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Short Communication

Efficacy of a single high oxfendazole dose against gastrointestinal nematodes in naturally infected pigs

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ABSTRACT

The goal of the current experiment was to assess the clinical efficacy of oxfendazole (OFZ) administered as a single oral dose (30 mg/kg) to pigs naturally parasitized with *Ascaris suum*, *Oesophagostomum* spp., *Metastrongylus* spp. and *Trichuris suis*. Thirty-six local eco-type piglets were divided into three independent experiments, named I, II and III ($n = 12$ each), respectively. Each experiment involved two different groups ($n = 6$): Untreated Control and OFZ treated. Animals were naturally parasitized with *A. suum* (Experiments I, II and III), *Oesophagostomum* spp. (Experiments I and II), *T. suis* (Experiments II and III) and *Metastrongylus* spp. (Experiment I). Pigs in the treated group received OFZ (Synanthic[®], Merial Ltd., 9.06% suspension) orally at 30 mg/kg dose. At five (5) days post-treatment, animals were sacrificed and the clinical efficacy of the OFZ treatment was established following the currently available WAAVP guidelines for a controlled efficacy test. None of the animals involved in this experiment showed any adverse events during the study. OFZ treatment given as a single 30 mg/kg oral dose showed a 100% efficacy against all the nematode parasites present in the three experiments. In conclusion, under the current experimental conditions, OFZ orally administered to naturally parasitized piglets at a single dose of 30 mg/kg was safe and highly efficacious (100%) against adult stages of *A. suum*, *Oesophagostomum* spp., *T. suis* and *Metastrongylus* spp.

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1. Introduction

Oxfendazole (OFZ), a benzimidazole (BZD) methylcarbamate compound, has demonstrated activity against *Taenia solium* cysticercus in pigs after its single oral administration at 30 mg/kg (Gonzalez et al., 1996). OFZ treatment of *T. solium*-infected pigs has been proposed as a tool to

interrupt the transmission cycle of this parasite, protecting people from neurocysticercosis, the most common parasitic infection of the human nervous system and the most frequent preventable cause of epilepsy in the developing world and endemic in many countries of Latin America, Africa and Asia (Gonzalez et al., 1996). The WHO estimated that globally, the parasite is estimated to cause 50 million human cases of taeniasis (infection with adult tapeworms) and cysticercosis, and 50,000 human deaths a year in Africa, Asia and Latin America (WHO, 2012).

Even if OFZ has proven efficacious against cysticercosis, many of the poorest livestock keepers whose pigs are affected are not aware of the problem, and hence reluctant

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to treat the pigs. The objective of this project was to demonstrate the efficacy against other parasites relevant in rural settings for pigs, making the use of OFZ more attractive to the poorest livestock keepers. OFZ was first marketed to be used in cattle, sheep and horses. An oral single dose is recommended in those species for the removal and control of tapeworms (heads and segments), abomasal and intestinal nematodes (adults and 4th stage larvae) and lungworms (adults and larval stages; Lanusse et al., 2009). Additionally, the anthelmintic activity of OFZ against *Trichuris vulpis* in dogs has been assessed (Dorchies and Arnaud, 1995), after its oral administration at a dose of 11.3 mg/kg/day for three consecutive days. However, OFZ has not been approved for use in pigs. Helminth parasite infections occur frequently in domestic pigs in different production systems worldwide (Roepstorff et al., 2011). The major helminth species include *Ascaris suum*, *Trichuris suis* and *Oesophagostomum* spp. (Roepstorff et al., 2011). A high prevalence of helminth infections has been found in organic pig farms (Carstensen et al., 2002). Despite the common subclinical course of infections, pigs infected with one or more of the above mentioned nematode species have shown reduced food utilisation and growth rates (Hale and Stewart, 1979; Hale et al., 1981, 1985).

