Administration of Triclabendazole Is Safe and Effective in Controlling Fascioliasis in an Endemic Community of the Bolivian Altiplano

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Abstract

Background: The Bolivian northern Altiplano is characterized by a high prevalence of Fasciola hepatica infection. In order to assess the feasibility, safety and efficacy of large-scale administration of triclabendazole as an appropriate public health measure to control morbidity associated with fascioliasis, a pilot intervention was implemented in 2008.

Materials and Methods: Schoolchildren from an endemic community were screened for fascioliasis and treated with a single administration of triclabendazole (10 mg/kg). Interviews to assess the occurrence of adverse events were conducted on treatment day, one week later, and one month after treatment. Further parasitological screenings were performed three months after treatment and again two months later (following a further treatment) in order to evaluate the efficacy of the intervention.

Results: Ninety infected children were administered triclabendazole. Adverse events were infrequent and mild. No serious adverse events were reported. Observed cure rates were 77.8% after one treatment and 97.8% after two treatments, while egg reduction rates ranged between 74% and 90.3% after one treatment, and between 84.2% and 99.9% after two treatments. The proportion of high-intensity infections (≥400 epg) decreased from 7.8% to 1.1% after one treatment and to 0% after two treatments.

Conclusion: Administration of triclabendazole is a feasible, safe and efficacious public health intervention in an endemic community in the Bolivian Altiplano, suggesting that preventive chemotherapy can be applied to control of fascioliasis. Further investigations are needed to define the most appropriate frequency of treatment.

Introduction

Preventive chemotherapy, the large-scale administration of anthelmintic drugs to population groups at risk, is recommended by WHO for control and elimination of lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminth infections [1]. The aim of preventive chemotherapy is to regularly reduce worm load in infected individuals, thus controlling the associated morbidity and decreasing transmission rates. Biological and epidemiological similarities between Fasciola spp. and the helminths responsible for the diseases mentioned above, suggest that morbidity associated with fascioliasis could also be controlled.
Fascioliasis is highly prevalent in the northern Altiplano of Bolivia. We wanted to ascertain whether a preventive chemotherapy approach, involving the large-scale distribution of triclabendazole within endemic communities, would be feasible for controlling morbidity associated with this disease. Consequently, we implemented a pilot intervention among schoolchildren in a community in the civil (sub-alcalde, head of the health post, director of the educational unit), and traditional (jilakatas and malkus) authorities convened by the WHO [24], the Ministerio de Salud y Deportes of Bolivia decided to opt for large-scale distribution of triclabendazole in endemic areas without individual diagnosis. Before this approach was widely implemented, a pilot study was conducted to test the safety and efficacy of such intervention. Safety assessments consisted of monitoring prevalence and intensity of infection and by calculating cure and egg reduction rates. Safety, in particular, was considered as a key component of the protocol as AEs are known to limit the feasibility of preventive chemotherapy interventions for helminth infections, as their occurrence confines treatment to a clinical setting where proper management of cases is ensured by health personnel. AEs also have the potential to jeopardize compliance to the intervention as effects of treatment can be perceived as a greater health risk than the disease itself [25].

Methods

Ethics

The study protocol was approved by the Comisión de Ética de la Investigación (CEI) of the National Bioethics Committee of Bolivia on September 10, 2007. A written informed consent form explaining the purpose and the modalities of the study was developed, translated into Aymara and obtained from the parents/guardians of each participating child. The initiative was agreed by the civil (sub-alcalde, head of the health post, director of the educational unit), and traditional (jilakatas and malkus) authorities of the community where the study was implemented.

Study setting

The study was conducted in Huacullani, a community in the Bolivian northern Altiplano, where prevalence of F. hepatica infection among school-aged children ranged between 31.2% and 100% based on arithmetic means [18,19], and 63% based on geometric means [21]. Triclabendazole is generally regarded as a safe drug, although adverse events (AEs) can occur following treatment [16,17]. Such events are directly proportionate to intensity of infection and can be classified as systemic or mechanical. Systemic AEs are caused by biological substances released by the dying worms and include mild/transient dizziness, headache, nausea, and urticaria. Mechanical events are generally linked to the expulsion of dead worms from the biliary system towards the intestinal lumen, and include biliary colic pain, possibly associated with jaundice.

