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Major Article

Efficacy and tolerability of two single-day regimens of triclabendazole for fascioliasis in Peruvian children

Vicente Maco[1], *Luis Marcos*[1], *Jaime Delgado*[2], *Julio Herrera*[3], *José Nestares*[3], *Angelica Terashima*[1], *Frine Samalvides*[1] *and Eduardo Gotuzzo*[1]

[1]. Institute of Tropical Medicine Alexander von Humboldt, Cayetano Heredia University, Lima, Peru. [2]. Health Care Center of Progreso, Asillo, Azángaro, Puno, Peru. [3]. Health Care Center of Canta, Lima, Peru.

ABSTRACT

Introduction: The therapeutic scheme of triclabendazole (TCBZ), the recommended anthelmintic against *Fasciola hepatica*, involves 10mg/kg of body weight administered in a single dose; however, clinical trials in children are scarce. We evaluated the efficacy and tolerability of 2 schemes of TCBZ. **Methods**: Eighty-four Peruvian children with *F. hepatica* eggs in their stools were allocated into 2 groups: 44 received 2 dosages of 7.5mg/kg each with a 12-h interval (Group I), and 40 received a single 10-mg/kg dose (Group II). Evaluation of efficacy was based on the presence of eggs in stools, and tolerability was based on the presence of symptoms and signs post-treatment. **Results**: A parasitological cure was obtained in 100% of individuals from Group I and 95% of individuals from Group II. The most common adverse event was biliary colic. **Conclusions**: The tested scheme was efficacious and tolerable, and it might be an optimal scheme in the region. To the best of our knowledge, this represents the largest series of children treated with TCBZ in a non-hospital setting.

Keywords: Fascioliasis. Treatment. Children. Highlands. Peru.

INTRODUCTION

Fascioliasis is a zoonotic disease caused by *Fasciola hepatica* (*F. hepatica*) or *Fasciola gigantica* (*F. gigantica*) that disproportionally affects poor people living in cattle-raising areas and has a diverse distribution in all continents[1] [2]. Humans acquire the disease through the consumption of aquatic, semi-aquatic, or waterside undercooked or raw vegetables; consumption of drinking water; or use of fomites infected with the larval stage metacercariae[3]. Human fascioliasis is an important public health problem that affects several regions in Peru[4] including the Mantaro Valley in Junín[5] [6] the Altiplano in Puno[7], the Cajamarca Valley[8], Arequipa[9], and Huarochirí in Lima[10].

Since the first cases reported in Peru by Edmundo Escomel in 1924[11] [12], the chemotherapeutic armamentarium to treat human fascioliasis has been limited for decades, and most treatments had to be discontinued due to adverse events. Emetine hydrochloride (30-60mg/day intramuscularly for 8-18 days) was effective but also highly toxic; it can cause cardiac arrhythmias including atrial ectopic beats, bradycardia, hypotension, and vomiting[11] [13] [14] [15] [16], had to sometimes be co-administered with steroids[11], and required hospitalization for monitoring. Chloroquine was also used, with limited efficacy[15]. Bithionol also caused abnormalities in cardiac rhythm such as extrasystoles, first-degree heart block, and hypertension as well as gastrointestinal disturbances such as diarrhea, abdominal pain, nausea, vomiting, anorexia, and urticaria[14] [17] [18] [19] [20]. Other drugs such as praziquantel[18] [19] [21] [22] [23] [24] [25], metronidazole[26], and niclofolan[27] had discouraging or discrepant results, and albendazole[28], mebendazole[29], and phanquinone[18] were not effective. Nitazoxanide had an efficacy of 94% after a 7-day course in a Mexican study and could be considered as a second line option[30]; however, it has lower cure rates in Peruvian children (40% as compared with placebo)[31] and requires a longer therapeutic time than a single dose of triclabendazole (TCBZ), resulting in greater expense for the rural communities of Peru.