Flubendazole (FLBZ; Bradley et al., 1983; Vanparijs et al., 1988), oxbendazole (OBZ; Muirhead and Alexander, 1997; Taylor, 2006) and fenbendazole (FBZ) (Corwin et al., 1984; Marchiondo and Szanto, 1987; Praslicka et al., 1997) are among the methyl-carbamate BZD compounds known to be effective in pigs. However, anthelmintic treatments in pigs with those drugs are commonly performed by mixing the drug into feed for 3 to 10 days. The potential of OFZ for use at the 30 mg/kg dose rate against helminth parasites in pigs should be investigated to prove a broader therapeutic indication for this anthelmintic compound when used at a single dose as indicated for the treatment of porcine cysticercosis. The goal of the current work was to assess the clinical efficacy of a 9.06% OFZ suspension administered as a single oral dose (30 mg/kg) in pigs naturally parasitized with *A. suum*, *Oesophagostomum* spp., *T. suis* and *Metastrongylus* spp.

2. Material and methods

2.1. Animals

Local ecotype commercial pigs naturally parasitized with adult gastrointestinal and lung nematodes were involved in three different experimental trials, Experiments I, II and III. Pigs were fed *ad libitum* with a commercial balanced food and had free access to water. A 15 days acclimatization period was allowed for the experimental animals. Animals were housed in two different pens with concrete floors, protected from rain and prevailing winds, but without temperature control.

2.2. Parasitological methods

In Experiment I, twelve pigs (18.8 ± 5.4 kg, 2.5–3 months old), naturally parasitized with adult *A. suum*, *Metastrongylus* spp. and *Oesophagostomum* spp. were randomly

distributed into two groups ($n = 6$ each): Untreated control and OFZ treated groups. Parasite infection (*A. suum* and *Oesophagostomum* spp.) was confirmed by faecal egg counts (FEC) performed by the McMaster technique modified by Roberts and O'Sullivan (1950). *Metastrongylus* spp. infection was confirmed after a test tube flotation test. The identification of eggs was assessed according to egg morphology (Soulsby, 1987). All animals were naturally infected with the above mentioned helminth nematode parasites.

In Experiment II, twelve pigs (34.0 ± 5.6 kg, 3.5–4 months old), naturally parasitized with adult *A. suum*, *Oesophagostomum* spp. and *T. suis*, were randomly distributed into two groups ($n = 6$ each) as previously described. Parasite infection was confirmed by FEC. All animals were parasitized with *A. suum* and *Oesophagostomum* spp.; according to faecal analysis, two animals from the untreated control and three animals from the OFZ treated Group were positive for *T. suis*.

In Experiment III, twelve pigs (43.8 ± 5.9 kg, 5–6 months old), naturally parasitized with adult *A. suum* and *T. suis*, were randomly distributed into two groups ($n = 6$ each) as previously described for Experiment I. Parasite infection was confirmed by faecal egg counts. All animals were infected with the mentioned parasites.

2.3. Treatment

In all experiments, treatment was performed by oral administration of OFZ (Synanthic®, OFZ 9.06%, Merial, France) at the dose of 30 mg/kg.

2.4. Efficacy assessment

Five days after treatment animals were sacrificed and direct nematode counts of animals from the untreated control and OFZ treated groups were performed following the WAAVP guidelines (Hennessy et al., 2006). The total number of *A. suum* (small intestine), *Metastrongylus* spp. (lungs), *Oesophagostomum* spp. and *T. suis* (large intestine) was assessed. The OFZ efficacy was determined by the comparison of worm burdens in treated versus untreated control animals. The following equation expresses the percentage of efficacy (%E) against a given parasite species (S) in a single OFZ treated group (T) when compared with an untreated control (C): $\%E = [(mean\ of\ S\ in\ C - mean\ of\ S\ in\ T) / mean\ of\ S\ in\ C] \times 100$. The geometric mean was used as it most accurately represents the distribution of nematode populations within each group (Hennessy et al., 2006). Animal procedures and management protocols were carried out in accordance with the Animal Welfare Policy (Act 087/02) of the Faculty of Veterinary Medicine, Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA), Tandil, Argentina (<http://www.vet.unicen.edu.ar>).

