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Clinical Study Evaluating Efficacy of Praziquantel in Clonorchiasis

BIENVENIDO G. YANGCO,[1]* CARLOTA DE LERMA,[2] GARY H. LYMAN,[3] AND DONALD L. PRICE[4]

Division of Infectious & Tropical Diseases[1] and Division of Medical Oncology,[3] Department of Internal Medicine, University of South Florida College of Medicine and James A. Haley Veterans Hospital, Tampa, Florida 33612; Pediatric Division, Pinellas County Health Department, St. Petersburg, Florida 33742[2]; and Devetec, Inc., Bradenton, Florida 33505[4]

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In 74 patients with clonorchiasis, the efficacy and safety of praziquantel was evaluated in a two-phase study: a double-blind, randomized controlled trial of praziquantel versus placebo (42 patients) and an open study (32 patients). All but one of the patients were Laotians. The intensity of clonorchiasis was light in 85% (63 of 74) and moderate in 15% (11 of 74) of the patients. Cure based on our established criteria was noted in 67 of 67 patients (100%) treated with praziquantel at a dose of 75 mg/kg per day. In contrast, four patients (20%) in the placebo group, each with light infection, ceased passing eggs and were, according to our established protocol, considered spontaneous cures ($P < 0.0001$). Adverse effects of praziquantel were transient and included nausea and vomiting (15%), vertigo (12%), hepatomegaly (4.5%), headache (1.5%), rash (1.5%), and hypotension (1.5%). Of 20 patients who received placebo, 1 (5%) developed transient skin rash, fever, and chills. Clinically minor and transient, but statistically significant, changes in hemoglobin, total protein in serum, and levels of uric acid, cholesterol, and bilirubin in serum were noted. Results of this study showed that praziquantel is safe, well tolerated, and effective and should be considered as the drug of choice for treatment of clonorchiasis. In moderate infections, a second course of praziquantel therapy may be necessary to eliminate infection.

Clonorchiasis, an infection caused by the liver fluke *Clonorchis sinensis*, is endemic in Southeast Asia and is acquired by eating raw, poorly smoked, or poorly steamed freshwater fish containing encysted larvae. Clonorchiasis may be mild and asymptomatic in many cases. Infection with this trematode, however, has been associated with cholelithiasis and intrahepatic calculi; severe cholangitis and liver abscesses; portal hypertension; and possibly, primary adenocarcinoma of the liver (15% of cases of primary carcinoma of the liver in Hong Kong have been linked to *C. sinensis* infection) (7, 8). Because of the ability of *C. sinensis* to survive in the host for a long time (up to 50 years) (23) and to produce morbidity with potentially serious consequences, possibly including cancer (8, 22), it has been suggested that every case should be treated regardless of symptoms (15).

Praziquantel, a derivative of isochinolinohydrazin, has been reported to be effective against cestode and trematode infections in animals (6, 13, 25, 26) and humans (4, 9, 17, 19–21). It has recently been approved in the United States for the therapy of schistosomiasis (14). In 1981, Rim et al. (19) reported its safety and efficacy in human clonorchis infections in a single-blind study.

C. sinensis infection affects 10 to 13% of Indochinese refugees in the United States (1, 11, 27, 28). During a recent survey among Laotians living in Pinellas County, Fla., *C. sinensis* ova counts ranging from 1,000 to 28,000 eggs per g of stool have been noted among these cases (B. G. Yangco, unpublished data). In Pinellas County the incidence of clonorchiasis is 27% among Laotians, 0.7% among Cambodians, and 0.5% among Vietnamese (C. De Lerma, unpublished data). In this study the clinical efficacy of praziquantel was evaluated in the treatment of *C. sinensis* infection among Indochinese refugees residing in Pinellas County. The high number of permanent residents with clonorchiasis and the ease of supervision and follow-up of treated cases, along with the fact that the parasite is not endemic, made Pinellas County an ideal setting for this study.

* Corresponding author.

