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Dose Titration Study of Praziquantel Oral Paste (170.02/60008) in the Treatment of Dogs Experimentally Infected with *Echinococcus granulosus*

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Abstract: A control trial study was conducted on 36 selected healthy vaccinated dogs, experimentally infected with *Echinococcus granulosus* (10000 viable protoscoleces/ 2 successive days for each animal). The study was designed to compare the efficacy of 4 tested drugs in a new paste formulation and various concentrations of praziquantel (2.5-10 mg PZQ/kg B.W.) and Droncit® tablets as a reference drug in treatment of *E. granulosus* infection in dogs. A single or fractionated administered dose of treatment with these oral pastes or Droncit® tablets (5 mg PZQ/kg B.W.) gave a similar degree of efficacy (100% clearance) against immature forms of *E. granulosus*. According to the experimental design, animals were examined after necropsy for worm burdens at 5, 7 and 9 days post treatment. Adverse reactions or side effects were not observed in the treated dogs. No serious risk was involved in administering the tested drugs. The administered pastes given orally were well tolerated without observable adverse effects. These new pharmaceutical preparations of praziquantel were effective and extremely convenient to administer for treatment of *E. granulosus* infection in dogs.

Key words: Praziquantel · *Echinococcus granulosus* · dog · protoscoleces · infection · treatment

INTRODUCTION

Echinococcosis is a zoonotic infection of public health importance caused by adult or larval (metacestode) stages of cestodes belonging to the genus *Echinococcus* and the family *Taeniidae*.Four species of *Echinococcus* are recognized namely *Echinococcus granulosus, E. mutilocularis, E. oligarthus and E. Vogeli. E. granulosus* has a cosmopolitan geographic distribution. The definitive hosts are, predominantly the domestic dogs and other wild canids of several genera may be involved, causing the intestinal form of echinococcosis which does not induce any major ill effects to the host [1, 2]. Infection with the metacestode stage of *Echinococcus spp.* occurs not only in a broad spectrum of natural intermediate host species, but also in accidental hosts. The *E. granulosus* infection in intermediate hosts (humans, sheep, cattle, buffaloes, camels, pigs, equines…etc) is typically asymptomatic. The infection with metacestodes of intermediate hosts may cause severe and lethal disease in horse [3].

Dogs are popular domestic pets, their life style is closely related to humans.

They represent an increasingly important point of direct contact between human and *E. granulosus* in both urban and rural environments.Therefore, regular anthelmintic treatment of dogs is being promoted now to minimize the risk or hazard for humans and for controlling transmission of unilocular echinococeosis to humans.

The control of any infections agents requires a well knowledge of the taxonomy and transmission cycles which perpetuate the agent in nature. This is essential for survillance and predictive epidemiology and in determining the aetiology and appropriate treatment regimes.Many studies have been dealt with treatment and control strategies of Echinococcosis/hydatidosis problem either in the definitive host or intermediate host levels, in both human and animals.These studies evaluated the selected drugs alone as Praziquantel [4 -11]. Praziquantel Also, under trade name of Droncit® or Droncit® spot-on, [12] Epsiprantel, [13], Mebendazole, [14]; Oxfendazole, [15]; Nitroscanate, [5]; Niclosamide; [16];

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Fospirate, [17]; Diuredosan, [18]; Biothionol Sulphoxide, [19]; Bunamidine Hydrochloride, [20]. Even as Streptothricin family was used against *E. granulosus* infection in dogs [21].Studying the comparative value of mixed or combination therapy of some of the previous pharmaceutical preparations as albendazole, mebendazole, praziquantel, pyrantel and febantel was performed by [22-24]. In addition, arecoline and bunamidine were used together to promote their effectiveness in the treatment of *E. granulosus* infection in dogs [25]. Concentration, dose, formulation, routes of administration and exposed time of these drug preparation were also evaluated for their effictiveness and efficacy against *Echinococcus* infections [11, 26]. Treating dogs with praziquantel (Droncit® & Drontal®) in tablets form is eventful and can be difficult due to easy vomiting and difficult swallowing. A new easy form or worming treatment for dogs is needed. Due to contradictory and conflicting results of some drugs against *E. granulosus* infection among definitive host, domestic dog, *Canis familiaris*, the present study aimed at:

Assess the efficacy of praziquantel in a new paste formulation against *E. granulosus* experimental infection in dogs.