3. Results

The faecal egg counts (mean \pm SD) obtained for the untreated control and OFZ treated group in Experiment I, II and III, are shown in Table 1. In the three experiments and according to parasite egg counts, animals were

Table 1

Nematode egg counts (epg, arithmetic mean and range) obtained from animals involved in Experiment I, II and III ($n = 6$ each), before (trial day -1) oxfendazole (OFZ) oral administration (30 mg/kg) to naturally parasitized pigs.

	Mean faecal egg counts (range) day -1			
	Untreated control		OFZ treated	
Experiment I				
<i>Ascaris suum</i>	6097	(400–20,840)	4440	(960–10,960)
<i>Metastrongylus</i> spp.	++		++	
<i>Strongylida</i>	1667	(280–3840)	1417	(220–3860)
Experiment II				
<i>Ascaris suum</i>	13,930	(140–53,840)	2870	(40–8980)
<i>Strongylida</i>	3843	(100–9940)	4877	(60–14,960)
<i>Trichuris suis</i>	17	(0–40)	7	(0–20)
Experiment III				
<i>Ascaris suum</i>	26,333	(10,800–54,000)	23,840	(18,240–31,120)
<i>Trichuris suis</i>	147	(60–220)	152	(40–280)

++ Indicate the presence of *Metastrongylus* spp. egg in faeces.

parasitized with a medium–high number of parasites, with the exception of *T. suis* burdens in animals in Experiment II, in which a low number of *Trichuris* eggs was observed in some animals from each group. Furthermore, since in this experiment only three animals from the treated group were positive to *Trichuris* in the FEC analysis at day -1, efficacy against this parasite could not be statistically assessed. The adult nematode counts and resultant clinical efficacy obtained for the OFZ treated animals and nematode counts in untreated control (Experiments I, II and III) are shown in Table 2. A large variation in worm burdens was observed among experimental animals. Furthermore, a 100% OFZ efficacy against all parasites assessed in Experiment I, II and III, was observed.

4. Discussion

None of the animals involved in the current trials showed any adverse events during the study. This was in agreement with a previously reported trial where the 9.06% OFZ formulation was orally administered to pigs at 30, 90 and 150 mg/kg daily for three consecutive days, without any significant change on the health status of the treated pigs (Alvarez et al., 2012a). The variation in worm burdens observed among experimental animals could be considered normal even among animals from the same herd, and may be due to differences in the immunological status of individual animals. OFZ treatment given as a single 30 mg/kg oral dose was highly efficacious (100%, $P < 0.05$) against *A. suum* (Experiment I, II and III), *Oesophagostomum* spp. (Experiment I and II), *Metastrongylus* spp. (Experiment I) and *T. suis* (Experiment III).

As a common practice, pig farmers administer anthelmintics mixed with food or water from one to ten consecutive days. The use of BZD compounds as broad-spectrum anthelmintics in all age groups of pigs is a common practice in different regions of the world (Theodoropoulos et al., 2001; Beloeil et al., 2003). The industrialized, indoor-type pig production systems facilitate drug administration in food. However, this practice could be hampered in extensive production systems, such as those observed in some areas of developing countries, where porcine cysticercosis is common (Acha and Szyfres, 1986). In such cases, the oral single-dose

therapy is an easier and more practical technique for pig deworming.