MATERIALS AND METHODS

Patients. Two hundred and fourteen southeast Asian immigrants with a diagnosis of clonorchiasis, based on clinical and laboratory examinations, were referred to this study by the Pinellas County Health Department, Indochinese Refugee Clinic. All individuals with stools positive for *C. sinensis* were considered and screened for the study. Patients were excluded from the study if they (i) had significant underlying disease that would interfere with the evaluation of response to praziquantel; (ii) had concomitant infection that would interfere with the evaluation of response to praziquantel, e.g., patients being treated for malaria with chloroquine or patients being treated for intestinal parasites with other antihelminthic agents; (iii) had treatment within the previous 6 months with drugs specifically for liver fluke infection; (iv) were pregnant; (v) were lactating and actively breast-feeding; (vi) were children less than 2 years of age; (vii) were alcohol or drug abusers; and (viii) were unreliable for follow-up.

Study design. The study was carried out in two phases: (i) a randomized double-blind trial and (ii) an open, controlled trial. In the randomized double-blind trial, patients were matched by age and egg count category. Patients of each pair received by random code either praziquantel or placebo. At the end of 30 days, patients whose stools were positive for eggs were retreated with the same agent given at the start of therapy. Sixty days after initial therapy, patients were re-evaluated, stools were re-examined, and the random code was broken. Patients who received placebo and whose stools were still positive for eggs were treated with praziquantel.

Those in the placebo group with negative stool examinations at 30 days but positive at 60 days were also treated with praziquantel. Patients who received two courses of praziquantel treatment 30 days apart and who still were passing eggs on the day 60 were considered failures. Final stool examinations for *C. sinensis* eggs were performed 6 months after the last negative examination.

Patients not initially included in the double-blind trial, along with those who were treatment failures in the double-blind trial or who received placebo, were included in the open phase of this study. After the diagnosis was established and appropriate work-up was performed, praziquantel treatment was initiated. Follow-up stool examinations were performed 30 days after therapy. Patients whose stool samples remained positive for *C. sinensis* eggs were retreated. The criterion for treatment failure was a positive stool sample 30 days after the second treatment course. Stool examinations for *C. sinensis* eggs were repeated on patients 6 months after evaluation of the last negative stool sample.

The total dose of praziquantel (supplied by Miles Pharmaceuticals, West Haven, Conn.) was a single-day therapy of 75 mg/kg per day divided into three doses, given orally after meals at least 4 h apart. For the double-blind trial, the placebo was administered in the same manner. The drug supplies were packaged, coded, and blinded in such fashion that a double-blind design was maintained up through the 60-day period. During the administration of the drug, which was performed by one of the investigators, patients were kept at the Pinellas County Health Department for the first two doses. The third dose was taken by the patient in his or her home in the presence of a trained interpreter. Full compliance among all patients was ensured by this method. A small snack was administered immediately before and after each dose of praziquantel was given.

Prior to therapy all patients were interviewed for their medical histories and a physical examination was performed. All data were recorded on a case report form. An interpreter assisted the investigators during all interviews. Follow-up interviews and physical examinations during and posttherapy were performed monthly up to 6 months, as indicated. These included subjective assessments and evaluations of any intolerance or adverse reactions to therapy. If adverse reactions occurred these were recorded on the case report form.

Blood chemistry; urinalysis; complete blood count, which included differential count; prothrombin time; and the direct Coombs test were performed on the patients prior to the initiation of therapy and 24 to 48 h after the last dose of the drug. Laboratory test results that became abnormal posttherapy were repeated and followed weekly to normalcy.

Egg counts in the stools were quantitatively determined by a modification (28) of the technique described by Beaver (2, 3). Three stool examinations were performed during the week prior to therapy. The degree of infection was classified by the geometric mean value of eggs per gram of stools as follows: light, 1 to 999 eggs per g; moderate, 1,000 to 9,999 eggs per g; heavy, ≥10,000 eggs per g. The geometric mean eggs per gram value was calculated from the eggs per gram findings observed in all fractions of each sample at follow-up examination.

