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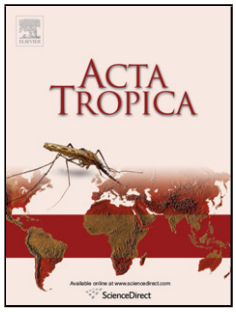

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PII: S0001-706X(14)00107-7
DOI: http://dx.doi.org/doi:10.1016/j.actatropica.2014.03.024
Reference: ACTROP 3331

To appear in: *Acta Tropica*

Received date: 27-12-2013
Revised date: 17-2-2014
Accepted date: 28-3-2014

Please cite this article as: Ortiz, P., Terrones, S., Cabrera, M., Hoban, C., Ceballos, L., Moreno, L., Canton, C., Donadeu, M., Lanusse, C., Alvarez, L.,Oxfendazole flukicidal activity in pigs, *Acta Tropica* (2014), http://dx.doi.org/10.1016/j.actatropica.2014.03.024

Oxfendazole flukicidal activity in pigs

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Running title: *Oxfendazole flukicidal activity in pigs*

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Abstract

Although oxfendazole (OFZ) is a well know broad-spectrum benzimidazole anthelmintic, the assessment of its potential trematodicidal activity remains unexplored. OFZ administration at single high doses has been recommended to control *Taenia solium* cysticercus in pigs. The current study investigated the flukicidal activity obtained after a single high (30 mg/kg) oral dose of OFZ in pigs harbouring a natural *Fasciola hepatica* infection. Sixteen (16) local ecotype pigs were randomly allocated into two (2) experimental groups of 8 animals each named as follow: Untreated control and OFZ treated, in which animals received OFZ (Synanthic®, Merial Ltd., 9.06% suspension) orally at 30 mg/kg. At seven (7) days post-treatment, all the animals were sacrificed and direct adult liver fluke counts were performed following the WAAVP guidelines. None of the animals involved in this experiment showed any adverse event during the study. OFZ treatment as a single 30 mg/kg oral dose showed a 100% efficacy against *F. hepatica*. In conclusion, the trial described here demonstrated an excellent OFZ activity against *F. hepatica* in naturally infected pigs, after its administration at a single oral dose of 30 mg/kg.

Key words: Oxfendazole, *Fasciola hepatica*, Efficacy, Pigs.

1. **Introduction**

Oxfendazole (OFZ) is a methyl-carbamate benzimidazole compound, indicated for the control of gastrointestinal and lung nematodes and cestodes. OFZ was first marketed to be used in cattle, sheep and horses. Additionally, OFZ has demonstrated activity against *Taenia solium* cysticercus in pigs after its single oral administration at 30 mg/kg (Gonzales 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 endemic areas of Latin America, Africa and Asia (Gonzales et al., 1996). The WHO estimated that globally, the parasite causes 50 million human cases of taeniasis (infection with adult tapeworms) and cysticercosis, and 50,000 human deaths per year in Africa, Asia and Latin America (WHO, 2012). In a recent study, 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 *Ascaris suum*, *Oesophagostomum* spp., *Trichuris suis* and *Metastrongylus* spp. (Alvarez et al., 2013).

Fascioliasis, caused by the trematode liver fluke *Fasciola hepatica*, is the cause of considerable loss in sheep and cattle production systems all over the world (Roberson and Courtney, 1995). Human fascioliasis occurs as an accidental zoonotic disease in Africa, Western Europe and Latin America (Mas-Coma et al., 2005). Considered a secondary zoonotic disease until the mid-1990s, human fascioliasis is at present emerging or re-emerging in many countries, including increases of prevalence and intensity and geographical expansion (Mas-Coma, 2005). Human fascioliasis is considered by the WHO as an important human parasitic diseases, with estimates of 2.4 million (Rim et al., 1994) up to 17 million infected people (Hopkins, 1992). These figures could be even larger depending upon the unknown situations in many countries, mainly in Asia and Africa (Mas-Coma, 2005). Sheep and cattle

are considered the main reservoir host species of *F. hepatica* (Hillyer et al., 1996; Mas-Coma et al., 1997; 1999) but other species may provide a reservoir of infection. Pigs may play an important role in fascioliasis transmission. For instance, fascioliasis has been reported in pigs from different geographical areas, including Africa (El-Rafaie et al., 1984), Asia (Boes et al., 2000) and South America (Mas-Coma et al., 1997). Valero and Mas-Coma (2000) found that there were no differences in the infectivity of the metacercariae between sheep, cattle and pig isolates from the Bolivian Altiplano, and in this geographical area *F. hepatica* adult development in the pig is similar to that observed in sheep and cattle. The available epidemiological data suggest that pigs may play an important role in fascioliasis transmission in hyperendemic areas and must, consequently, be taken into account when applying control measures (Valero et al., 2001).