The increase on ABZ dose rate in sheep was associated with enhancement in the plasma exposure of ABZ metabolites (Alvarez et al., 2012b). In the same way, a 235% increment in OFZ plasma concentration in pigs, was observed at 5 days post-treatment after 90 mg/kg ($5.7 \pm 2.6 \mu\text{g/ml}$) compared with 30 mg/kg dose ($1.7 \pm 1.1 \mu\text{g/ml}$; Alvarez et al., 2012a). It is clear that at least under a certain dose range, the higher the OFZ dose given to pigs the greater the amount of drug absorbed at the GI level. The 30 mg/kg dose in pigs ensures high OFZ peak plasma concentration ($5.40 \pm 0.65 \mu\text{g/ml}$) and AUC ($209.9 \pm 33.9 \mu\text{g.h/ml}$) (Moreno et al., 2012). The enhancement in the OFZ plasma exposure after a single “high” dose of OFZ in pigs, may account for parasites being exposed to toxic drug concentrations for extended periods of time, explaining the high efficacy observed against different gastrointestinal and lung nematodes in the current work. It is important to highlight the high efficacy of OFZ against *T. suis*, a nematode parasite located in the large intestine and normally “refractive” to anthelmintic treatments. In fact, the single oral dose of FBZ failed to control this parasite (Biehl, 1986). On the other hand, the enhanced systemic drug exposure achieved after treatments with increased ABZ doses, correlated with significant increment in drug efficacy against a resistant *H. contortus* isolate in sheep (Barrère et al., 2012). The improved drug concentrations of active BZD molecules may account for a greater parasite exposure to active drug and increased anthelmintic efficacy. This statement is supported by previously reported work, where a general upward trend in the efficacy against nematodes was observed after the enhancement of BZD drug systemic availability (Ali and Hennessy, 1995; Hennessy et al., 1995; Moreno et al., 2004; Sanchez Bruni et al., 2005; Barrère et al., 2012) in different animal species.

In rural poor endemic settings where neurocysticercosis is a problem, farmers do not tend to deworm the pigs for cysticercosis due to the lack of awareness between the human disease and the pigs. In many cases the control of cysticercosis will be for the public good, where government or international organizations will have to intervene in a holistic manner, including not only the treatment in

Table 2
Adult nematode worm counts^a (range) and efficacy^b (%) obtained at 5 days post treatment with oxfendazole (OFZ, 30 mg/kg), by the oral route to pigs (n= 6 for each experimental group). Nematode worm counts recorded in the untreated control group are also shown.

Parasites	Experiment I			Experiment II			Experiment III		
	Untreated control	OFZ treated	Efficacy (%)	Untreated control	OFZ treated	Efficacy (%)	Untreated control	OFZ treated	Efficacy (%)
Small intestine									
<i>Ascaris suum</i>	41 (3–137)	0	100	29 (4–75)	0	100	51 (6–120)	0	100
Lung									
<i>Metastrongylus</i> spp.	120 (40–250)	0	100	–	–	–	–	–	–
Large intestine									
<i>Oesophagostomum</i> spp.	1268 (100–3000)	0	100	438 (80–1100)	0	100	–	–	–
<i>Trichuris suis</i>	–	–	–	12 (0–20)	0	100	185 (23–345)	0	100

^a Arithmetic means.

^b The percent of efficacy was calculated using geometric mean as suggested by Wood et al. (1995).

pigs, but also in humans, education and sanitation. Unfortunately, cysticercosis is not seen as a priority so other solutions need to be explored. A possibility to make the control a private good, would be to educate the farmers about the benefits of the intervention with OFZ. The expanded label claims of OFZ as demonstrated in these experiments might make the treatment more attractive for the farmers, and therefore more likely to be implemented. Treatment of pigs with OFZ would have to be combined with a vaccine for the prevention of new cases. A commercial cysticercosis vaccine based on the TSOL18 antigen developed by the University of Melbourne, and transferred to a commercial manufacturer (Indian Immunologicals Limited) with the support of the Global Alliance for Veterinary Medicines (GALVmed) is expected to be in the market soon. The bundling of the OFZ with the vaccine could be a tool to start controlling cysticercosis, while more holistic approaches take place.

In conclusion, OFZ administered as a single oral dose of 30 mg/kg to naturally parasitized pigs, was safe and highly efficacious (100%) against adult stages of *A. suum*, *Oesophagostomum* spp., *T. suis* and *Metastrongylus* spp. The findings reported here may have a great impact for parasite control in swine, particularly in those production systems where in-feed medication is not attractive from the practical point of view or where it can incentivise the use of OFZ for the control of cysticercosis.

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