The posttherapy follow-up period in our study was carried out at 30, 60, 90, 120, 150, 180, and 210 days, as indicated. The schedule for stool collections was as follows: three stool specimens were collected (one per day, preferably on consecutive days), starting approximately on day 28 after medication and days 58, 88, 128, 148, 178, and 208. Stool specimens that were negative by the Beaver egg-counting technique were examined by a concentration method.

The efficacy of the drug was measured and expressed in the following terms: cure, patients whose stools were negative after 30 and 60 days of one or two courses of therapy; failure, patients whose stools were still positive after two courses of therapy, at 6 months of therapy, or both.

Informed consent was written and translated in the native language of the patient. With the help of an interpreter, the contents of the informed consent were explained to the patient prior to participation in this study.

The proportion of subgroups of patients evaluated for therapeutic efficacy and adverse effects were compared by the chi-square test. The differences between pre- and posttreatment measurements were assessed by using the paired sample Student *t* test and the paired sample exact test. For the exact test, the number of abnormal tests was assumed to be distributed as a binomial distribution and the probability of a given number of abnormal tests could be calculated exactly. Because measurements on subjects that were abnormal or normal on both determinations contributed no meaningful information, only discordant pairs were utilized in the analysis. The paired sample exact test that was used provided the probability, under the null hypothesis, of obtaining results at least as extreme as those observed with a two-tailed test of significance.

RESULTS

Of the 214 patients referred to the study, 74 were evaluable for safety purposes and 73 of 74 patients were evaluable for both safety and efficacy. One patient moved to Rhode Island and was subsequently lost to follow-up after receiving the blinded study drug, which later was found to be placebo. The remaining 140 patients were not included in this study but are being treated in an ongoing praziquantel study. Table 1 shows the demographic features of the 74 patients included in this study. The age range was between 4 and 53 years (mean age, 27 years). There was a slight preponderance of males to females in both study groups. Except for one Cambodian, all of the patients were Laotians.

The intensity of infection and efficacy of praziquantel are shown in Table 2. The intensity of infection was as follows: light, 63 of 74 (85%); moderate, 11 of 74 (15%). A total of 67

TABLE 1. Demographic features of the 74 patients studied

Study design (no. of patients)	Antimicrobial agent	Country of origin (no.)		No. of patients	Sex (no.)		Age (yr)	
		Laos	Cambodia		Male	Female	Range	Mean
Double-blind (42)	Praziquantel	42	0	22	15	7	8–51	25
	Placebo			20[a]	10	10	9–48	26
Open (32)	Praziquantel	31	1	32	17	15	4–53	28

[a] Thirteen of these patients were later entered in the open study (see Table 2).

TABLE 2. Intensity of *C. sinensis* infection and efficacy of praziquantel in *C. sinensis* (n = 74)

Study design	Agent	Infection	No. of patients	No. cured	No. of failures	No. unevaluable
Double-blind	Praziquantel[a]	Light	17	17	0	0
		Moderate	5[b]	5	0	0
	Placebo[c]	Light	16	4	11	1[d]
		Moderate	4	0	4	0
Open	Praziquantel[a]	Light	30	30	0	0
		Moderate	2	2	0	0
	Previously placebo treated but eventually received praziquantel[a,c]	Light	9	9	0	0
		Moderate	4	4	0	0

[a] The total number of patients treated with praziquantel was 67.
[b] One patient was cured only after a second course of praziquantel therapy.
[c] Thirteen patients with light infection (nine patients) and moderate infection (four patients) were included in the open study and treated with praziquantel. All patients were cured.
[d] One patient was lost to follow-up and did not receive praziquantel.

patients who participated in the double-blind trial and open study received praziquantel. Among these were 13 patients in the placebo group who were treatment failures and who were later given praziquantel as part of the open study. All 67 patients who were treated with praziquantel were cured of their infection. Of 11 patients 1 patient with moderate clonorchiasis had to be given a second course of praziquantel therapy before clinical cure could be achieved. Of 20 patients in the placebo group, 4 (20%) patients with light infections stopped passing eggs and were considered cured according to our established criteria. There was a statistically significant difference ($P < 0.0001$) between cure rates in the praziquantel group (67 of 67; 100%) and the placebo group (4 of 20; 20%). Two patients who were treatment failures in the placebo group did not receive praziquantel because one patient refused to participate in the study and the other patient moved out of the county before we could offer praziquantel.

