Human fascioliasis: prevalence and treatment in a rural area of Peru

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Abstract
During a study in a rural community of San Juan, Department of Cajamarca, Peru, using randomly selected samples, we found a 15% (n=80) of prevalence of Fasciola hepatica infection in humans. The prevalence in a sample from the urban area of Cajamarca (n=140) was 3.5%. Human carriage of F. hepatica eggs in faeces was also determined by direct examination. Positive individuals from both areas were invited to participate in a study on the efficacy of triclabendazole in the treatment of human fascioliasis. Twelve individuals from the rural community of San Juan and five from the urban area of Cajamarca were treated with triclabendazole, the active ingredient of the veterinary preparation Fasinexâ (10 %) at an oral dose of 12 mg/kg on two consecutive days while fasting. Treatment was 100% effective as determined by the absence of detectable F. hepatica eggs in faeces. The patients were monitored for evidence of infection for three months after treatment. The drug was well tolerated as evidenced by close clinical monitoring, though mild eosinophilia was observed in six patients. No increase in activities of gamma-glutamyltransferase (gGT) and glutamate dehydrogenase (GLDH) were observed in the infected patients before treatment. Treatment with triclabendazole at the regimen given, can be considered highly effective and a useful alternative method for the treatment of human fascioliasis due to F. hepatica.

Introduction
Human fascioliasis due to F. hepatica is a common health problem in many countries, especially in rural areas (1-5). Prevalences between 6% (6) and 13% (7), have been recorded in school aged children in the Northern valley of Cajamarca, Peru. The infection in this area is endemic (8,9) and, like other Andean areas, is directly related to environmental conditions, which facilitate the presence of the intermediate host Lymnaea viatrix (10,11). The infection is maintained by domesticated animals, notably dairy cattle and sheep commonly reared in this area. The major source of infection for man is the consumption of vegetables such as lettuce (1), water cress (12) or lupin seeds, which are frequently soaked and washed with contaminated irrigation waters (13). Various drugs such as bithionol and praziquantel are used for treatment of human fascioliasis with variable results (14-18). Emetine and dehydroemetine are used frequently with significant efficacy in the treatment of human fascioliasis (14,19,20), but cause a variety of serious and toxic side-effects (18,21). Moreover, these drugs are not affordable for many people from rural communities or they are simply not available.

Preliminary studies on the therapeutic effects of triclabendazole have demonstrated that this drug is highly effective in the treatment of human chronic fascioliasis caused by F. hepatica. Variable results have been obtained using a single dose of 10 mg/kg of body weight (4,22-24), in some cases complete cure was achieved after a second treatment with the same dose (4,22). Here we report a study of the prevalence of F. hepatica infection in two sample populations in the inter-Andean valley of Cajamarca, Peru, and the treatment of positive individuals with triclabendazole administered orally at 12 mg/kg body weight for two consecutive days in patients of different ages.

Materials & methods
Study area
The study was conducted in Peru, which is on the Pacific coast of South America, within the Province of Cajamarca in the rural community of San Juan and the city of Cajamarca (Figure 1). San Juan district is situated about 40 km South East of Cajamarca, at approximately 2,800 meters above sea level, with a population of approximately 10,000 inhabitants. The city of Cajamarca is situated in a fertile Andean valley at 2,700 meters above sea level and a longitude of 78º 30’ West and a latitude of 7º 10’ South, with a population of approximately 120,000 inhabitants (INEI, 1995). Cajamarca is the capital city of the department of the same name, with 13 provinces, accounting for 35,400 km² of the national territory of Peru.

Prevalence of fascioliasis
A total of 80 stool samples were collected from people of rural San Juan and 140 from urban Cajamarca were analysed in the Laboratorio Regional del Norte de Sanidad Animal de Cajamarca, by faecal examination for the eggs of F. hepatica by the sedimentation technique (see below) (25). The results were recorded and positive individuals were identified and informed.
Treatment with triclabendazole
Individuals found positive for *F. hepatica* eggs, were informed and invited to participate in a prospective study on the efficacy of triclabendazole in the treatment of human fascioliasis. With the written consent of the individuals who chose to participate in this study or that of their parents, in the case of children, and the ethics committee of the Hospital Regional de Salud de Cajamarca, treatment was administered to a total of 17 individuals, 13 of which were between 3 to 17 years, and four were adults between 20 to 60 years. Of the 17 patients, 12 were males and five were females.

