A randomized, double-blind, placebo-controlled trial of safety and efficacy of combined praziquantel and artemether treatment for acute schistosomiasis japonica in China

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Objective To evaluate the safety and efficacy of combining artemether (AM) and praziquantel (PZQ) in different regimens for treating acute schistosomiasis japonica.

Methods We undertook a randomized, double-blind, placebo-controlled trial within four specialized schistosomiasis hospitals in the Dongting Lake region, Hunan province, China, between May 2003 and December 2005. Study participants were randomized into one of four treatment regimes: group A received 60 mg/kg PZQ + 6 mg/kg AM; group B received 60 mg/kg PZQ + AM placebo; group C received 120 mg/kg PZQ + 6 mg/kg AM; and group D received 120 mg/kg PZQ + AM placebo. All participants were followed up over a 45-day period. The primary endpoint of the trial was human infection status (determined by positive stool examination). Secondary endpoints involved clinical observations and blood biochemistry, including monitoring haemoglobin and alanine aminotransferase levels over time.

Findings Treatment efficacies of the four different treatment regimens were 98.0%, 96.4%, 97.7% and 95.7% for group A, B, C, and D respectively ($P > 0.05$). The group B had a greater treatment efficacy (96.4%) than the group D (95.7%) ($P > 0.05$). Group A treatment was better for clearance of fever ($P < 0.05$) and resulted in a shorter hospitalization time ($P < 0.05$).

Conclusion This is the first report of a randomized, double-blind, placebo-controlled trial for evaluating combined chemotherapy with AM and two different dosages (60 mg/kg and 120 mg/kg) of PZQ in the treatment of acute schistosomiasis japonica in China. The combination of AM and PZQ chemotherapy did not improve treatment efficacy compared with PZQ alone. PZQ given as a dosage of 60 mg/kg (1 day, 3 × 20 mg/kg doses at 4–5 hour intervals) may be as effective as a dosage of 120 mg/kg (6 days, 20 mg/kg for each day split into 3 doses at 4–5 hour intervals).

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Schistosomiasis japonica, caused by *Schistosoma japonicum*, was highly prevalent in China[1,2] but an effective control programme has substantially decreased its endemicity, prevalence, intensity and associated morbidity.[3–5] Elimination, however, is a major challenge.[1,6–9] Chemotherapy remains the main tool for control.[1,2,10] The clinical features of schistosomiasis japonica can be severe.[6] Recent evidence suggests that the burden of disease attributable to *S. japonicum* (and other human schistosomes) has been under-recognized.[11]

Schistosomiasis japonica can be divided into three disease stages: acute, chronic and advanced. Acute *S. japonicum* infection (Katayama syndrome),[12] which appears 14–84 days after non-immune individuals are exposed to a primary infection or heavy reinfection, is common in high transmission areas in China.[2,7] Disease onset is related to migrating schistosomula larvae and egg deposition by adult female worms, with individuals typically presenting with nocturnal fever, cough, myalgia, headache and abdominal tenderness.[12]

Treatment for acute schistosomiasis in China is praziquantel (PZQ) at a dose of 120 mg/kg body weight over a 6-day period.[6,13,14] However, this is only effective on adult worms and early (3–8 hour) skin-stage schistosomula.[15] The co-existence of mature and immature worms in infected subjects may prolong fever after PZQ treatment, necessitating additional chemotherapy.[16] Furthermore, some individuals do not respond well to PZQ, especially if they have had repeated water exposure before the onset of disease.[12]

Artemether (AM), used for the treatment of malaria, is also effective against juvenile schistosomes in animals[17–21] and humans,[22–27] and it has been developed as a prophylactic for the prevention of patent schistosome infections.[26,27] In animals, combination therapy with PZQ plus AM is safe and results in higher worm reduction rates than PZQ alone,[28,29] a finding that has yet to be confirmed in human studies.

Here, we assessed the safety and efficacy of combining PZQ plus AM in different doses to treat acute schis-

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tosomiasis japonica in a randomized, double-blind, placebo-controlled trial carried out in a hospital setting in China.

Methods

Study objectives

The main objective of the study was to determine the safety and efficacy of combination therapy with AM and PZQ for acute cases of schistosomiasis japonica. Secondary objectives were to assess the safety and efficacy of PZQ in varying doses, either alone or in combination with AM, in the treatment of acute disease.