The clinical assessment of the dogs tolerance of the product.

Evaluating comparatively the effect of this new paste formula (4 test products) and Droncit®, as a reference drug.

MATERIALS AND METHODS

Animals: The participating animals were housed under confinement conditions and remained in the professional care of the test facility for the duration of the study. The test facility was complied with pertinent animal welfare regulations during confinement and scientific procedures.Although arrival dates may differ, the onset date (Day-14) was the same for all animals as one group. Final housing was available at least 7 days prior to the start of the study (Day-7) to allow suitable acclimation to the surroundings and feed. Puppies had been kept individually in stable/pens, with sufficient air space and no contact with animals not participating in the study. The animals were subjected to ambient conditions and complete diagram of the test facilities, including details on the orientation of operational buildings, facilities, pen/box dimension and the location of feeding and watering equipment.

Thirty six weaned puppies 2-3 months were involved in the study trial. The study is divided into two replicates. Both replicates are conducted similarly with 18 puppies. In each replicate, 18 puppies were vaccinated selected, dewormed and distributed into six treatment groups of 3 dogs. The animals were vaccinated before the acclimation period. Prophylactic or therapeutic treatment are neither anticipated or allowed with exception of Drontal® plus and a weekly treatment against fleas.

Feed: A dry commercial feed was available in both quantity and quality necessary for maintenance. The feed contains no anthelmintic ingredients. The constituents of the diet is not changed during acclimation or the study period. Tested animals were starved 12 hrs prior necropsy to minimize the volume of processed ingesta.

Canido Euro-Mix (20 kg), Germany was used as complete pet food for dogs.The feed contains no artificial colouring and flavouring agents. Storage in a dry and cool space. Fully grown, normally active dogs need a daily quantity of food as listed below.

Dog weight (kg)	5 kg	6-10 kg	11-20 kg	21-30 kg
Quantity/gram	65-110 g	110-190g	190-315g	315-430 g

The feed could be introduced as feed simply dry or as mix in warm water, stir a little and the meal list ready. Clean fresh water is provided *ad libitum*. The water contains no anthelmintic ingredients and is not expected to contain contaminants to avoid any negative impact on the study.

Protoscoleces: *E. granulosus* protoscoleces were obtained from fertile hydatid cysts recovered from the lungs of naturally infected camels on Day 0. Viability of protoscoleces was checked by Eosin exclusion dye test [27] and observation of flame cell activity [28]. The used protoscoleces for experimental infection had a mean viability of at least 75%.An homogenous suspension containing approximately 10000 viable protoscoleces was given orally to each animal on day 0 in each replicate (group A to F) and similar dose was fed at the next day (Day 1) [29].

Treatment preparation and administration: Group A, animals were left as untreated positive controls. All treatments (according to the last individual body weight determined on Day 25 for the first replicate and Day 19 for the second replicate), were given between 8.00 and

11.00 A.M. on Day 26 and Day 20 for both 1st and 2nd replicates, respectively. Groups B,C,D,E and F of both replicates were treated before the morning feeding.

Treatment in groups B to E: The posology to be given to the dogs is corresponded to 1.5 g the 170.02 oral paste per 2kg body weight. The quantity of paste for each dog was calculated as follows: the actual volume of the evacuated syringe was 6ml. The volume is equal to 8 kg body weight, according to the instructions of Virbac, S.A. So one kg B.W = 6/8 = 0.75 ml paste/kg B.W. the syringes were labeled and marked according to each tested batch from the oral pastes.