The main strategy for the effective control of fascioliasis is based on chemotherapy. However, there are not anthelmintic compounds approved for the control of *F. hepatica* in pigs. The halogenated benzimidazole triclabendazole has demonstrated to be active against liver flukes in pigs artificially infected with *F. hepatica* metacercariae (Olaechea et al., 1989). However, at present triclabendazole is not indicated to be used in pigs. In spite of its broad-spectrum activity against gastrointestinal nematodes, OFZ is not indicated against *F. hepatica* (McKellar and Scott, 1990). However, some *in vitro* ovicidal activity against *F. hepatica* eggs was previously reported (Alvarez et al., 2009), and it is likely that a high dose of this benzimidazole compound may have flukicidal activity in domestic animals, including pigs. In fact, in a recent study (Gomez-Puerta et al., 2012) performed in sheep, flukicidal activity measured by the faecal egg count reduction test (FECRT), was reported after a single OFZ dose. The potential of OFZ use in pigs at 30 mg/kg as a single oral dose against *F. hepatica* should be investigated to search for a broader therapeutic indication for this anthelmintic compound, when used as a single oral dose for the treatment of porcine cysticercosis. The goal of the current work

was to assess the flukicidal activity of a 9.06% OFZ suspension administered as a single oral dose (30 mg/kg) in pigs naturally infected with *F. hepatica*.

2. Material and methods

2.1. Animals

Local ecotype commercial pigs naturally parasitized with *F. hepatica* were involved in the current trial. Pigs were fed *ad libitum* with a commercial balanced food and had free access to water. A 10 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. The animal phase of the current experiment was performed in the Faculty of Veterinary Science, Universidad Nacional de Cajamarca, Cajamarca, Perú.

2.2. Experimental design

Sixteen pigs (28.0 ± 4.9 kg, 6-7 months old), naturally parasitized with *F. hepatica* were randomly distributed into two groups (n= 8 each): Untreated control and OFZ treated group. Parasite infection was confirmed by faecal egg counts (FEC) performed according Mooney et al., (2009). Briefly, 3 g of faeces was added with water, and the contents was mixed thoroughly and poured through a tea strainer to remove large debris. The filtrate was then allowed sediment for 10 min after which the supernatant was siphoned off taking care not to disturb the sediment. The sediment was stained with two drops of methylene blue and the entire sediment were assessed for liver fluke eggs using an optical microscope (x40 magnification). The number of *F. hepatica* eggs observed was counted and the eggs per gram (epg) of faecal material was calculated. In the OFZ treated group, treatment was performed by oral

administration of OFZ (Synanthic®, OFZ 9.06%, Merial, France) at the dose of 30 mg/kg. Seven days after treatment, animals were sacrificed and direct trematode 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 *F. hepatica* was recovered and counted according to Hennessy et al., (2006). Briefly, at necropsy, the gall bladder and liver of pigs was examined for living and dead *F. hepatica*. After incising the gall bladder and bile ducts, the liver was cut along the large and small bile ducts and hepatic veins and searched for flukes. Then the liver was cut into thin slices (0.5–1.0 cm in width), soaked in warm (37 °C) saline in appropriate trays. The recovered liver flukes were transferred to Petri dishes, filled with saline, and examined for vitality and appearance. The evaluation of adult liver fluke burdens was done "blindly". 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 *F. hepatica* for the OFZ treated group (T) when compared with the untreated control (C): %E= [(mean of S in C – mean of S in T) / mean of S in C] x 100. The geometric mean was used as it most accurately represents the distribution of parasite populations within each group (Hennessy et al., 2006). The criterion for efficacy was statistically significant differences in fluke burdens between treated and untreated control groups and efficacy ≥ 90%. Nematode counts were compared by non parametric unpaired test (Mann-Whitney) of log-transformed data. A value of $P<0.05$ was considered statistically significant. The statistical analysis was performed using the Instat 3.0 Software (Graph Pad Software, CA, USA). Animal procedures and management protocols were carried out in accordance with the Animal Welfare Policy (Act 087/02) of the Faculty of Veterinary Science, Universidad Nacional de Cajamarca, Cajamarca, Peru.

