Praziquantel failure in the treatment of *Fasciola hepatica*

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DM PATRICK, J ISAAC-RENTON. Praziquantel failure in the treatment of *Fasciola hepatica*. Can J Infect Dis 1991;3(1):33-35. A case of human fascioliasis is presented in which the patient remained symptomatic after treatment with praziquantel and other agents but eventually responded to bithionol. The difficulties in finding an efficacious and tolerable drug therapy for this condition are reviewed with reference to the life cycle and pathogenesis of the parasite. It is concluded that while bithionol remains the current drug of choice, triclabendazole may play a dominant role in the near future.

Key Words: *Bithionol*, Fasciola hepatica, *Praziquantel*, *Triclabendazole*

Echec du praziquantel dans le traitement de la fasciolase

RESUME: On présente un cas de distomatose hépatique due à *Fasciola hepatica* chez l'être humain. Les symptômes ont persisté après traitement sous praziquantel et autres agents thérapeutiques mais le patient a éventuellement réagi au bithionol. Les auteurs examinent les difficultés de trouver un traitement médicamenteux efficace et tolérable en rapport avec le cycle de vie et la pathogenèse du parasite. Ils concluent que, si le bithionol reste le médicament de choix, le triclabendazole pourrait jouer une rôle prépondérant dans un avenir proche.

THE INTRODUCTION OF THE BROAD SPECTRUM ANTHELMINTIC praziquantel has simplified treatment of many human metazoan infections. *Fasciola hepatica*, the sheep liver fluke, has historically been a difficult parasite to eradicate. The authors add to the growing body of evidence for the inefficacy of praziquantel for this indication by reporting the failure of two separate regimens of the drug in a woman who was later cured of fasciola infection by alternative therapy. The relevant pharmacotherapeutic literature is reviewed and recommendations made regarding the most appropriate available therapy.

CASE PRESENTATION

A 36-year-old woman was referred to the tropical diseases clinic with a past history of fascioliasis. She and her husband had been resident on a large cattle and sheep farm in New South Wales, Australia, where she had consumed watercress on at least one occasion. Three years prior to presentation to the authors' clinic, the patient had suffered fever, tachypnea and right-sided pleuritic chest pain, but had recovered spontaneously. Increasingly severe right upper quadrant pain occurred three months later, bringing her to medical attention. Although stools were negative for ova and parasites and there was no peripheral eosinophilia, an irregularity of biliary mucosa on cholangiography led to a diagnostic aspiration of the biliary tree, which yielded ova of *F hepatica* on microscopy. The patient was treated with praziquantel 25 mg/kg/day for five days. She tolerated the medicine well and was most careful to avoid future ingestion of watercress. Right upper quadrant pain recurred two years later, and microscopy of a common bile duct aspiration once again yielded *F hepatica* ova. The patient was given mebendazole at that time; three months later when the pain returned a stool examination was positive for fasciola ova.

Upon leaving Australia, the patient had no

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symptoms, but stool examination on presentation to the authors' clinic revealed persistence of fasciola ova. She was treated with praziquantel 75 mg/kg for one day in accordance with then current recommendations (1). One month later, her stools were still positive for fasciola ova and the abdominal pain subsequently recurred. The patient was started on bithionol 3 g every two days. Relief of abdominal pain was rapid, but because of vomiting and diarrhea, the dose was reduced by 40% for the second half of the treatment period, for a total of 15 doses. At four years of follow-up the patient has remained symptom free with no recurrence of ova on repeated coprological examination.

DISCUSSION

Life cycle: *F hepatica* commonly infects livestock in temperate climes. Though it is not a common cause of human disease, 2594 cases have been reported globally in the past two decades (2). As with many infectious diseases, this figure likely represents a substantial underestimate of the true burden of disease. The fully grown, leaf-shaped, unsegmented and hermaphroditic trematode measures 30x13 mm^2. It resides in the bile ducts of sheep, the definitive host, as well as in other livestock and, very occasionally, in humans. There it excretes its 140x70 μm^2 oval and operculated eggs. These eggs hatch in the feces to free miracidiae, which may infect the intermediate host, the freshwater limnaea snail. The latter host excretes cerceriae which encyst upon waterside plants such as watercress. When such plants are consumed by sheep, cattle or humans, the immature flukes excyst, mature, invade the intestinal wall, and make their way to the liver. Having penetrated Glisson's capsule, the flukes must then burrow through the hepatic parenchyma to the bile ducts, where they mature to complete the cycle.