Batches No. are BRA 01248 contains 5.0 mg PZQ/kg B.W.BRA 01249 contains 2.5 mg PZQ/kg B.W.BRA 01250 contains 10 mg PZQ/kg B.W&BRA 01254 contains 5.0 mg PZQ/kg B.W.Each dog has been received the number of graduation corresponding to the last body weight. The tested paste was administered from syringes as follows: the paste had been delivered directly on the tip of the tongue into the dog mouth. The mouth was kept tightly closed for few seconds after dosing and help the dog to swallow the paste by massaging the throat. If paste is rejected, re-administration of the paste had been performed again.

Treatment in group F: The reference product (Droncit® tablets) at a dose of 5 mg PZQ/kg B.W. had been given to each animal directly into the mouth. The number of tablets given to each dog was calculated according to the last body weight (1 Tablet/10 kg B.W.). Droncit® tablets are divisable and doses were adjusted to the nearest ¼ tablets. A scale giving the number of graduation for a given body-weight were available from the study monitor.

Animals autopsy: Infected animals were starved 12 hours before being killed on days 31,33 and 35 for the first replicate and on Days 25,27 and 29 for the second replicate (one animal per day for each group).Animals were euthanised after intramuscular injection with anaethetic agent Zoletil® 50 VIRBAC S.A., at the dose of 1 ml/3 kg B.W, followed by total exsanguinations.The infected dogs of each group were killed separately. The small intestine of each dog was cut into three sections and opened longitudinally. Each section was placed in warm saline (0.9% NaCl) for at least one hour, to help the easy detachment of *Echinococcus* worms form the intestinal mucosa.The worms were left for sedimentation. The supernatant was discarded and replaced by a fixative solution containing 10% formaline. The obtained material were washed several times through sieves for easy separation of the worms from the mucous and debris. Finally, the supernatant was adjusted to 100 ml of the fixative solution in which the worms were counted. At each step the used beaker(s) were labeled with the number of the dog, according each group and replicate for accuracy. Special attention was paid to avoid any confusion or worm losses during the process.On days 32,34 and 36 for the first replicate and on days 26, 28 and 30 for the second replicate, *E. granulosus* worms (segmental stages) in each section were counted with the aid of stereo-microscope/binocular lens. From a 5% homogenous aliquot (mean of three samples of 5ml that taken from the homogenous suspension of the 100 ml described above).In case of a low worm burden for a given dog i.e. *E. granulosus* worm counts comprised between 0 and 20, three other samples of 5 ml (from the original 100 ml) were counted in order to check 30% of the contents of the small intestine.

RESULTS

E. granulosus were recovered from all dogs in untreated control positive groups either in replicate 1 or 2. (Table 1 and 2). The worm burdens ranged between 2460-8800 per dog Variation in parasite development was observed within the same period of infection. *Echinococcus* worms were observed concentrated in the proximal third of the small intestine Generally, *E. granulosus*, worms of the untreated (A), positive control group (replicate 1) showed distinct growth, banding and segmentation is very clear. Common genital pore is also observed at the last segment as well as cirrus and testes. Whereas the *Echinococcus* worms of the untreated (A) group of the 2nd replicate revealed relative lower growth, distinct banding and segmentation, also, appearance of cirrus and testes were noted.Inspite the varied concentration of PZQ within the 4 used tested oral pastes, no worms were recovered from any of the animal groups from B to E either in replicate 1 or 2 with exception of one dog in the D group (first replicate, 0785, female) revealed 3 *Echninococcus* worms (Table 1). These parasites were damaged, dewarfed and stunted in their growth. For accuracy we examined the whole intestinal suspension (100 ml) to avoid any worm losses and prove that the efficacy of the tested paste is high. F group (Droncit group), treated dogs revealed no worms in both replicates. Whatever the replicate, all the treated groups

Table 1: Efficacy of Praziquntel oral paste in the treatment of *E. granulosus* infection in dogs (Replicate one)