Study design

A randomized, double-blind, placebo-controlled trial, within four specialized schistosomiasis hospitals in the Dongting Lake region Hunan province, China, was carried out between May 2003 and December 2005. Study participants were randomized into one of four treatment regimens (Table 1) and were followed up over a 45-day period. The primary endpoint of the trial was human infection status. Secondary endpoints included haemoglobin and alanine aminotransferase (ALT) levels over time.

Study participants

Patients were admitted to the study based on the following inclusion criteria: (i) diagnosed to have acute schistosomiasis japonica, (ii) aged 10–60 years, (iii) weighed > 25 kg, (iv) willing to be followed up for 45 days post-treatment, and (v) provided informed consent. A confirmed case of acute schistosomiasis japonica was based on the following criteria formulated by the Ministry of Public Health in China[13]: (i) positive stool examination for *S. japonicum* eggs by the Kato–Katz method, (ii) positive serology for schistosomiasis, (iii) recent history of water exposure, (iv) fever and/or other relevant symptoms, and (v) peripheral blood eosinophilia comprising ≥ 15% of the total leukocyte count.

Exclusion criteria included any of the following: (i) pregnancy confirmed by a positive pregnancy test, (ii) known hypersensitivity to PZQ or AM, (iii) had received anti-schistosomal treatment before hospitalization, (iv) had water contact within the 45-day post-AM/placebo treatment, or (v) had severe clinical signs/symptoms of disease such as jaundice, caput medusae, ascites, hepatosplenomegaly or telangiectasias as determined by haematological, biochemical, radiological and physiological assessment that included a full blood count, liver function tests, including measurement of ALT, renal function tests, chest X-ray, abdominal ultrasound and electrocardiography (ECG).

Baseline

Study participants were interviewed by questionnaire for history of water exposure before hospitalization and were subjected to medical and physical examination. Each patient had urine and two stool samples collected. Urine samples underwent routine testing and stool samples were examined for the presence of schistosome eggs by the miracidial hatching test and the Kato–Katz thick smear method (3 × 50 mg smears/stool).[30] Serological testing for *S. japonicum* infection by indirect haemagglutination and enzyme-linked immunosorbent assays (ELISA), using soluble *S. japonicum* egg antigen, was also performed.[13] A complete haematological and biochemical assessment, including measurements in blood levels of urea nitrogen, ALT, creatinine and haemoglobin, and eosinophil count, was also carried out using standard procedures.

Treatment regime

PZQ (batch no. 0306092, 200 mg/tablet, Anhui, China) was provided by the Hunan Provincial Anti-Schistosomiasis Office. AM, formulated as a 40 mg capsule (batch no. 20030891) or indistinguishable placebo capsules containing starch (batch no. 20030892), was obtained from Kunming Pharmaceutical Corporation (Kunming, China). The products were manufactured to international standards and licensed for human use. A full dose of AM or placebo (360 mg; 9 capsules/person) plus PZQ (7200 mg; 36 tablets/person) was prepared and packed in two different medication bags according to the randomization list by a pharmacologist at the Hunan Institute of Parasitic Diseases.

The AM (6 mg/kg body weight) or placebo was administered as a single dose at 20:00 on day 0. The four treatment regimens, designated as A, B, C and D, are described in Table 1. Treatment groups were named accordingly. Supporting and symptomatic treatment was administered according to the condition of each patient. Those with an axillary temperature over 39.0 °C were treated for 2–3 days with oral prednisone post-commencement of PZQ treatment.