Triclabendazole, the active ingredient in the veterinary drug Fasinexâ 10%, was used in all the individuals. A dose of 12 mg/kg body weight was administered on each day, for two consecutive days, while fasting. All the individuals were weighed and doses were calculated exactly. The drug was measured using a pipette, and it was diluted in approximately 50 ml milk and administered orally.

Figure 1. Map of Peru showing the location of the province of Cajamarca (shaded).

Five of the seventeen individuals were treated in the Hospital Regional de Salud de Cajamarca. After treatment, these individuals were hospitalised for 24 h. The twelve patients from the rural area were treated in the Departamento de Acción Social de Cajamarca (DAS) premises, which were specially adapted for the treatment and control of these individuals. In both cases close medical supervision was ensured for 24 h after treatment, after which individuals were allowed to leave. Drug tolerance was recorded for three days after treatment in the patients’ clinical records.

Haematological and biochemical procedures
Blood samples were collected from all the patients from the radial vein before treatment. Two blood samples from each patient were collected into plain and EDTA vacutainer tubes (Becton Dickinson, Oxford, UK). The samples collected into plain tubes were allowed to clot for 3-4 h, then centrifuged at 1,500g for 10 min. The serum was removed and aliquoted at -20 °C and used to determine the activity of hepatic gamma-glutamyltransferase (gGT) and glutamate dehydrogenase (GLDH) enzymes (Randox Laboratories Ltd, Antrim, UK). The following were measured in blood samples: haemoglobin, haematocrit, red blood cells, white blood cells and differential cell counts.

Sedimentation technique to detect *F. hepatica* eggs
Prior to treatment, the presence of *F. hepatica* eggs was determined by the sedimentation technique. Approximately 2g of faeces were mixed in 10ml of water and passed through a sieve of mesh 0.5mm. The filtrate was made up to approximately 300ml of mixture and allowed to stand for at least five minutes. The supernatant fluid was poured off and the faecal material re-suspended in approximately 300ml and allowed to sediment for at least five minutes. The same process was repeated twice, then the supernatant fluid was poured off and all the sediment examined under a stereo microscope for the presence of fluke eggs at x50 magnification. Eggs present were counted and the count recorded as eggs per 2g faeces (ep2g). After treatment with triclabendazole, all the individuals were monitored for the presence of *F. hepatica* eggs in their stool samples by the technique described above. Stool samples were analysed monthly, for three months; the first of these follow-up samples was obtained two weeks after treatment.

Results
Prevalence and symptoms of fascioliasis
In rural San Juan, 12 of 80 (15%) samples were positive for *F. hepatica* eggs. In urban Cajamarca, 5 of 140 (3.5%) samples were positive for *F. hepatica* eggs. The clinical signs of fascioliasis at the time of treatment with triclabendazole were epigastric pain (n=12), drowsiness (n=11), diarrhoea (n=3), anorexia (n=2), and icterus (n=1). The jaundiced patient also had positive serology for *Salmonella* antigen.

Efficacy and tolerability of triclabendazole treatment in chronic human fascioliasis
The number of *F. hepatica* eggs before and after treatment with triclabendazole was investigated by the sedimentation technique. The 17 positive individuals excreted on average 3.5 ep2g of faeces before treatment, with ranges 1-8 ep2g. Individuals were followed from two weeks to three months after treatment. Following treatment with triclabendazole, in all 17 individuals parasites were undetectable.

Tolerance to triclabendazole was excellent. Only two patients showed mild stomach pain, which was alleviated with anti-spasmodic drugs and pain killers. None of the patients had raised gGT or GLDH activities prior to treatment. Mild eosinophilia (600-1000 eosinophils/mm³) was observed in six of the patients. One individual had 1,152 eosinophils/mm³ which can be considered a high eosinophilia. Other haematological parameters such as...
The results of this work also show that the prevalence to contaminated with metacercaria of *F. hepatica* (13). Seeds) which are soaked with waters that may be to eat vegetables such as watercress and "chocho" (lupin hours. This leads them to drink unboiled fresh water and performing these activities stay away from home for many tendings of animals. Thus adults and children, whilst performing these activities stay away from home for many hours. This leads them to drink unboiled fresh water and to eat vegetables such as watercress and “chocho” (lupin seeds) which are soaked with waters that may be contaminated with metacercaria of *F. hepatica* (13).