Dog Identification	D-25 body weight	Group (treatment)	Quantity of product administere (in tablets or ml) D-26	D-27*	*E. granulosus* worm count at necropsy Total 1	Total 2 (if second counting)
0791,M.	5.4 kg	A	_	_	3040	_
0783,M.	2.7	A	_	_	8800	_
0796,F.	3.1	A	_	_	2460	_
0797,M.	4.0 Kg	B	1.6 ml	1.4 ml	0	0
0789,F.	6.5	B	2.6	2.3	0	0
0787,F.	3.5	B	1.4	1.2	0	0
0782,M.	4.3 Kg	C	1.7 ml	1.5 ml	0	0
0790,F.	5.0	C	2.0	1.8	0	0
0786,F.	3.5	C	1.4	1.2	0	0
0798,M.	4.1 Kg	D	1.6 ml	1.5 ml	0	0
0792,F.	5.8	D	2.3	2.1	0	0
0785,F.	3.2	D	1.3	1.1	Three worms*	0
0784,M.	3.2 Kg	E	1.3 ml	1.1	0	0
0788,M.	3.0	E	1.2	1.1	0	0
0795,F.	3.3	E	1.3	1.2	0	0
0781,M.	4.0 Kg	F	½ tab.	_	0	0
0780,M.	2.4	F	¼	_	0	0
0794,F.	3.0	F	½ tab.	_	0	0

*These worms were small, damaged, degenerated and showed stunted growth, *Re-administration of product for 2 sucessive days

Table 2: Efficacy of Praziquntel oral paste in the treatment of *E. granulosus* infection in dogs(replicate two)

Dog Identification	D-19 body weight	Group (treatment)	Quantity of product administere (in tablets or ml) D-20	*E. granulosus* worm count at necropsy Total 1	Total 2 (if second counting)
0 153,M	6.3 Kg	A	_	5340	_
0 161,F	6.8	A	_	3740	_
0 155,F	4.3	A	_	6100	_
0 146,M	7.0	B	5.3 ml	0	0
0 136,M	4.3	B	3.2	0	0
0 149,F	6.4	B	4.8	0	0
0 151,M	5.2	C	3.9	0	0
0 156,M	3.4	C	2.6	0	0
0 165,F	3.4 Kg	C	2.6	0	0
0 145,M	4.7	D	3.5	0	0
0 160,M	3.9	D	2.9	0	0
0 148,F	5.4	D	4.1	0	0
0 162,M	6.8	E	5.1	0	0
0 140,F	7.2	E	5.4	0	0
0 141,F	3.6	E	2.7 ml	0	0
0 164,M	5.8	F	¾ tab.	0	0
0 158,F	7.7	F	¾ tab.	0	0
0 144,F	3.8 Kg	F	½ tab.	0	0

*Administration of oral paste in one dose at 20 d.p.i., * Necrospy at 5,7 & 9 days after treatment as 1st replicate

demonstrated 100% reduction in worm counts. The modification of the treatment date and the fraction dose administration in replicate No. 1 did not have any impact on the results of the study (Table 1 and 2). No serious adverse reaction were noted after treatment and during this trial study. Excessive salivation was noted in some dogs after treatment but, it is not considered serious event. This excessive salivation began from 5 to 30 min after paste administration. All animals were examined 5, 7 and 9 days post treatment in both replicates. The difference between the treated and untreated groups were clear but there was no obvious differences between the 4 tested pastes and Droncit group.

DISCUSSION

Until the late 1970s, treatment of *Echinococcus granulosus* in the canine definitive host depended on purging with arecoline hydrobromide. The value of this drug is its expulsion effect on worms for diagnosis. Up to 9 treatments or more might be needed to eliminate all worms in 99.9% of dogs [30]. However, it is time consuming, biohazardous, variable in sensitivity [7, 31] and it has failure rate of purgation (10-20%) [32]. The forementioned disadvantages make this method unsuitable. Recent studies had been focused on the use of chemotherapeutic drugs as praziquantel and others for treatment of canine echinococcosis as an effective alternative approach of arecoline purgation. In most of the studies, a single oral administration of praziquantel (PZQ) (5.0 mg kg^{-1} B.W.) was 100% effective against *E.granulosus* and *E.multilocularis* in all of the treated dogs. Although the efficacy of praziquantel is highly reliable in almost all cases, the possibility of low residual worm burdens in some of the treated animals can not be excluded [33, 34].

