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Plasma pharmacokinetics, faecal excretion and efficacy of pyrantel pamoate paste and granule formulations following *per os* administration in donkeys naturally infected with intestinal strongylidae

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ABSTRACT

The plasma disposition, faecal excretion and efficacy of two formulations of pyrantel pamoate in donkeys were examined in a controlled trial. Three groups of seven donkeys received either no medication (control) or pyrantel paste or granule formulations at horse dosage of 20 mg/kg B.W. (equals 6.94 mg/kg PYR base) of body weight. Heparinized blood and faecal samples were collected at various times between 1 and 144 h after treatment. The samples were analysed by high-performance liquid chromatography. The last detectable plasma concentration (t_{max}) of paste formulation was significantly earlier (36.00 h) compared with granule formulation (46.29 h). Although, there was no significant difference on terminal half lives ($t_{1/2}$: 12.39 h *vs.* 14.86 h), t_{max} (14.86 h *vs.* 14.00) and MRT (24.80 h *vs.* 25.44 h) values; the C_{max} (0.09 μg/ml) AUC (2.65 μg h/ml) values of paste formulation were significantly lower and smaller compared with those of granule formulation (0.21 μg/ml and 5.60 μg h/ml), respectively. The highest dry faecal concentrations were 710.46 μg/g and 537.21 μg/g and were determined at 48 h for both paste and granule formulation of PYR in donkeys, respectively. Pre-treatment EPG of 1104, 1061 and 1139 were observed for the control, PYR paste and PYR granule groups, respectively. Pre-treatment EPG were not significantly different ($P > 0.1$) between groups. Post-treatment EPG for both PYR treatment groups were significantly different ($P < 0.001$) from the control group until day 35. Following treatments the PYR formulations were efficient (>95% efficacy) until day 28. In all studied donkeys, coprocultures performed at day−3 revealed the presence of Cyathostomes, *S. vulgaris*. Faecal cultures performed on different days from C-group confirmed the presence of the same genera. Coprocultures from treated animals revealed the presence of few larvae of Cyathostomes.

1. Introduction

Pyrantel (PYR) is an imidazothiazole derivative, which belongs to the tetrahydropyrimidine group of anthelmintics. PYR is available as tartrate and pamoate

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(syn. embonate) salts. Different salts of PYR have different pharmacokinetic properties and consequently different toxicities to the host. The pamoate salt is almost insoluble in water, poorly absorbed from the gastrointestinal tract, and most passes unchanged in the faeces (Arundel, 1983). Reduced systemic absorption of the pamoate form potentially increases availability in the lumen of the intestine (Bjorn et al., 1996). The tartrate salt of PYR is soluble in water and absorbed rapidly and extensively from the intestine of monogastric animals (Faulkner et al., 1972).

The daily administration of PYR tartrate to horses at a continuous low level was highly effective against common equine parasites, including adult large strongyles (*Strongylus vulgaris*, *Strongylus edentatus*, and *Triodontophorus* spp.), adult small strongyles (*Cyathostomum* spp., *Cylicocyclus* spp., and *Cylicostephanus* spp.) and adult and fourth-stage *Parascaris equorum* (Valdez et al., 1995). It was reported that the recommended dose level of PYR (13.2 mg/kg, bodyweight) pamoate paste formulation was effective (95–98%) against infections of *Anoplocephala perfoliata* (FDA, 2005). Moreover, a recent investigation by Reinemeyer et al., 2010 indicated that PYR pamoate paste formulation was highly effective against adult (91.2%) and fourth-stage *Oxyrus equi* larvae (>99%).

