. All paste doses were administered by the horse owner or designee, who was blinded to the treatment assignment. Horses were restrained and the nozzle end of the syringe was inserted into the mouth through the interdental space and directed backward. Paste was deposited on the dorsum of the tongue, as far back as possible, and the horse's head was raised for a few seconds immediately after dosing to minimize rejection. Animals were observed once daily on TD −14 to −1 and from TD 2 to TD 16 to assess general health. Clinical and neurological observations were conducted by a veterinarian prior to treatment on TD −3 and TD 0, between 4 and 8 h after treatment, and ∼22–26 h post-treatment on TD 1. Neurological assessment included categorical, ordinal and interval description of mental status/depression, behavioral attitude, locomotion/musculature, papillary light reflex, head and neck movement, and overall neurological condition.

2.4. Data analysis

Data from all sites were combined for analysis. Horses with at least one cestode egg in any pre-treatment or post-treatment fecal sampling day were considered positive and those without any cestode eggs were considered negative. Since pre-treatment test day comparisons of the pyrantel pamoate paste and placebo vehicle paste were not influenced by treatment, efficacy determination was based on post-treatment cestode egg counts on TD 7, 8, 9, 14, 15 and 16. Egg counts were transformed [log (count + 1)] and geometric means were calculated. Percent efficacy was calculated using the formula: $100[(C - T)/C]$, where C is the geometric mean cestode egg count for the placebo vehicle paste and T is the geometric mean cestode egg count for the pyrantel pamoate paste. A mixed model analysis was used for treatment comparisons with a significance level ($P < 0.05$) where treatment and day were fixed effects and study by location and horse within study were random effects. This modeling approach provided a repeated measures analysis (Littell et al., 1996) where day is the repeated measurement. Unequal variances for the two treatments were used in the model for the horse level analysis.

3. Results

3.1. Study sites and test animals

Study sites included privately owned horses in eastern Oklahoma, southwestern Wisconsin, eastern Tennessee, western Virginia and southwestern Idaho. A total of 53 complete sets of four animals each were enrolled, plus incomplete sets consisting of six sets of three horses, four of two horses, and three of one horse. The total of 241 horses of various breeds included 141 mares, 16 stallions and 84 geldings ranging in age from 6 months to 30 yrs and weighing between 173 and 646 kg (Table 1). A physical examination conducted on TD −14 confirmed that the general health of the enrolled animals was excellent to good.

3.2. Prevalence of Anoplocephala spp.

The prevalence of *Anoplocephala* spp., as determined by fecal examination of enrolled horses, ranged from a low of 38.3% at the Idaho site to a high of 68.1% in Tennessee with an overall prevalence of 52.3% (Table 1).

3.3. Treatment and animal observations

Ninety cestode-positive and 88 cestode-negative horses were treated with pyrantel pamoate paste, and

Table 1
Characteristics of enrolled horses by USA field sites for efficacy and safety evaluation of pyrantel pamoate paste (19.13%, w/w)

Site	Geographical location	Sets		No. of horses and sex distribution[a]				No. of horses positive for *Anoplocephala* Spp.[b] (% prevalence)	Age range	Body weight range (kg)	Cumulative list of breeds (number)
		Complete[c]	Incomplete	T	M	S	G				
A	Oklahoma	11	1[d]	47	42	3	2	28 (59.6)	1–21 yrs	205–541	Appaloosa (2), Arabian (7),
B	Wisconsin	10	1[d], 1[e], 1[f]	46	20	9	17	19 (41.3)	6 months–20 yrs	173–575	Hanovarian (1), Morgan (5),
C	Tennessee	14	3[d], 2[e]	69	26	1	42	47 (68.1)	1–30 yrs	337–636	National Show (3), Paint (4),
D	Virginia	4	1[e], 1[f]	19	14	0	5	9 (47.4)	3–24 yrs	410–591	Quarter horse (67), Racking horse (1),
E	Idaho	14	1[d], 1[f]	60	39	3	18	23 (38.3)	1–27 yrs	436–646	Rocky Mountain (23), Saddlebred (11),
Summary	Five sites	53	6[d], 4[e], 3[f]	241	141	16	84	126 (52.3)	6 months–30 yrs	173–646	Standardbred (2), Spanish Barb (1), Thoroughbred (62), Crossbreeds (52) 13 Purebreeds, numerous crossbreeds

[a] T = total, M = mare, S = stallion, G = gelding.
[b] Positive fecal sample from Test Day −28 to 0.
[c] Set of four horses.
[d] Set of three horses.
[e] Set of two horses.
[f] Set of one horse.