Clinical manifestations: The incubation period after ingestion of the parasite is not well defined in humans, but is probably about two months (3). The present patient suffered fever, tachypnea and pleuritic chest pain some time after consuming watercress. These symptoms, as well as abdominal pain and headache, are classic manifestations of the acute phase of infection, which corresponds to the migration of immature flukes through the peritoneum and liver. Urticaria has also been reported at this stage (4). The liver may be enlarged; mild anemia is common; and eosinophilia in excess of 5% is the rule (2). Hepatic scarring in the path of the parasite may result. There follows a variable period of latency during which the fluke matures. It is usually during this period, about three or four months after ingestion, that the first eggs are detectable in stool (5). Unexplained eosinophilia and a positive coprological examination may be the only clues to disease at this point. The chronic or obstructive phase of infection, when symptomatic, usually presents as in the present patient, with symptoms indistinguishable from biliary colic or cholangitis (2). Clinical manifestations of cholestasis may be evident, and the liver is often enlarged. Complications such as hemobilia and biliary cirrhosis occur, but there is no known association with cholangiocarcinoma. Mature adults have been known to survive in the liver for up to 13 years (6).

Diagnosis: The diagnosis might be suspected on the basis of the above symptoms, particularly when a history of aquatic plant ingestion is elicited. The leukocytosis and elevated erythrocyte sedimentation rate seen in acute infection are not specific, but eosinophilia is a frequent finding throughout all stages of infection and may serve as a valuable clue.

Definitive diagnosis has usually been based upon demonstration of ova in feces or upon serological testing. Sensitivity of fecal examinations is enhanced by the processing of several samples using parasite concentration techniques. Since the number of ova produced is small, multiple sediments from each concentration procedure should be examined. Rapid sedimentation has proved more sensitive than merthiolate-iodine formaldehyde concentration or string test, likely because more stool is sampled in the former technique (7).

Because of the long prepatent period, coprological examination is of little use in acute and early latent infection. Serological testing based on somatic or excretory-secretory antigens may be positive within two to four weeks of infection in experimental animals, and reach peak titres between four and 10 weeks after infection in livestock (8). Serology is also reactive prior to positive stool examinations in man (9). Of the available tests, enzyme-linked immunosorbent assay (ELISA), immunofluorescent antibody and counterimmunoelectrophoresis techniques have the best sensitivities and specificities (2). Genus-specific antigens have been used in ELISA to reduce cross-reactivity with other trematodes, and a reduction of ELISA titre has followed effective treatment in experimental animals (10). The present patient had a titre of 1:64 (1:128 is considered diagnostic) by ELISA for fascioliasis. As applied in Canada, however, this test has limited usefulness due to the undefined cutoff and sensitivity of the procedure used. The assay used for the present patient's titre is based on crude adult *F hepatica* antigen, also implying potential problems with cross-reactivity and specificity (personal communication). There is no current consensus on the best available serological test for use in human cases.

Treatment: The present case illustrated the difficulties inherent in the selection of agents which are both effective and well tolerated for the treatment of human fascioliasis. Temporary improvement was seen after treatment with two separate regimens of praziquantel, which later gave way to recurrent symptoms and excretion of ova. This late failure has been witnessed by other clinicians and has been attributed to the inability of most anthelmintic agents to kill the less mature flukes,

which may later mature to secrete ova and obstruct the bile ducts (11).

Historically, chloroquine was the first line of defence for *F hepatica* infection. Its celebrated effects in improving symptomatology in acute disease are dampened by its inability to eradicate the parasite from the biliary system (5).

Emetine, an amebicidal alkaloid derived from ipecac, has been recommended in the past as the drug of choice for *F hepatica* (12). It has been used successfully in the treatment of large outbreaks (9). The drug must be given in repeated doses by deep intramuscular injection, causes substantial gastric irritation in 30 to 50% of recipients, and more importantly, has been associated with arrhythmias, hypotension, congestive heart failure and death. It is also toxic to skeletal muscle (13). No deaths have been reported from emetine in the treatment of fascioliasis. Reasonable success of the order of 50% cure has been observed in the treatment of acute fascioliasis with an initial course of parenteral dehydroemetine in children (14,15). This agent is associated with fewer adverse effects than the parent compound.