The pretreatment clinical manifestations of patients with *C. sinensis* infection were nonspecific. These include nausea and vomiting (19 of 74; 25%), vertigo (16 of 74; 21%), headache (11 of 74; 15%), fatigue (6 of 74; 8%), and myalgia (4 of 74; 5%). Other manifestations noted in <4% of cases include anorexia, numbness, agitation, fever, and hypotension. The transient subjective and objective side effects of praziquantel found during posttherapy medical evaluations were considered not statistically significant compared with pretherapy evaluation. These findings included nausea and vomiting (10 of 67; 15%), vertigo (8 of 67; 12%), hepatomegaly (3 of 67; 4.5%), headache (1 of 67; 1.5%), skin rash (1 of 67; 1.5%), and hypotension (1 of 67; 1.5%). Of 20 patients who received placebo, 1 patient (5%) developed transient skin rash, fever, and chills.

Clinically minor but statistically significant changes in laboratory parameters were found, when compared with results before and after treatment. These changes included transient decrease in hemoglobin by ≥1 g/dl in 16 of 68 (24%) patients ($P < 0.001$); cholesterol changes, ≥30-mg/dl decrease in 14 of 73 (19%) versus increase in 1 of 73 (1.3%) patients ($P = 0.001$); uric acid changes, ≥0.5-mg/dl decrease in 24 of 73 (33%) versus increase in 3 of 73 (4%) patients ($P < 0.001$); bilirubin changes, ≥0.3-mg/dl decrease in 15 of 73 (21%) versus increase in 4 of 73 (5%) patients ($P = 0.02$); total protein changes, ≥0.5-g/dl decrease in 17 of 73 (23%) versus increase in 2 of 73 (3%) patients ($P < 0.001$).

DISCUSSION

Effective therapy for clonorchiasis has been unsatisfactory. Drugs clinically used for this condition have been toxic, poorly tolerable, ineffective, or all of these. Examples of these drugs are gentian violet (5), parenteral antimony preparations (24), 1,4-bis-trichloromethylbenzene (Hetol) (29), toluene-2, 4-diisothiocyanate plus Hetol (12), dihydroementine (16), and niclofalan (18). Chloroquine phosphate, the current drug of choice for clonorchiasis, requires treatment for up to 30 to 40 days and is only partially effective (23). Komiya (10) noted that chloroquine administration for up to 10 weeks did not completely eradicate the disease in animals and humans. Furthermore, some serious adverse effects such as mental, visual, and gastrointestinal disturbances have been commonly observed with chloroquine therapy (10).

The safety and efficacy of a single-day course of praziquantel therapy was demonstrated in this study. The drug was well tolerated with no significant side effects. A second course of praziquantel therapy may be necessary in moderate infections.

The ingredients of the placebo used in this study are as follows, in milligrams per tablet: starch, 256; lactose, 800; microcrystalline cellulose, 48; povidone, 24; sodium lauryl sulfate, 6.0; hydroxypropyl methylcellulose, 7.2; polyethylene glycol, 1.8; titanium dioxide, 3.0 (Miles Pharmaceuticals medical research data, report no. 246). Except for lactose, all of these ingredients were also present in the praziquantel preparation used. The occurrence of fever, chills, and skin rash in a patient who received placebo indicated that ingredients other than the active agent may have been responsible for some of the adverse effects noted among the praziquantel-treated patients.

Results of the study also suggest that light infections with *C. sinensis* may resolve without therapy, as observed in 20% of our cases. While this might be true in a small percentage of cases, the known complications of *C. sinensis* infection mentioned earlier and the availability of a drug with relative low toxicity, such as praziquantel, should justify this drug as the choice in the treatment of clonorchiasis.

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