Triclabendazole, or 5-chloro-6-(2,3-dichlorophenoxy)-2[methylthio] benzimidazole, acts against the microtube-dependent secretory processes in *F. hepatica*, was first used in animals in 1983 and humans in 1986[32] [33], and has a well-established therapeutic use in human fascioliasis and paragonimiasis[34]. The compound represents the first-line treatment against fascioliasis in different regions of the world[23] [24] [25] [26] [27] [28] [29] [32] [33], and is recommended by the World Health Organization (WHO) as the first-line drug in all cases of fascioliasis[35]. However, most of these studies have been performed in adults, and few data are available for children[31] [36], who are generally the most affected

Corresponding author: Dr. Vicente Maco. Institute of Tropical Medicine Alexander von Humboldt/Cayetano Heredia University. Av. Honorio Delgado s/n, San Martin de Porres, Lima, Peru.
Phone: 51 1 613 9797
e-mail: vicente_maco@hotmail.com
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in Peru, Bolivia, and Egypt[2]. The veterinary TCBZ formulation (Fasinex®), successfully used for the first time in 1986, has proven to be effective and tolerable in humans[32] [33].

We aimed to evaluate the efficacy and tolerability of two therapeutic schemes of TCBZ among children using both a TCBZ suspension (Fasinex®) and TCBZ tablets (Egaten®) in an open-label, randomized study in different endemic areas in Peru under field conditions.

METHODS

Study sites and design

This open-label, phase II, multicentric clinical trial was conducted between 2001 and 2006 in 5 rural areas of several endemic areas **(Figure 1)**: 1 in the district of Asillo (3,895m/12,778 f) in the province of Azángaro, Puno (recruited between March and August 2001); 1 in the district of Lachaqui (2,819m/9,248 f) in the province of Canta, Lima (recruited between March and August 2005); 1 each in the districts of Anta (3,345m/10,974 f) and Sicuani (3,552 m/11,653 f) in the provinces of Anta and Canchis, Cusco, respectively (recruited between March and August 2005); and 1 in the district of Jauja (3,353m/11,000 f) in the province of the same name, Junín (recruited between July and August 2005). Participants were recruited from a field validation study using a serological test against *F. hepatica*[37] and a series of coprological-based, longitudinal epidemiological studies[10] [38].

Case definition

A case was defined as an individual aged 2-16 years residing in a study site at the time of recruitment with confirmed fascioliasis (presence of characteristic eggs of the fluke