3. Results

None of the animals involved in the current trial showed any adverse event 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, with a partial reduction on feed intake during two to three days post-treatment in the groups treated with the highest OFZ doses as the main clinical change on the health status of the treated pigs (Alvarez et al., 2012a). OFZ has a large therapeutic index in the mammalian host, which explains the absence of appreciable toxic effect in pigs treated with a single dose of 30 mg/kg. The individual FEC and adult liver fluke counts obtained for the untreated control and OFZ treated group, and the efficacy observed after the OFZ treatment are shown in Table 1.

A large variation in worm burdens was observed among experimental animals. In the control group, 4 to 140 adult flukes were recovered from the biliary duct. Furthermore, the FEC showed a large variability ranging from 1 to 820 eggs/3 g of faeces. However, no statistical difference ($P > 0.05$) was observed in FEC between the treated and untreated animals. Animal #4 in the untreated control group had an unusually high egg count in 3 g of faecal material (820). The variation in liver fluke burdens observed among experimental animals could be explained by the fact that them were obtained from different farms, likely with different environmental contamination levels. Consequently, experimental pigs could had been exposed to different metacercariae infection pressure. Even though the large parasite infection variability observed in the current trial, a high efficacy (100%) against *F. hepatica* in pigs was observed after the OFZ treatment at 30 mg/kg.

4. Discussion

Anthelmintic drugs are the main available tool to control parasitic infections, including liver flukes. There are many compounds derived from different chemical families approved as flukicidal drugs for use in sheep and cattle. However, available information on successful anthelmintic treatments against liver flukes in pigs is scarce. Earlier work by Olaechea et al., (1989) demonstrated the activity of triclabendazole at doses of 10 to 40 mg/kg, given to pigs at day 21 after the experimental infection with 100 *F. hepatica* metacercariae. However, no effective anthelmintic treatment is currently available for removing liver flukes from pigs. The use of benzimidazole 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 oral OFZ single-dose therapy is a practical and easy technique for pig deworming in extensive production systems, such as those observed in some areas in developing countries. This OFZ treatment is useful for cysticercosis (Gonzales et al., 1997) and adult nematode control (Alvarez et al., 2013). Additionally, the single OFZ oral administration at 30 mg/kg dose reached an outstanding flukicidal activity in the experimental work described here.

The benzimidazole anthelmintics active against *F. hepatica* include the methylcarbamate derivative albendazole, and the halogenated thiol benzimidazole derivative, triclabendazole. The pro-benzimidazole netobimin is also active against *F. hepatica*, but since it is metabolically converted to albendazole in the rumen of treated sheep/cattle (Lanusse and Prichard, 1993), its activity must be linked to albendazole. While albendazole activity is restricted to flukes older than 12 weeks (McKellar and Scott, 1990), triclabendazole has been shown to have an excellent efficacy against both the mature and immature adult stages of *F. hepatica* (Boray et al. 1983), which explain why this compound has been the drug of choice for treating liver fluke infections in livestock for over 20 years. In previous studies in sheep, OFZ at the oral dose of 5 and 15 mg/kg reached flukicidal efficacies of 14% and 20%,

respectively (Furmaga et al., 1982). This low efficacy could be related to a "pharmacodynamic limitation" due to a lack drug-receptor affinity. However, a recent report demonstrated that none of the sheep treated with OFZ (single oral dose, 30 mg/kg) showed *F. hepatica* eggs in faeces after 10 days of treatment (Gomez-Puerta et al., 2012). The same oral dose was highly effective against adult flukes in pigs, as show in the current reported trial. Thus, the limited efficacy observed in earlier efficacy trials appears to be due to a pharmacokinetic-based limited parasite exposure and/or a lower OFZ receptor affinity. As it has been described in nematodes (Alvarez et al., 2012b), the higher the OFZ accumulation within the liver fluke, the greater the resultant clinical efficacy.