Only limited data are available on the pharmacokinetics and efficacy of anthelmintic drugs used in donkeys because donkeys are often a neglected species for studies in domestic animals. Most of drugs in different classes used in horses and ruminants are commonly extrapolated for use in donkeys without optimization of dosing regimens and determination of pharmacokinetic properties (Veneziano et al., 2011). Because of the lack of drugs approved for use in donkeys, anthelmintics licensed for use in horses or ruminants are used at the same dosages for treatment of parasitic infections in donkeys. It has been reported that donkeys have a greater capacity to metabolize certain drugs, compared with the capacity for horses; thus, higher dosages or shorter intervals could be required to maintain effective drug concentrations in donkeys (Welfare et al., 1996; Matthews et al., 1997; Coakley et al., 1999; Peck et al., 2002; Lizarraga et al., 2004; Grosenbaugh et al., 2011). Hence, in the present study, the pharmacokinetic disposition, faecal excretion and anthelmintic efficacy of two different formulations (paste and granule) of PYR pamoate are reported in donkeys naturally infected with intestinal strongylidae after oral administration.

2. Materials and methods

2.1. Study Animals

Twenty-one female crossbreed donkeys (*Equus asinus*) weighing 200–280 kg were used in this study. The bodyweight (BW) of each animal was estimated 1 day prior to treatment (day−1) using the nomogram proposed by The Donkey Sanctuary (2003). The animals had a mean age of 9.8 (±1.5) years and they had a history of grazing pasture contaminated with equine nematode parasites and have not been treated with any anthelmintics during the previous 9 months. Faecal examinations (individual Faecal Egg Counts and pooled coproculture) performed before the beginning of the study (day−3) showed individual counts >150 eggs per gram (EPG) and a high prevalence of intestinal nematodes (Cyathostomes, *S. vulgaris*) in all studied donkeys. The study animals were tagged for identification and housed communally in an indoor pen until the day 0 of the trial. The animals were kept indoors and fed hay-based diet. Water was provided *ad libitum* throughout the course of the study. This investigation was approved by the Animal Ethic Committee of University of Naples Federico II.

2.2. Experimental groups

On day−3, 21 of the experimental donkeys had an average of 1101 ± 583 EPG. The animals were ranked from lowest to highest EPG counts. Based on increasing EPG counts, replicates of 3 animals were formed. Within each replicate, animals were randomly assigned to treatment. The 21 selected donkeys were assigned consecutively to the following treatment groups of 7 animals each: PYR paste treated group (PYR-P group), PYR granule treated group (PYR-G-group), and untreated control group (C-group).

2.3. Drug administration

Commercially available equine formulations of PYR paste (Strike PYR paste pamoate 38%, Acme, Italy) and PYR pamoate granulate (Strike, PYR pamoate 20%, Acme, Italy) licensed for horses were administered orally to donkeys at a recommended dosage rate of 20 mg/kg B.W. which equals 6.94 mg/kg PYR base.

2.4. Sampling procedure

Heparinized blood samples were collected by jugular venipuncture prior to drug administration and 1, 2, 4, 8, 12, 16, 24, 30, 36, 48, 56, 72, 96, 120 and 144 h thereafter. Faecal samples (>10 g) were collected per rectum throughout the blood-sampling period, before drug administration and then at 4, 8, 12, 16, 24, 30, 36, 48, 56, 72, 96 and 120 h in order to determine faecal excretion of PYR under study. Blood samples were centrifuged at $1825 \times g$ for 30 min and plasma was transferred to plastic tubes. All the plasma and faecal samples were stored at −20 °C until estimation of drug concentration.

2.5. Analytical procedure

The parent compound of PYR was analysed by high performance liquid chromatography (HPLC). The liquid–liquid phase extraction procedure used for PYR was adapted from that described by McKellar et al. (1993a). Briefly, 1 ml drug-free plasma samples were fortified with PYR standard to reach the following final concentrations: 0.01, 0.05, 0.1, 0.5, 1 and 5 μg/ml. Morantel citrate was used as an internal standard. Sodium hydroxide (NaOH) (0.5 ml, 0.4 M) was added to tubes. After vortex for 15 s, 6 ml chloroform was added. The tubes were shaken for 2 min. After centrifugation at $2000 \times g$ for 15 min, 4 ml of the organic phase was transferred to the glass tube and evaporated to dryness at 43 (C in a sample concentrator—Maxi-dry plus, Heto Lab. Equipment, Denmark). The dry residue was dissolved in