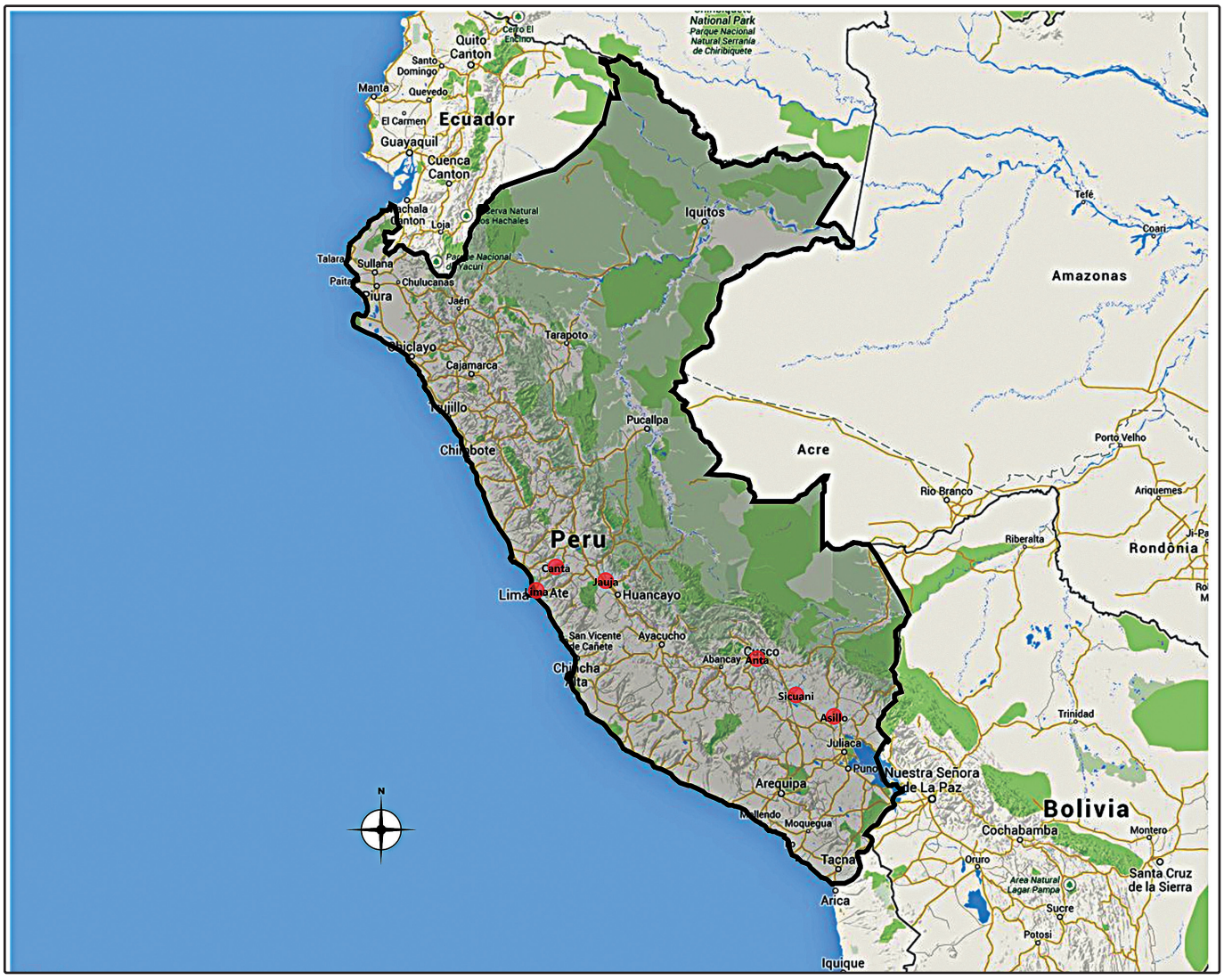

FIGURE 1 - Study sites along the Highlands of Peru, which are hyperendemic areas for human fascioliasis. The Asillo irrigation canals are located in the district of the same name in Azángaro, Puno, at an altitude of 3,895m.

F. hepatica [130-150µm × 80-85µm operculate eggs] in at least 1 single stool sample using the rapid sedimentation technique (RST)[39], and/or the Kato-Katz (KK) method[40]. Exclusion criteria were any acute or severe illness during the study period or a known chronic liver disease; known pregnancy, lactation, or a positive urine test for β-human chorionic gonadotrophin (β-hCG) hormone; drug therapy for *F. hepatica* or other parasitic infection administered 30 days before enrollment; history of allergy to benzimidazoles; and/or concurrent use of drugs with known TCBZ interactions.

Anthelmintic and therapeutic schemes

Given the unavailability of the human TCBZ formulation in Peru in 2001 (the compound was approved by the Ministry of Health of Peru in 2005 owing to the high prevalence of human fascioliasis), we had to use the veterinary TCBZ formulation (Fasinex®) for all participants in the district of Asillo, under strict surveillance, monitoring of side effects, and local ethical approval. The human TCBZ formulation (Egaten®, 250-mg tablets, donated by Novartis Pharma AG, Basel, Switzerland) was used in the remaining study sites.

Eligible volunteers were sequentially assigned to 1 of 2 therapeutic schemes based on a block randomization schedule: Group I received 15mg/kg TCBZ orally in two 7.5-mg/kg doses after a meal (breakfast and dinner), separated by a 12h-interval; Group II received a single 10mg/kg dose of TCBZ after breakfast or dinner. The meals were consumed a maximum of 30 min before drug administration to improve systemic bioavailability[41] [42].