Niclofolan, a biphenyl compound, has been employed in the treatment of two patients (16,17). While favorable anthelmintic results were seen in both cases, treatment also induced severe sweating and abdominal pain in one patient, and pruritis, jaundice and elevated aspartate aminotransferase and alanine aminotransferase in the other.

Albendazole is an experimental benzimidazole anthelmintic with demonstrated efficacy in *Necator americanus* infections (18), hydatid disease (19), ascaris and trichuris infections (20), and strongyloidiasis (21). Activity of albendazole in human fascioliasis awaits clarification.

Praziquantel is a broad spectrum anthelmintic agent possessing an excellent therapeutic ratio and demonstrated efficacy against several trematodes, including clonorchis, opisthorchis, paragonimus and most cestodes (22). Minimal toxicity in the form of abdominal pain, headache and dizziness has been reported. In lower concentrations, the drug acts by causing contraction and paralysis of the susceptible adult flatworms. Higher doses result in vacuolization and vesiculation of the parasitic tegument and an increase in its permeability to cations. Although success has been seen in the treatment of *F hepatica* with dosages of 75 mg/kg tid for one day (23), there are many reports of post therapy relapse in both acute and chronic fascioliasis, even when dosages as high as 75 mg/kg/day are used for seven days (7,24-26). Such a treatment failure was observed in the present patient. Failure may relate to the resistive properties of the *F hepatica* tegument. Vacuolization of this layer is observed when *Schistosoma mansoni* and dicrocoelium are treated with praziquantel in vitro, but such changes are conspicuously absent when *F hepatica* is subject to the same therapy (27). One source recommends treatment of *F hepatica* with praziquantel 25 mg/kg tid for seven days (28). The authors would not hold out much hope of success with this drug, but if it is to be employed as a trial, the higher dosage outlined above should be employed given the observed failure of lower dosage regimens.

The present patient responded to therapy with bithionol. This experience has been shared by the authors of several other case reports (29,30). The usual dosage has been 30 to 50 mg/kg daily in three divided doses on alternate days for a total of 10 to 15 doses. Lower doses have been used when this regimen is poorly tolerated. Despite its success, most series reporting bithionol therapy of *F hepatica* report just under 50% long term cure (14,31). An approximate 50% incidence of vomiting and abdominal pain can be expected. Skin rashes, urticaria, photosensitivity and diarrhea have also been reported. Bithionol is currently recommended as the drug of first choice by at least one source (32).

In contrast to praziquantel, the new benzimidazole triclabendazole has more effect against *F hepatica* than against other trematodes. In vitro, it has been shown to inhibit motility and to diminish the tegumentary potential of flukes (33). In animals, it is well tolerated and nonteratogenic in doses well above those used therapeutically (34,35). In sheep and cattle, triclabendazole in dosages of 5 to 10 mg/kg as a single dose has proven 90 to 100% effective against both immature and mature flukes (36,37). Six patients with well documented fascioliasis have been treated with dosages of triclabendazole in the neighbourhood of 10 mg/kg (38-40). Of these, two had transient fever and elevation of liver function tests after treatment. All responded but two later relapsed. These two responded well with retreatment. In the one patient for whom comparative data are available, postprandial absorption was considerably better than absorption in the fasting state. In addition to these reports, five patients have been successfully treated in Bordeaux, France with indeterminate follow-up, and some authors are already recommending triclabendazole as the drug of choice for human fascioliasis (41). Further work should clarify its role in the treatment of fascioliasis.

CONCLUSIONS

F hepatica is a rare but treatable cause of biliary tract symptomatology in first world populations. Published accounts of therapeutic experience suffer from the absence of case control studies. It seems clear, however, that no drug approved for human use, including praziquantel, has 100% efficacy against the trematode. Because of consistently acceptable cure rates, bithionol constitutes current first-line therapy. Triclabendazole, if approved for regular use in humans, may supplant bithionol because of its generally more tolerable side effect profile.

As medications currently applied to treatment can cause symptomatic improvement without fully eradicating the parasite, cure should never be taken for granted until long term follow-up fails to reveal the presence of ova on repeated and careful examination of stool, or until endoscopic retrograde cholangiopancreatography shows normal mucosa and biliary aspirate.

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