The current study describes the use of 4 different concentrations of praziquanel in a new oral paste formulations for treatment of *E.granulosus* in experimentally infected dogs.The results indicated that the 4 concentration were highly effective (100% clearance) in removing *E.granulosus* worms from the small intestine of dogs infected with immature infections of (26-days-old) and (20-days-old) parasites in both replicates, respectively. Comparable approach was adopted by [35]. They administered Droncit® orally in tablet form at dose rates of 1.25, 2.5, 5.0 and 10.0 mg PZQ/kg B.W. against immature stages of *E. granulosus* and at a dose rate of 5.0 mg PZQ/kg B.W. against gravid worms. Droncit® was found to be 100% effective against both immature and gravid worms.They added that adverse reactions were not observed in the treated dogs and no risk was involved at administration of the drug. However, [36] mentioned that few dogs remained infected with *E. granulosus* after a single treatment within the range of dose rates tested (0-31 mg kg^{-1} to 10-0 mg PZQ/kg B.W.). No toxicity to dogs was observed.

It is worthy to note that many studies utilized praziquantel in treatment and control of *Echinococcus* infection [6,8-10]. Although, the use of praziquantel is common as effective anthelmintic against tape worms of dogs and cats. A 100% efficacy will be normally achieved by a single treatment of praziquantel. In some cases, it does not usually lead to satisfactory results, low residual worm burdens may be persist after this treatment [7]. These results encouraged the adoption of our approach in the present study which proved promising success (100% efficacy) among the treated infected dogs of first and second replicates, respectively.

Presumably, not all the routes of praziquantel administration are equal or specific in their efficacy against *Echinococcus* infection [37]. They mentioned that the oral and intramuscular routes exhibited similar efficacy in treatment of dogs infected with *E.granulosus* but less effective by the subcutaneous route. This may explain the less specificity or sensitivity of subcutaneous route than other routes. However, [38,39] stated that praziquantel compound was efficacious (100% clearance) if injected via either routes, subcutaneously and intramuscularly or if administered orally at a dose level of 5 mg kg^{-1} B.W. against mature and immature *E. granulosus*. Such of these results may be promote selection of one of these routes to be specific which could be of great value in both specific treatment and control of *Echinococcus* infection in dogs.

It is clear that the use of several concentrations of praziquantel ranged from 2.5-10 mg kg^{-1} B.W. were found useful in evaluation of the tested drug efficacy. Although the time of treatment was different in the two replicates (26 and 20 days post infection, respectively), the dose was divided per two days in the first replicate and the necropsy was carried out 5, 7 and 9 days treatment, all groups of both replicates from B to E proved 100% reduction in the worm burdens indicating higher efficacy of these new oral paste formulations. Exceptionally, we found few (3 damaged, dewarfed and stunted growth) worms *E. granulosus* at necropsy (5 days post treatment).

Interestingly, the study revealed that all evaluated praziquantel concentrations either low or high ones proved 100% elimination of *Echinococcus worms* from all dogs. It was found that the way to mask the bitterness of