We hypothesized a dose-response cure rate (efficacy), with limited side effects and using oral antispasmodic therapy as needed (tolerability). The spasmolytic agent was anticholinergic hyoscine butylbromide, based on body weight (kg).

Efficacy evaluation

The primary outcome of efficacy was evaluated at 60 days post-treatment according to the presence (parasitological failure) or absence (parasitological cure) of eggs compatible with *F. hepatica* using either RST or KK of a stool sample.

One pre-treatment KK thick smear was performed on all stool samples. A total of 6 post-treatment stool samples were also examined for each individual. Stool samples were collected on post-treatment days 1, 3, 5, 10, 30, and 60 in Asillo and on post-treatment days 30, 60, 90, 120, 150, and 180 in Lachaqui, Anta, Sicuani, and Jauja. All of the stool samples were transported to the Laboratory of Parasitology of the Institute of Tropical Medicine Alexander von Humboldt (ITM AvH), Cayetano Heredia University (UPCH) in Lima and examined by an experienced technician using RST for qualitative diagnosis.

Tolerability

Secondary outcomes for the TCBZ tolerability were documented by evaluating the symptoms and signs at each site (Peripheral Primary Health Care Centers) daily during the first 7 days post-treatment for close surveillance and directed intervention of any adverse events. A local, trained physician at each site recorded demographic data and daily signs, symptoms, and adverse events (biliary colic, abdominal and epigastric pain; nausea or vomiting; diarrhea; anorexia; jaundice; pruritus; skin rash; headaches; dizziness; dyspnea; cough; cervical, thoracic, lumbar or muscular pain; and use of antispasmodics). Because pain intensity is inherently subjective, we stratified pain as severe (symptoms required observation and treatment by the physician at the health care center), moderate (symptoms were managed at home and did not require physician intervention), or mild (symptoms did not require any intervention but were only reported to the physician during follow up). Routine physical examinations were performed on a periodic schedule until day 90.

Quantitative assessment of infection intensity

To quantify the infection intensity (egg output), we collected and conducted KK thick smears with post-treatment stool samples from all participants only in the district of Asillo on a more frequent basis: every other day during the first week (days 1, 3, and 5) and then on days 10, 30, and 60. Serology and eosinophilia were assessed to evaluate the subgroup homogeneity prior to treatment allocation. An enzyme-linked immunosorbent assay (ELISA) assessment was also offered to detect immunoglobulin G (IgG) against the 25KDa excretory/secretory antigen Fas 2. A cut-off value of >0.20 units of optical density (OD) measured at 450nm was considered positive[43]. A complete blood count to measure baseline eosinophilia (eosinophils >500/cc) was also performed.

Statistical analysis

Data were double entered and analyzed using Statistical Package for the Social Sciences (SPSS)®, v21 (IBM® Corp, Armonk, NY) and STATA 12.1 (StataCorp, College Station, TX). A sample size calculation was not performed because the study was designed to estimate the dose-response and safety of TCBZ.

First, univariate analyses were performed to calculate frequencies and percentages (and 95% confidence intervals [CIs]) for discrete variables and mean and standard deviation for continuous variables. Bivariate analyses using Chi-square tests (X^2) or Student's *t*-tests were performed for discrete or continuous variables, respectively. A p value <0.05 was considered statistically significant for all tests. The adverse events were reported and tabulated for each regimen.

Geographical data and coordinates for the map with the study sites **(Figure 1)** were obtained from the National Geographic Institute of Peru and manually entered into the visual processor Smart Draw® v2012 (San Diego, CA).

Ethical considerations

Written informed consent was obtained from the participants' parents or guardians before recruitment. Because this clinical trial involved a vulnerable population, and, most importantly, given that the human TCBZ formulation was not available in Peru at the time of the study, we verbally emphasized the use of the veterinary compound to the parents and community leaders as well as in the consent form (see supplemental file).

Confidentiality was maintained at all points of the study. Treatment was provided free-of-charge. Efficacy and tolerability results were reviewed by an independent medical monitor.