Follow-up

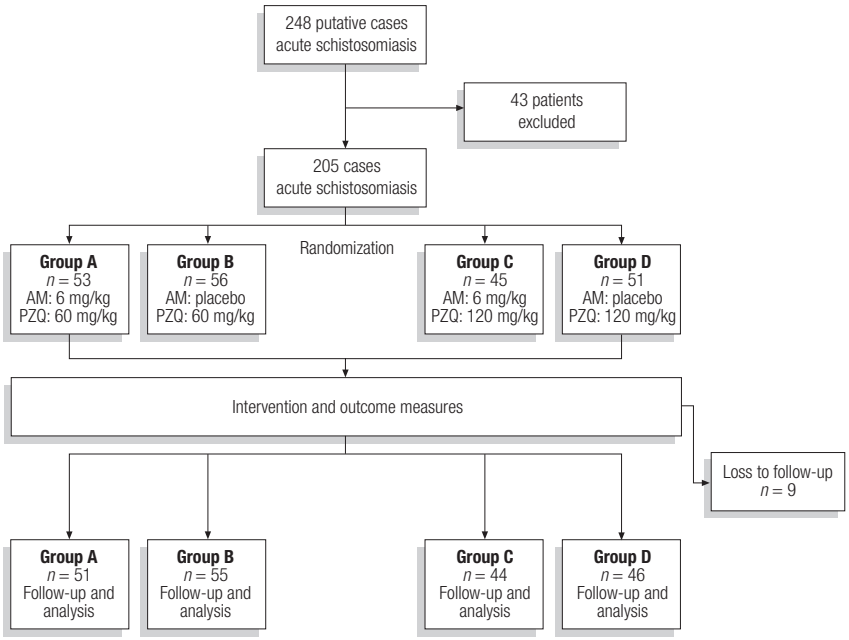
Clinical evaluations were carried out throughout the treatment and hospitalization period. Patients were observed for clinical improvement, drug side-effects and any serious or unexpected adverse events. At days 10 and 20, liver and renal functions and haematological status were assessed for any abnormality. Faecal egg examinations were performed on day 45 after initial treatment with AM or placebo as described above.

Safety was assessed by incidence of any serious or unexpected adverse events 4 hours after AM and PZQ administration and during the hospitalization period. An adverse event was determined by one or more of the following: (i) death, (ii) threat of death, (iii) prolongation of existing hospitalization, or (iv) persistence of or significant disability/incapacity. When any adverse events occurred, patients were examined by the physicians appointed to the project, and the events were recorded on a specially-designed case report form. Necessary interventions for adverse events were delivered to patients as required.

Table 1. **Treatment regimens for patients categorized randomly into four groups**

Group	Artemether (day 0)	Praziquantel (day 1)	Praziquantel (days 1–6)
A	6 mg/kg	60 mg/kg	–
B	Placebo	60 mg/kg	–
C	6 mg/kg	–	120 mg/kg
D	Placebo	–	120 mg/kg

Fig. 1. **Trial profile**



AM, artemether; PZQ, praziquantel.

Blinding, randomization and quality control

Two physicians from the Hunan Institute of Parasitic Diseases coordinated the clinical assessment and diagnosis of acute schistosomiasis japonica and treatment. All study investigators, hospital staff and patients were blinded as to which patients were given AM or placebo. Laboratory staff was blinded as to which patients received differing doses of PZQ. Random allocation of treatment regimens using a computer-generated random number list was performed by a senior scientist from the Hunan Institute of Parasitic Diseases who was independent of the treatment and laboratory testing. An independent experienced technician rechecked 10% of the Kato–Katz thick smears for parasitological examination. The final analysis included only those patients who completed the treatment regimen, had been clinically evaluated during the hospitalization, and were followed up at days 10, 20 and 45 after treatment with AM or placebo.

Power

Power calculations at the design phase of this trial were based on the assumption that PZQ-based chemotherapy had an efficacy of 80–85% and so the study would have 80% power to detect the additive treatment effect of AM at the $\alpha = 0.05$ level.

Data management and statistical analysis

Data were double entered into a Microsoft Access database (Microsoft Corporation, Redmond WA, United States of America). Statistical analysis was performed in SPSS 11.0 (SPSS Inc., Chicago, IL, USA) and SAS (SAS Institute Inc., Cary, NC, USA). *P*-values were calculated using the χ^2 test for categorical variables, one-way analysis of variance for continuous variables, Kruskal–Wallis for non-parametric continuous variables and the Fisher exact test for categorical variables with small sample size. Treatment efficacy (%) was determined by:

$$[I_{45} / I_0] \times 100$$

where I_{45} represents positivity for *S. japonicum* eggs 45 days post-AM/placebo treatment and I_0 represents positivity for *S. japonicum* eggs pre-AM/placebo treatment. Trial endpoints were determined by comparing the efficacies of the various treatment regimes.

Ethical issues

Written approval to perform the trial was obtained from the Institution Review Board of the Hunan Institute of Parasitic Diseases and the WHO Secretariat Committee for Research Involving Human Subjects (SCRIHS), Geneva, Switzerland. Eligible study subjects or their legal guardians (for children aged less than 16) were invited to discuss the details and possible risks of the trial with the physician in charge. Informed consent was obtained from all study participants and/or legal guardians. Study participants who were still positive for *S. japonicum* following the trial were treated with PZQ (60 mg/kg).