The results of this work also show that the prevalence to *F. hepatica* in urban population, although comparatively low (3.5%), may be regarded as an important cause of liver pathology, which is often misdiagnosed. Lack of sanitation and education makes the infection difficult to control. Human fascioliasis was reported in 1971 (29) in school children in the valley of Cajamarca. Since then various studies have been carried out on the prevalence of *Fasciola* infection in this area, reporting prevalences between 6 (6,30) and 13% (7). Prevalences in the Bolivian Altiplano have been reported to fluctuate from 27.6 (5) to as high as 55.6% in school children (31). An estimated prevalence of 20% was reported in a population of 1.8 million subsistence farmers in the Bolivian Altiplano (32). Thus the prevalence of fascioliasis in the Bolivian Altiplano is much higher than that in Cajamarca, Peru.

For chemotherapy of human fascioliasis, an effective and safe drug is required. The high efficacy achieved in our work with a daily dose of 12 mg/kg of triclabendazole for two consecutive days, suggests that this drug may be valuable in the treatment of *F. hepatica* infection in areas where human infection occurs. Furthermore, tolerance to triclabendazole was excellent. Patients within a wide age-range were treated safely (3 to 60 years). No mutagenic or teratogenic effects have been reported for this drug (Koval, 1988, Ciba-Geigy Ltd, Basel, Switzerland; unpublished data). This is the first report in which *Fasciola*-infected patients of different ages were 100% successfully treated with this particular dose regimen (one dose of 12 mg/kg of triclabendazole per day on two consecutive days).

Triclabendazole belongs to the group of benzimidazoles and a maximum tolerated dose of 200 mg/kg has been determined in sheep, for which the normal therapeutic dose is 10 mg/kg (33). The use of this drug in human fascioliasis was first reported in 1987 (22). There is another report in which a single patient infected with *F. hepatica*, who had been unsuccessfully treated with multiple high doses of praziquantel, mebendazole and albendazole, was treated successfully with triclabendazole at 12 mg/kg in two single doses, two days apart (34). The more extensive use of this drug in humans achieved a 79.2 % of cure with a single dose of 10 mg/kg of triclabendazole (4).

Various drugs are used to treat human fascioliasis, among which emetine, dehydroemetine, bithionol and praziquantel are marketed and licensed for human use. The effectiveness of these drugs is controversial and some have been reported to have side effects (21,18). Bithionol is considered the drug of choice for fascioliasis and is administered orally at 50 mg/kg daily divided into three doses on alternate days for 15 days (18,35). Disadvantages of treatment with bithionol are the long treatment period required and the necessary hospitalisation of the patients. Praziquantel is also used in treatment of human fascioliasis but its efficacy is variable. In one study it was found to be effective in 72% of cases (36) and in other in only 21% of cases (16). Other reports found praziquantel to be completely ineffective against *F. hepatica* infection in children (37).

In Cajamarca, the most commonly used drugs against *F. hepatica* infection are dehydroemetine and praziquantel. Apart from the high cost of these drugs, they are not always commercially available and have to be specially ordered from the country's capital or imported. Furthermore, the dehydroemetine produces a variety of side-effects in people including hypotension, tachycardia, electrocardiographic changes, vomiting and diarrhoea (21,18). For this drug to be effective it has to be administered intramuscularly or subcutaneously daily over 10 consecutive days, which is stressful for the patient.

In the present study, serum gGT and GLDH were normal, suggesting only mild liver damage as a consequence of the parasite migration through the liver parenchyma. This, together with the mild eosinophilia observed in six of the patients suggests a more chronic presentation of the disease. No significant changes in the concentration of haemoglobin, haematocrit or in red and white cell counts, were seen in any of the individuals.

In conclusion, triclabendazole appears effective in the treatment of human fascioliasis and could be considered an alternative drug for the treatment of this parasitic infection in humans.

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