The study protocol was approved by the Institutional Ethics Committee of the UPCH in September 04, 2001 (Project No. 01086) and then renewed and registered by the same committee under the Research Project No. 0000050647 on July 01, 2005 (http://www.upch.edu.pe/vrinve/duict; see supplemental files).

RESULTS

Total population

The mean age of the 84 individuals (Asillo: n = 59; Canta: n = 4; Anta and Sicuani: n = 3; and Jauja: n = 18) was 9.27 (2.48) years. No statistically significant differences in age, sex, or infection intensity were found between the groups (Group I, n = 44, 52.4%; Group II, n = 40, 47.6%) (p-value > 0.05). None of the children had a high-intensity infection [>400 eggs per gram (EPG) of stool].

Efficacy results

All cases were cured in Group I (100%); persistent *F. hepatica* infection was present in 2 individuals (2/40; 5%) in Group II (1 each from Asillo and Lachaqui), resulting in a cure rate of 95% (38/40). These 2 individuals in Group II were retreated with a similar TCBZ dose and cured, reaching an efficacy of 100% after the second dose. One from Asillo had positive results on day 60 and 1 from Lachaqui had positive results on days 14 and 30. The latter received a further single 10-mg/kg TCBZ dose on day 30 (on day 60, no eggs were detected in his stool). On day 60, all of the participants showed negative results for the stool samples.

Signs, symptoms, and adverse events

The signs, symptoms, and adverse events from post-treatment days 1 to 7 are shown in **Table 1**. The most common adverse event was biliary colic, which occurred in 25% of Group II (95% CI: 11.9-38.9) on day 2 post-treatment and subsequently decreased on days 3 (12.5%, 95% CI: 4.8-24.3), 4 (15%, 95% CI: 3.1-22.4), 5 (5%, 95% CI: 0.0-11.7), and 7 (2.5%, 95% CI: 0.0-8.9). While the intensity varied from mild to severe during days 1 to 7, only severe intensity was experienced on days 2 and 4 in 2.5% of Group II (95% CI: 0.0-6.8). Severe biliary colic occurred in 4.5% of Group I (95% CI: 0.0-15.2) on day 2. All of the cases (n = 4) with severe biliary colic responded to antispasmodic medication within 2 hours and did not require any further medical or surgical intervention.

Mild to moderate abdominal pain was reported on days 1 to 5, affecting 20% of Group I (95% CI: 11.8-33.1) and 15% of Group II (95% CI: 3.1-29.2) on day 2. Mild to severe epigastric pain was reported on days 1 to 6, affecting 18.2% of Group I (95% CI: 8.2-32.1) and 17.5% of Group II (95% CI: 6.1-30.7) on day 2. Only 2.5% of Group II (95% CI: 0.0-6.8) experienced severe abdominal pain on day 2.

TABLE 1 - Percentages of adverse events from days 1 to 7 post-treatment with triclabendazole in children in Peru.

Adverse effects (%)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Abdominal pain							
Group I	11.0	21.0	7.0	7.0	11.0	0.0	0.0
Group II	5.0	8.0	10.0	15.0	8.0	0.0	0.0
Nausea and vomiting							
Group I	0.0	2.3	2.3	4.5	6.8	0.0	0.0
Group II	0.0	2.5	0.0	0.0	0.0	2.5	0.0
Biliary colic							
Group I	0.0	11.4	9.1	20.5	13.6	4.5	0.0
Group II	2.5	25.0	12.5	15.0	5.0	2.5	2.5
Anorexia							
Group I	0.0	2.3	9.1	6.8	0.0	0.0	0.0
Group II	0.0	2.5	0.0	0.0	0.0	0.0	0.0
Use of antispasmodics							
Group I	0.0	2.3	0.0	2.3	0.0	2.3	0.0
Group II	0.0	0.0	2.3	0.0	2.5	0.0	0.0
Headaches							
Group I	4.5	11.4	4.5	6.8	0.0	0.0	0.0
Group II	10.0	10.0	10.0	10.0	0.0	0.0	0.0

Group I (n = 44): 7.5mg triclabendazole administered twice postprandially; **Group II** (n = 40): single 10-mg/kg triclabendazole dose.