Table 2
Number of horses treated with pyrantel pamoate paste or placebo vehicle paste during clinical field studies

Geographical location	Site	No. of cestode-positive horses treated with pyrantel pamoate paste	No. of cestode-positive horses treated with placebo vehicle paste	No. of cestode-negative horses treated with pyrantel pamoate paste	No. of cestode-negative horses treated with placebo vehicle paste	Total no. of treated horses
Oklahoma	A	20	8	15	4	47
Wisconsin	B	14	5	20	7	46
Tennessee	C	31	16	19	3	69
Virginia	D	7	2	7	3	19
Idaho	E	18	5	27	10	60
Summary	–	90	36	88	27	241

36 cestode-positive and 27 cestode-negative horses treated with placebo paste (Table 2). Overall, 178 horses were treated with pyrantel pamoate paste, and 63 horses were treated with placebo vehicle paste. Of the 178 horses treated with pyrantel pamoate paste, no drug related clinical or neurological health problems were observed. Treatments of pyrantel pamoate paste were well accepted and no doses were refused or lost during dosing.

3.4. Efficacy

Geometric means of *Anoplocephala* spp. egg counts and percent efficacy of the pyrantel pamoate paste are summarized in Table 3. Cestode-positive horses treated with pyrantel pamoate paste had significantly ($P < 0.0115$) fewer cestode eggs than did the cestode-positive horses treated with placebo paste at each post-treatment time interval. Percent efficacy on TD 7, 8, 9, 14, 15 and 16 post-treatment ranged from 92 to 98% for all sites combined, with an overall efficacy of 95%. Twenty-one of 90 horses from all sites combined produced fecal samples that were positive for cestode eggs following pyrantel pamoate treatment (Table 4). The pattern of cestode egg shedding in these treated horses was sporadic and highly variable. On the final sampling day (TD 16), 15 of 21 horses had negative fecal results, and 6 of 21 horses were positive.

4. Discussion

Pyrantel is a member of the tetrahydropyrimidine class of anthelmintics and is marketed as the pamoate (also known as embonate), hydrochloride, citrate, and tartrate salts. The pamoate salt of pyrantel is practically insoluble in water (<0.1 mg/mL water between 15 and 25 °C; European Pharmacopeia, 2005). This property offers the advantage of reduced absorption from the gastrointestinal tract of horses and allows the drug to reach the microenvironmental sites

Table 3
Percent efficacy and geometric mean cestode egg counts of horses treated with pyrantel pamoate paste (19.13%, w/w) vs. placebo vehicle paste for all sites combined

Test day	Geometric mean cestode egg counts placebo vehicle paste[a]	Geometric mean cestode egg counts pyrantel pamoate paste[a]	Percent efficacy	*P*-value
7	1.34	0.11	92	0.0114
8	1.85	0.04	98	0.0009
9	2.02	0.08	96	0.0007
14	2.86	0.15	95	0.0001
15	2.86	0.15	95	0.0001
16	1.48	0.08	95	0.0052
Overall	1.78	0.09	95	0.0008

[a] Cestode eggs per 10 g of feces.

Table 4
Cestode egg shedding patterns of pyrantel pamoate (19.13%, w/w) paste treated horses on Test Day (TD) 7, 8, 9, 14, 15 and 16 post-treatment from all five geographical study sites

Animal ID-site	TD 7	TD 8	TD 9	TD 14	TD 15	TD 16
142-WI	1	0	0	0	0	0
105-TN	1	0	0	0	0	0
128-TN	1	0	7	0	0	0
109-WI	2	0	1	0	4	0
24-OK	1	0	0	1	0	0
116-TN	1	1	0	0	0	0
30-TN	3	1	0	0	1	0
27-TN	3	1	0	3	1	0
140-WI	0	1	0	0	0	0
4-OK	0	0	1	0	0	0
30-OK	0	0	1	0	0	0
18-TN	0	0	2	0	0	0
14-OK	0	0	0	1	0	0
112-TN	0	0	0	0	1	0
8-ID	0	0	0	0	3	0
141-WI	1	0	0	0	0	1
119-TN	0	0	1	0	0	2
103-TN	0	0	0	4	4	1
9-OK	0	0	0	1	0	2
3-OK	0	0	0	1	2	2
10-TN	0	0	0	1	26	3

Cestode egg counts per 10 g feces.