Treatment with triclabendazole has usually been implemented in a clinical setting while its use in public health interventions is limited. In Egypt, however, a triclabendazole treatment programme based on selective chemotherapy (test-and-treat) of school-age children has been implemented in six districts in the Nile Delta area since 1998 [22,23], while in Vietnam treatment has been decentralized since 2006 and is administered in peripheral hospitals and health posts based on a simplified diagnostic protocol [AF Gabrielli, personal communication]. In Bolivia, where prevalence of infection is higher than in Egypt or Vietnam, a more inclusive strategy offering treatment to entire population sectors without individual diagnosis might be appropriate in order to reduce costs and logistics related to the implementation of screening exercises. This approach would mirror the one currently recommended for schistosomiasis and soil-transmitted helminthiasis in areas of moderate and high risk [1]; the procurement of larger quantities of medicines needed for its implementation has been made possible via the donation of triclabendazole (Egaten) by Novartis Pharma AG through the WHO.
and 38.2% in the 1990s [9]. Huacullani (16°26′0″S, 68°14′0″W) is located at an altitude of 3,850 metres, approximately 500 meters from the shores of Lake Titicaca, in the municipality of Tihuanaku (province of Ingavi, department of La Paz). At the time of the survey, the population of Huacullani was 2,472.

Study population
School-aged children (5–14 years) were selected as the target group of the intervention, as they are at higher risk of infection and morbidity. Children are more likely than adults to become infected, as exemplified by their higher levels of prevalence of infection, and to develop mechanical AEs following treatment, because of the smaller size of their bile ducts and thus higher likelihood of blockage. Consequently, they are considered both the group at highest risk and the one most sensitive for detection of AEs following treatment. All children attending the primary school and the junior high school of Huacullani were considered eligible for enrolment in the study.

Study design
A Scientific Committee formed by the Ministerio de Salud y Deportes, the Servicio Departamental de Salud de La Paz, the Universidad Mayor de San Andrés and the PAHO/WHO was established with the aim of developing a protocol and supervising the implementation of the pilot intervention. The protocol consisted of five consecutive study phases: baseline data collection; treatment; monitoring of AEs at day 0, day 7 and day 30; first parasitological follow-up 3 months after treatment, with further treatment of any cases still positive; and second parasitological follow-up 2 months after the first follow-up (Figure 1). After a few preparatory meetings, field activities started in April 2008, and were completed in November 2008.

Baseline data collection. Each participating child was given a plastic numbered container on the day of the survey and was asked to return it with a fresh stool sample. A single Kato-Katz thick smear [26,27] was prepared from each stool sample. The Kato-Katz test was chosen as – in spite of its recognized low

Figure 1. Study flow diagram.
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Parasitological follow-ups. Three months after administration of triclabendazole, the efficacy of treatment among all treated children who had tested positive at baseline was assessed by another single Kato-Katz thick smear. All children testing positive at this first parasitological follow-up were treated again (triclabendazole, 10 mg/kg single administration) and reasessed two months later (second parasitological follow-up), with the same technique as the first follow-up. Based on measured prevalence and arithmetic mean intensity of infection, cure and egg reduction rates were calculated for the population under study at both follow-ups. For logistic reasons, only positive cases were progressively followed up; children negative at baseline were therefore not included in the first follow-up, and children negative at first follow-up were not included in the second follow-up.

Data management and analysis. Data were collected and analysed by staff of the Ministerio de Salud y Deportes, the Servicio Departamental de Salud de La Paz, the Universidad Mayor de San Andrés and the PAHO/WHO who directly supervised and participated in the activities described in this paper.

Results

Baseline data collection

At the time of the baseline survey (April 2008), the school population of Huacullani consisted of 459 children aged 5 to 14 years, who were all considered eligible for treatment. 447 children returned the plastic container. In total, 437 faecal samples from an equivalent number of children were examined by the Kato-Katz thick smear technique – 4 children returned an empty plastic container, and 6 other children provided insufficient stool quantities to prepare a Kato-Katz slide. Stool samples were transported to the Faculty of Medicine of the Universidad Mayor de San Andrés in La Paz and processed. Slides were read within 24 hours of preparation.