The frequency of mild to moderate headaches varied from 4.5% on days 1 and 3 to 11.4% on day 2 in Group I. The occurrence of nausea and vomiting in Group I varied from 2.3% (95% CI: 0.0-8.4) on days 2 and 3 to 6.8% (95% CI: 0.0-14.4) on day 5. The occurrence of anorexia in Group I ranged from 2.3% (95% CI: 0.0-6.6) on day 2 to 9.1% (95% CI: 2.5-18.2) on day 4.

A sharp decrease in the occurrence of clinical signs and symptoms was observed in all groups at 7 days post-treatment. Patients remained without signs and symptoms 60 days post-treatment, and no cases of diarrhea, jaundice, pruritus, skin rash, dizziness, dyspnea, cough, or cervical, thoracic, lumbar, or muscular pain were reported. None of the participants were withdrawn from the study due to adverse events during the follow-up period. All of the participants completed the study period (60 days in Asillo, 180 days in the remaining sites).

Population subset of Asillo

All 59 participants in Asillo (Group I, n = 31; Group II, n = 28) provided stools samples on days 1, 3, 5, 10, 30, and 60; 81.3% (48/59) and 62.7% (37/59) provided sera for Fas 2 ELISA and baseline eosinophilia, respectively. At the time of recruitment (2001), they all received the veterinary TCBZ formulation (Fasinex®). **Table 2** summarizes the age, sex, infection intensity, serology studies, and baseline eosinophilia in the Asillo population subset.

The entire subset had a mean OD of 0.35 (0.13) with the Fas 2 ELISA: 0.33 (0.15) in Group I (25/48) and 0.38 (0.12) in Group II (23/48) (p - value = 0.65). The entire subset had a mean eosinophil count of 876.46 (1,403 cells/cc) (range, 0-7,150): 745 (1,121) cells/cc (range, 0-5,124) in Group I (21/37) and 1,049 (1,729) cells/cc (range, 0-7,150) in Group II (16/37) (p -value 0.61).

Assessment of post-treatment infection intensity

The post-treatment infection intensity in the subset of Asillo (n = 59) is summarized in **Table 3**. The mean EPG was higher in Group II than in Group I on post-treatment days 1 (56.00 vs. 50.52; p-value = 0.05) and 10 (6.00 vs. 1.87; p-value = 0.05). The mean EPG in Group I steadily decreased from 50.82 on post-treatment day 1 to 1.87 on day 5 and became undetectable on days 30 and 60. In contrast, the mean EPG in Group II decreased from 56.0 on post-treatment day 1 to 6.0 on day 5 and remained unchanged until day 60. There were no statistically significant differences between the two groups on days 1 (p-value = 0.85), 3 (p-value = 0.92) 5 (p- value = 0.57), or 10 (p-value = 0.46).

DISCUSSION

The overall cure rate with TCBZ was >95% using either the veterinary (Fasinex®) or human formulation (Egaten®) in 84 children aged 2-16 years, which represents the largest pediatric series under field conditions (non-hospital settings).

TABLE 2 - Baseline characteristics of children from Asillo, Peru (n = 59) treated with the veterinary triclabendazole formulation.

	Group I (n = 31)	Group II (n = 28)	Total (n = 59)
Age (years)			
mean	9.71	9.21	9.47
min	6	2	2
max	15	13	15
Sex			
male	15	14	29
female	16	14	30
EPG (arithmetic mean)	240.0	254.8	247.2
min	144	144	144
max	528	480	528
EPG (geometric mean)	226.4	241.5	233.6
Eosinophils[a] (cells/cc)	745	1049	876
min	0	0	0
max	5,125	7,150	7,150
Fas 2 ELISA[b] (OD)	0.33	0.38	0.35
min	0.01	0.02	0.01
max	0.50	0.53	0.53

Group I: 7.5mg/kg triclabendazole administered twice postprandially; **Group II:** single 10-mg/kg triclabendazole dose; **EPG:** eggs per gram of stool; **ELISA:** enzyme-linked immunosorbent assay; **OD:** optical density measured at 450nm. [a]mean eosinophil count calculated using 37 available serum samples; [b]mean Fas 2 ELISA OD calculated using 48 available serum samples.