of the target parasites. In contrast, pyrantel tartrate is more soluble in water and hence is more readily absorbed from the gastrointestinal tract. Pyrantel tartrate is rapidly metabolized and predominately excreted in the urine with small amounts excreted in the feces. This physicochemical property of increased gastrointestinal absorption of pyrantel tartrate has led to daily low-dose feeding regimens for the control of adult and larval nematodes in horses (Cornwell and Jones, 1968; Conway et al., 1970). Like pyrantel pamoate, the tartrate salt has also been shown to be efficacious against *Anoplocephala* spp. in horses given daily administration at 2.6 mg/kg b.w. (Greiner and Lane, 1994; Kivipelto et al., 1998). However, a recent report of pyrantel pamoate resistance in cyathostomes speculated on the possible connection of daily feeding of low-dose pyrantel tartrate (Kaplan et al., 2004). Gastrointestinal absorption of pyrantel tartrate may provide a selection pressure on cyathostome larvae as immature stages of nematodes have been suggested to play an important role in the selection and development of anthelmintic resistance (Jackson, 1993). The lack of larvicidal activity of pyrantel pamoate provides an unselected population of susceptible parasites (refugia). Thus, consideration should be given to restricting the use of pyrantel tartrate on horse farms with pyrantel pamoate susceptible cyathostomes.

Pyrantel is a cholinergic agonist possessing nictotinic-like properties similar to acetylcholine and acts as a depolarizing neuromuscular blocking agent (Rew and Fetterer, 1986), thereby paralyzing helminths that are then expelled intact from the gastrointestinal tract. In contrast, praziquantel ''another drug used against horse tapeworms'' causes an irreversible focal vacuolization with subsequent breakdown and disintegration of the cestodal tegument (Becker et al., 1980, 1981; Conder et al., 1981). Host anaphylactic reaction due to parasite antigens released by praziquantel-induced disintegration of the tapeworm tegument may cause colic and diarrhea in praziquantel treated horses with serological evidence of high tapeworm burdens (Barrett et al., 2005). The drug of choice would then be pyrantel pamoate in horses deemed to be at high risk of praziquantel post-dosing colic.

The disposable syringe of pyrantel pamoate equine paste (19.13%, w/w) offers the convenience of treating horses with concomitant infections of both susceptible nematodes and tapeworms with a single active ingredient. Such a feature would be highly desirable in treating foals, weanlings and yearlings particularly in the case of macrocyclic-lactone resistance in *Parascaris equorum* (Boersema et al., 2002; Hearn and Peregrine, 2003; Slocombe et al., 2004). Combining pyrantel pamoate with another anthelmintic would limit the potential selection pressure of a single chemical formulation.

The overall prevalence of *Anoplocephala* spp. in horses of 52.3% as determined by fecal sample in the five geographical regions of the USA as reported herein is consistent with previous reports (Lyons et al., 1983, 1984) and provides additional geographical prevalence data for Oklahoma, Virginia and Idaho.

Persistent, yet sporadic, cestode egg shedding was observed on TD 16 in 6/90 (6.7%) horses treated with pyrantel pamoate, demonstrating that *Anoplocephala* spp. may not have been completely eliminated from all treated horses (Table 4). Cestode-positive fecal results post-treatment could be due to: (1) <100% efficacy of the treatment, (2) incorrect dosage or loss of paste

during oral administration, (3) ingestion of cestode eggs from the environment on a heavily contaminated tapeworm positive premise, (4) contamination during fecal sample collection or processing procedure, or (5) a combination of the above.

A modified critical test of twice the nematocidal dosage with a 48 h post-treatment period by Slocombe (2004) yielded efficacy against *A. perfoliata* ranging from 75.3% in one horse to 100% in 8 of 13 horses with an overall efficacy of 96.6%. Most tapeworms were expelled between 24 and 48 h after treatment. The efficacy of pyrantel pamoate paste (19.13%, w/w) against *Anoplocephala* spp. in horses has been further substantiated in two dose confirmation studies that demonstrated efficacies of 95.5 and 98.4% (Reinemeyer et al., submitted for publication). Based on these efficacy results (Reinemeyer et al., submitted for publication) and those of the five field studies reported herein, a cestode egg(s) on one or more days post-treatment could be expected. In conclusion, the results of the clinical field studies of pyrantel pamoate paste (19.13%, w/w) showed that the formulation and dosage was highly efficacious (95% efficacy) against *Anoplocephala* spp. and is safe for use in horses with no clinical or neurological adverse health effects observed following oral administration under field conditions.

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