Overall, 95 children had positive and 342 had negative Kato-Katz smears. The parasitological prevalence of *F. hepatica* infection in this population was therefore 21.7%. Among the 95 children with positive Kato-Katz smears, 15 had an intensity of infection $\geq$300 epg (15.8%), and 11 a high-intensity infection ($\geq$400 epg, 11.6%). The mean intensity of infection among all surveyed children (including the ones with negative smears) was 72.9 epg.

Treatment

Triclabendazole was administered in June 2008 to each child testing positive to the Kato-Katz test. Among the 15 children with an intensity of infection $\geq$300 epg, 10 were hospitalized before treatment, while 5 could not be treated as their parents refused hospitalization and/or treatment. By contrast, all the 80 Kato-Katz positive children with an intensity of infection $<300$ epg were treated as outpatients at school premises. In total, 90 children were administered triclabendazole: among them, the mean intensity of infection was 264.3 epg, and 7 had a high-intensity infection ($\geq$400 epg, 7.8%).

Adverse events following treatment

Among the 90 treated children, the number reporting one or more AEs on treatment day and one week after treatment (June 2008) was 11 and 10, respectively. One month after treatment (July 2008), only 82 children were interviewed, as 8 were neither at school nor could be traced in Huacullani; among them, only three children reported any AE. Details are provided in Table 2.

The number of reported AEs on treatment day, one week after treatment and one month after treatment was 15, 13 and 3,
respectively. Headache was the most frequent event reported on treatment day, and abdominal pain was the most frequent one week later. All fevers were below 38°C. Only 3 of the children experiencing AEs on treatment day also reported an AE one week after treatment. Only 1 of the children with a high-intensity infection (≥400 epg) reported an AE one week after treatment (abdominal pain).

Among children treated at school, only one girl requested to be taken to the local health post on treatment day, but after a medical examination, she did not require any specific medical attention, and all the signs and symptoms resolved spontaneously. None of the other children contacted the health post for medical assistance during the follow-up period.

Overall, no medications were administered to treat AEs with the exception of antipyretics in case of fever. No SAEs occurred.

**Efficacy of treatment**

**First parasitological follow-up.** The first parasitological follow-up was carried out approximately three months after treatment (September 2008). Collection and processing of faecal samples followed the same procedures as baseline data collection.

Among the 90 treated children, 20 were still positive by Kato-Katz smear at the first parasitological follow-up (22.2%); this is equivalent to a parasitological cure rate of 77.8%. Among the 20 positive children, only 1 had a high intensity (≥400 epg). Table 3 summarizes this information.

At first parasitological follow-up, the mean intensity of infection among all those sampled at baseline was 7 epg, and among the whole treated population 33.9 epg. The respective ERRs from baseline levels were 90.3% and 87.2%. The mean intensity of infection among the 20 positive cases alone was 152.4 epg. Table 4 summarizes this information.

Following completion of the first parasitological follow-up, the 20 children still classified positive by Kato-Katz smear were treated again following the schema presented in Table 1.

**Second parasitological follow-up.** Collection and processing of samples at the second parasitological follow-up (November 2008) also followed the procedure for baseline data collection. After the second dose of triclabendazole, only two children were still positive by the Kato-Katz test; parasitological cure rate from baseline was therefore equivalent to 88/90 (97.8%) (Table 3). Mean intensity of infection for the two positive cases at second parasitological follow-up was 24 epg, while that among all those followed up was 0.5 epg. ERR between baseline an 2nd follow-up was 84.2% when calculated only among those still positive at 1st follow-up, 99.8% among those positive and treated at baseline, and 99.9% among all those sampled at baseline (Table 4).