TABLE 3 - Mean egg count per gram of stool during the 60-day triclabendazole treatment in Asillo, Peru, calculated using a 1 Kato-Katz thick smear.

Egg count/gram of stool	Day 1	Day 3	Day 5	Day 10	Day 30	Day 60
Arithmetic mean (Group I/II)	50.82/56.0	30.84/29.76	12.80/9.0	1.87/6.0	0/3.0	0/2.0
minimum	0/0	0/0	0/0	0/0	0/0	0/0
maximum	240/240	168/384	96/72	48/44	0/48	0/48

Furthermore, the tolerability was high with both treatment schemes, contributing to the safety data of this anthelmintic.

Although the therapeutic scheme involving 15mg/kg oral TCBZ administered as two post-prandial doses of 7.5mg/kg each with a 12-h interval had a higher cure rate (100%) than the single postprandial 10mg/kg TCBZ dose, the difference was not statistically significant. Similar results (cure in at least ~80%) have been reported previously; however, these studies also included adults[44] [45] [46] [47] [48], administered different doses of TCBZ[45], included fewer subjects (n ≤10)[28] [44] [49], or administered a fasting or post-prandial dose[50].

Case reports and series evaluating the efficacy of flukicidal drugs in children are scant or limited. Before the advent of TCBZ, praziquantel was administered to 34 individuals in Peru (n = 19, 8-15 years old), with an overall cure rate of 21%[21]. In Egypt, a small series of 7 children (aged 4-10 years) were unsuccessfully treated with praziquantel[23], whereas another series of 8 children (aged 4-16 years) were treated with bithionol but required long-term therapy[17]. In Cuba, 40 children (aged 1-14 years) were treated with emetine hydrochloride, but efficacy was not evaluated[16]. Case reports[51], small series[28] [44] [49] [52], and larger trials of TCBZ treatment in pediatric populations have been described. A cure rate of 79.2% was obtained in 24 individuals (14 children, 11-16 years old) in Chile with a single 10-mg/kg TCBZ dose (Fasinex®) administered after an overnight fast, which might have altered the absorption of the drug[53]; similarly, a cure rate of 77.5% was obtained after a single 10-mg/kg post-prandial dose in 40 children (4-15 years old)[54]. One of the largest series to assess the efficacy of TCBZ included 38 children (aged 0-15 years) in Peru, with an overall cure rate of 83%[50]. More recently, a cure rate of 77.8% in 80 pediatric outpatients and 10 pediatric inpatients (aged 5-14 years) was achieved in Bolivia with a single 10-mg/kg dose[36].

Although the cure rates with a single 10-mg/kg dose of TCBZ range from 69 to 79.4%, the cure rates with a double dose are reportedly higher (76.9 vs. 69%[45] and 75 vs. 69.8%[47]) in adults. A higher cure rate was obtained with two 10-mg/kg doses (mean age, 16.10 years) than with 1 dose (mean age, 14.20 years) (93.9 vs. 79.4%)[55]. In Peru, cure rates of 83%[50], and 100% (13 children aged 3-17 years)[8] were reported after administering two 12-mg/kg TCBZ doses in a fasting state. Therefore, a dose-response relationship might exist with TCBZ treatment of fascioliasis. While 1 dose might increase compliance among patients, a higher dose divided in 2 could reduce the side effects and be more effective and tolerable than the standard single 10-mg/kg dose. Further studies comparing 2 doses in children with similar infection intensities are needed to prove this hypothesis.