PZQ has not an impact an drug efficacy in the two similar concentrations (5 mg PZQ/kg B.W.). The new oral paste formulations after these satisfactory results was extremely convenient to administer for treatment of *E. granulosus* infection in dogs. The high efficacy of the tested drug observed in this study may be attributed to the sensitivity and specificity of the oral paste and the experimental design. Collectively, minimum concentration of praziquantel 2.5 mg PZQ/kg B.W. was sufficient for total clearance of *E.granulosus* worms. So, it has the potential to reduce the prevalence of *Echinococcus* infection in dogs. In this aspect [40] found that a single oral dose at 1 mg PZQ/kg B.W. completely removed 14-days-old *T. hydatigena* infection in all dogs. 2.5 mg PZQ/kg was completely effective against 7, 14 and 28-days-old worms whereas 5.5 mg PZQ/kg completely removed two-days-old infection. No side effects were seen in any treated dogs. Contrary to this finding, total clearance of 41-day-old *E. granulosus* worms only occurred in dogs given the highest dose of epsiprantel 7.5 mg kg^{-1}. [41], Whereas in 7-day-old infections, doses of 5, 7.5 and 10 mg kg^{-1} produced greater than 94, 90 and 99.8% reduction in worm burdens [13]. Moreover, [12], indicated that praziquantel applied dermally at a dose of 8 mg kg^{-1} B.W. was highly effective in removing immature and mature forms of *E. multilocularis* from the small intestine of infected cats.

The tolerance of praziquantel was noted at the various concentration ranged between 2.5-10 mg PZQ/kg B.W. after treatment till the end of the study. Results indicated that no toxicity to any dog, no side effects, no adverse reactions and no serious events were observed in treated animals, with exception, some dogs showed only excessive salivation. So, the dogs were well tolerated at administration of this new oral paste formulations. In this aspect the tolerance of praziquantel in oral doses 1x20 mg kg^{-1}, 1x50 mg kg^{-1}, 3 x10 mg kg^{-1} and 3x35 mg kg^{-1} B.W. in normal volunteers. No clinically relevant changes were found in any of the laboratory parameters, nor in the medical-neurological or clinico-physiological examinations [42]. Moreover, praziquantel is safe (safety index in dogs >36) to use in pregnant animals and dogs tolerate high doses for extended period without organ damage or disturbance to the reproductive process [43, 44].In contrast to praziquantel, epsiprantel is poorly absorbed by the host. Therefore, a direct action against tapeworms is assumed [45]. Various other drugs are partially effective against *E. granulosus* infection, but they do not reach the efficacy level of praziquantel or epsiprantel.Because, of its very wide therapeutic index [43], praziquantel is particularly suited for eradication programmes e.g. echinococcosis but, it is proposed that a mass-dog dosing schedule using praziquantel should take into consideration the short prepatent period of *E. granulosus*. Treating dogs with praziquantel should be at intervals 6, 12 and 16 weeks. Six weeks interval was based on the prepatent period of *E.granulosus* infection whereas 12 and 16 week intervals were based on the rate of reinfection with tapeworms in dogs. Dogs had become reinfected with *E.granulosus* between 2 and 4 months after treatment [11]. Sporadic petecheal haemorrhage areas were observed in the small intestine at necropsy. Inspite of these changes no other pathological lesions were noted in any internal organs. It is not clear, if worms select specific sites which provide the most favourable condition for the development or whether there is a relationship between site for selection and host immune response. An association was found between heightened, gut immune response and *E.granulosus* infection [46]. However, this response is confounded by variability of worm burdens and parasite development. A very interesting observation was that most of the infected dogs did not show the clinical symptoms of an intestinal parasitic infection such as diarrhoea, emaciations and mucoid discharge. So, the *Echinococcus* infection is very serious as these dogs have not any clinical manifestations and at the same time had a wide spread transmission to human and animals. The same finding was also observed by [2].

In conclusion, treatment of *E.granulosus* infection in dogs using various concentrations of praziquantel as a new oral paste formulation has been carried out with complete success and satisfactory results. The 4 tested oral pastes were found to be 100% effective against *E.granulosus* infection in dogs. A higher dose of 10 mg kg^{-1} B.W. PZQ did not increase the average efficacy. They could be a promising pharmaceutical preparations of choice in the future.Simple antibiotic such as Neomycin sulphate and coating substances as Koalin should be added to the tested paste to protect the intestinal mucosa of the host from the marked inflammation during development of *E. granulosus*, if these proposed materials have not negative impact on the activity of oral pastes, very useful results will be obtained.

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