The increase on the albendazole dose was associated with enhancement in the plasma exposure of its metabolites in sheep (Moreno et al., 2004; 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 ± 2.6 µg/mL) compared with 30 mg/kg dose (1.7 ± 1.1 µg/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. After OFZ treatment in pigs (30 mg/kg), an OFZ peak plasma concentration of 5.40 ± 0.65 µg/mL and an AUC of 209.9 ± 33.9 µg.h/mL were reported (Moreno et al., 2012). This OFZ plasma exposure is much larger than that observed in pigs, after the administration of the parent thioether fenbendazole, which is rapidly and extensively converted *in vivo* into its active sulphoxide metabolite OFZ (Lanusse and Prichard, 1993). After a fenbendazole oral dose (5 mg/kg) in pigs the observed OFZ peak plasma concentration (Cmax) and area under the plasma concentration vs time curve (AUC) values were 0.66 ± 0.22 µg/mL and 15.6 ± 5.24 µg.h/mL, respectively (Petersen and Friis, 2000). The high OFZ plasma exposure observed after a single OFZ dose of 30 mg/kg in pigs assures the trematode parasite being exposed to toxic drug concentrations for extended periods of time,

which may help to explain the high efficacy against *F. hepatica* in naturally infected pigs, described in the current work.

5. 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 *F. hepatica.* The findings reported here may have a great impact for liver fluke control in swine, particularly in those geographical areas where pigs play an important role as reservoirs for human fascioliasis.

6. Acknowledgments

The authors would like to acknowledge Merial, France, who kindly provided the OFZ formulation (Synanthic®, OFZ 9.06%) used in the current work. The technical advice of Dr. Fermín Olaechea is gratefully appreciated. This research was supported by the Agencia Nacional de Promoción Científica y Tecnológica, Argentina and Consejo Nacional de Ciencia y Tecnología (CONCYTEC), Peru.

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Table 1: Individual pre-treatment (trial day -1) faecal egg counts (FEC), post-treatment fluke counts (trial day 7) and efficacy against *Fasciola hepatica*, obtained in naturally infected pigs from the untreated control group and the orally treated (30 mg/kg) with oxfendazole (OFZ).

Animal #	FEC		Adult *F. hepatica* counts	
	Control	**OFZ-treated**	**Control**	**OFZ-treated**
1	32	7	4	0
2	2	1	4	0
3	4	7	23	0
4	820	13	140	0
5	34	6	9	0
6	14	48	5	0
7	27	33	8	0
8	1	85	8	0
Geometric mean	**15.1**	**12.3**	**8.3**	**0***
Efficacy (%)	-	-	-	**100**

FEC is expressed as egg in 3 g of faeces, estimated at trial day -1 (pre-treatment). No statistical difference (P> 0.05, Mann-Withney test) in the FEC was observed between the Control and the OFZ treated group. *Statistically different (P< 0.05, Mann-Withney test) adult fluke counts between the Control and the OFZ treated group.

HIGHLITGHTS

- Control measures in *F. hepatica*-endemic areas should include treatments in swine.
- There are not available anthelmintic treatments to control *F. hepatica* in pigs.
- The flukicidal activity of oxfendazole in pigs was assessed.
- Oxfendazole (oral, 30 mg/kg) was 100% efficacious against *F. hepatica* in pigs.

Oxfendazole flukicidal activity in pigs

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The current study investigated the flukicidal activity obtained after a single (30 mg/kg) oral dose of oxfendazole in pigs harbouring a natural *Fasciola hepatica* infection.

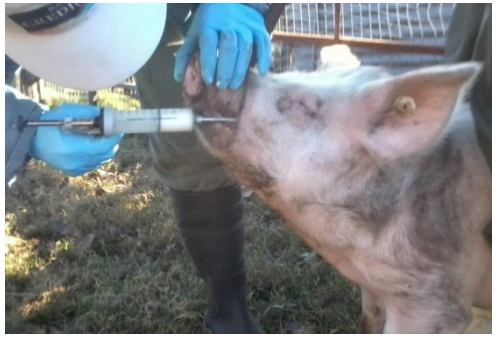
Typical image of animal handling by the poorest people in Peru

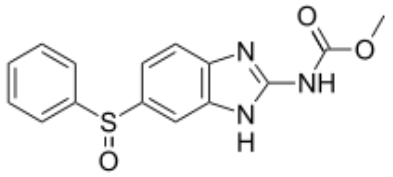
Trial design

Animal Selection

(*Fasciola hepatica*-naturally infected pigs)

Treatment





OXFENDAZOLE

Drug efficacy assessment