The tolerability of TCBZ was high in both arms of the study. Most of the adverse events were mild in severity and more frequently reported from individuals in Group I than from individuals in Group II, likely because of the higher total dose in the former group. The most common adverse event was biliary colic, which occurred in 25% of individuals in Group II; this value subsequently declined to 4.5% on day 6 and was not reported by day 7.

Overall, the majority of the mild adverse events were recorded in Group I, while the majority of moderate events were reported in Group II, including biliary colic (mild and moderate severity), which explains the more frequent use of antispasmodics in this group. On day 1, complaints were more frequent in Group I. On day 2, mild abdominal pain was more frequent in Group I ($p = 0.028$); however, epigastric pain and biliary colic were more frequent in Group II. Mild biliary colic was of longer duration in Group I, whereas moderate biliary colic lasted longer in Group II; biliary colic was better tolerated in Group I except for one individual with severe biliary colic who responded well (within 2h) to the antispasmodic therapy. Between days 3 and 6, the frequency of abdominal pain was similar in both groups.

Only 2 participants from Group I reported severe adverse events (biliary colic), which rapidly subsided after administration of antispasmodics. However, these adverse events might not have been related to the toxicity of the drug itself, but rather to the expulsion of damaged or dead parasites induced by TCBZ. Some clinical observations support this hypothesis. First, the biliary colic presented from days 2 to 6 post-treatment, peak serum TCBZ concentration occurred at 4-10h post-administration, and elimination of the foreign bodies (dead parasites) occurred 48h post-administration. Second, other studies have shown that liver enzymes significantly increase on post-treatment day 7 but not day 3 during fascioliasis, indicating that these hepatic markers increase after the onset of biliary colic[55] [56] [57]. Third, biliary colic and increased liver enzymes do not occur in individuals treated with TCBZ for other indications such as paragonimiasis[58]. Last, ultrasonographic studies of the liver fluke have shown that the parasites stop moving on post-treatment day 3, and the whole parasite or its fragments are eliminated through the biliary tract, with a transitory increase in the diameter of the biliary duct[59] [60].

Biliary colic usually occurs 2-5 days after therapy and might be related to dead parasites passing the common bile duct, with

antispasmodics serving as an appropriate therapeutic option to minimize abdominal pain. Therefore, biliary colic during TCBZ treatment for fascioliasis might represent an early indicator of treatment efficacy (Lumbreras; unpublished data). We conclude that treatment and follow up can be performed in the outpatient clinic (Terashima: unpublished data). No patients required in-hospital interventions or presented with biliary obstruction.

The veterinary formulation has been shown safe and tolerable in different countries worldwide since 1986, when it was first used in humans[32] [33] as an alternative therapy in view of the inefficacy and low tolerability of other drugs. An exhaustive literature review with no language restriction produced a total of 554 (441 adults and 113 children) documented cases between 1986 and 2002 from Germany[32] [33] [61], Switzerland[62], France[63] [64], Belgium[41], Australia[29], Venezuela[65], Spain[66] [67] [68], the US[69], Japan[24], Iran[45] [70], Chile,[53] and Egypt[28] [44] [54] [55], that received the veterinary formulation with no or minimal adverse events. In Peru, it has been administered since 1996[8] [42]. In the present subgroup of participants from Asillo (n = 59) that received the veterinary TCBZ formulation, the adverse events were minimal; only 1 individual reported severe biliary colic that subsided upon treatment with antispasmodics, as documented in the safety documentation.

In conclusion, TCBZ is an effective and tolerable anthelmintic for the treatment of chronic fascioliasis among children in rural areas of the Peruvian Highlands. Adverse events might be related to the high efficacy in inducing parasite expulsion through the biliary tract. The therapeutic scheme involving an oral, post-prandial, double dose of 7.5mg/kg TCBZ, administered with a 12-h interval, had greater efficacy (100% vs. 95.83%) and a similar tolerability profile than a single 10-mg/kg dose, making it a reasonable therapeutic alternative. Because the 15-mg/kg dose divided into two administrations was well tolerated, we recommend that this dose be tested in future treatment studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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