**Discussion**

Overall, 21.7% of the children surveyed were found to be infected with *F. hepatica* at baseline. This was less than the prevalence of infection previously detected in Huacullani [9], but was nevertheless high when compared with the usually low levels of *F. hepatica* in most endemic countries across the world, such as Egypt, Iran, Vietnam or Yemen for example, where prevalence of infection by faecal examination rarely exceeds 5% [10,22,23,30–32]. It is also likely that the true prevalence of infection is higher due to the low sensitivity of a single Kato-Katz smear.

Treatment with a single administration of triclabendazole (10 mg/kg) did not elicit frequent or considerable AEs, neither among children with a high intensity of infection, nor among the

| Table 2. Adverse events experienced by children treated with triclabendazole. |
| --- |
| **Adverse event** | **Day 0** | **Day 7** | **Day 30** |
| Abdominal pain | 2 | 4 | 2 |
| Fever | – | 1 | – |
| Nausea | 1 | – | – |
| Fatigue | – | 1 | – |
| Headache | 5 | 2 | 1 |
| Abdominal pain and nausea | 1 | – | – |
| Abdominal pain and headache | – | 1 | – |
| Headache and fever | 1 | – | – |
| Abdominal pain, headache and fever | 1 | – | – |
| Headache, fatigue and fever | – | 1 | – |
| **Number of AEs reported or observed** | 15 | 13 | 3 |
| **Number of children with AEs** | 11 | 10 | 3 |
| **Proportion of children with AEs among those observed** | 12.2% | 11.1% | 3.7% |

*an = 90 children;*  
*b n = 90 children;*  
*cn = 82 children*  

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| Table 3. Chronological evolution of the number of positive cases and the cure rate. |
| --- |
| **Baseline (n = 437)** | **1st follow-up (n = 90)** | **2nd follow-up (n = 20)** |
| Negative | 342 | 70 | 18 |
| Positive n<400 epg | 84 (83) | 19 | 2 |
| Positive n≥400 epg | 11 (7) | 1 | 0 |
| **Cure rate** | 77.8% | 97.8% |

Note: figures in brackets refer to children who were treated (n = 90).  
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Table 4. Chronological evolution of intensity of infection and egg reduction rates (ERRs).

| Time of observation | Among those sampled at baseline (n = 437) | Among those treated at baseline (n = 90) | Among those positive at 1st follow-up (n = 20) |
|---------------------|-----------------------------------------|----------------------------------------|---------------------------------------------|
|                     | Mean epg       | ERR          | Mean epg       | ERR          | Mean epg       | ERR          |
| Baseline            | 72.9          | –            | 264.3          | –            | 585.4          | –            |
| 1st follow-up       | 7*            | 90.3%        | 33.9           | 87.2%        | 152.4          | 74%          |
| 2nd follow-up       | 0.1*          | 99.9%        | 0.5            | 99.8%        | 24             | 84.2%        |

*As children negative at baseline were not followed up, calculations are based on the assumption that all of them remained negative at 1st and 2nd follow-up.

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Notably, triclabendazole was well tolerated across the population examined, including individuals with a high intensity of infection: AEs elicited were self-limiting, did not require any specialist medical attention and could be managed by the local health staff. In terms of efficacy, a single administration of triclabendazole was effective in reducing considerably the number of infected individuals, the mean intensity of infection and the proportion of high-intensity infections, and in keeping these indicators at low levels for a few months after treatment.

Surveys with a longer follow-up are recommended in order to ascertain for how long a single administration of triclabendazole can sustain low prevalence and intensity of infection in endemic areas. Such a study would allow the most appropriate interval of re-treatment to be determined.

Following the successful implementation of the pilot intervention, the health authorities of Bolivia decided to implement distribution of triclabendazole on a large scale.

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Author Contributions

Conceived and designed the experiments: FV RA MAV SKA AM DE SMC AFG. Performed the experiments: FV RA RB GB MAV SMC. Analyzed the data: FV RA RB GB MAV SKA AM DE SMC AFG. Contributed reagents/materials/analysis tools: FV RA RB GB MAV KH HG SKA AM DE SMC AFG. Wrote the paper: FV RA MAV SMC AFG. Revised the manuscript: RB GB KH HG SKA AM DE SMC AFG. Facilitated shipment of TCZ tablets: KH HG.

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