Results

A total of 248 subjects presenting with supposed acute schistosomiasis japonica were recruited for the trial. Of these, 43 were excluded based on the criteria previously provided, leaving 205 who were randomized into the four treatment regimens. A further 9 were lost to follow-up due to migration out of the Dongting Lake area, resulting in a final cohort of 196 (group A: $n = 51$, group B: $n = 55$, group C: $n = 44$, group D: $n = 46$) for a coverage of 95.6% (Fig. 1).

Baseline demographics and clinical observations

Table 2 shows the baseline demographic and clinical characteristics along with recent water exposure of the study participants. Of the 205 recruited, 192 (93.7%) were male (average age: 22.4 years) and 13 (6.3%) female (average age: 21.3 years). There were 117 (57.1%) schoolchildren, 31 (15.1%) businessmen, 28 (13.7%) farmers and 29 (14.1%) fishermen. Participants who had only one or two contacts with cercariae-infested water numbered 117 (57.1%), whereas 55 (26.6%) had regular water contact of more than 30 days in the 2 months before hospitalization. More than half (61.5%; $n = 126$) of the patients were infected through playing or swimming in schistosome-infested water. No significant differences were observed between the treatment groups in relation to water exposure ($P = 0.097$).

Most patients (171; 83.4%) had no history of schistosomiasis infection and many had sought and received treatment for common cold symptoms before presenting for hospitalization. The number of days with fever before hospitalization ranged from 1 to 46, with a mean of 12 days (standard deviation, SD: 8.6). Axillary temperature on admission ranged

Table 2. **Demographic/clinical data and water exposure of subjects in various treatment groups at baseline**

Characteristics	Group A (*n* = 53)	Group B (*n* = 56)	Group C (*n* = 45)	Group D (*n* = 51)	*P*-value
Mean age in years (SD)	24.9 (15.1)	23.6 (14.0)	19.4 (10.4)	20.7 (12.3)	0.147
Male/female	49/4	51/5	43/2	49/2	0.674
Mean weight in kg (SD)	48.6 (15.6)	47.1 (14.8)	45.0 (15.8)	43.9 (16.1)	0.420
Occupation					
Farmer	9 (17.0%)	10 (17.9%)	1 (2.2%)	8 (15.7%)	0.067
Fisherman	14 (26.4%)	9 (16.1%)	3 (6.7%)	3 (5.9%)	0.009
Businessman	6 (11.3%)	4 (7.1%)	13 (28.9%)	8 (15.7%)	0.123
Student	24 (45.3%)	33 (58.9%)	28 (62.2%)	32 (62.7%)	0.630
Water exposure in days					
Mean (SD)	15.0 (17.9)	8.7 (15.9)	12.6 (17.9)	10.2 (16.4)	0.097
Median (range)	2 (1–49)	1 (1–61)	3 (1–60)	1 (1–56)	0.078
Mean number of days of fever before hospitalization (range)	9 (1–46)	9 (1–38)	10 (2–30)	9 (2–30)	0.711
Mean temperature in °C on admission (SD)	38.3 (1.0)	38.5 (0.8)	38.7 (1.2)	38.2 (1.1)	0.108
Clinical symptoms					
Fatigue	48 (90.6%)	45 (80.4%)	44 (97.8%)	43 (84.3%)	0.450
Loss of appetite	33 (66.0%)	36 (67.9%)	34 (82.2%)	33 (68.6%)	0.288
Cough	23 (43.4%)	25 (44.6%)	28 (62.2%)	31 (60.8%)	0.100
Dizziness	27 (50.9%)	26 (46.4%)	28 (62.2%)	22 (43.1%)	0.267
Diarrhoea	19 (35.8%)	29 (51.8%)	17 (37.8%)	17 (33.3%)	0.199
Abdominal distension	12 (22.6%)	16 (28.6%)	15 (33.3%)	11 (21.6%)	0.522
Abdominal pain	6 (11.3%)	12 (21.4%)	9 (20.0%)	10 (19.6%)	0.521
Hepatomegaly	23 (43.4%)	27 (48.2%)	17 (37.7%)	18 (35.3%)	0.535
Splenomegaly	6 (11.3%)	11 (19.6%)	6 (13.3%)	5 (9.8%)	0.459

SD, standard deviation.

from 37.5 °C to 41.2 °C with a mean of 38.4 °C (SD: 1.0 °C). Other clinical features observed included fatigue, loss of appetite, cough, dizziness, diarrhoea, abdominal distension and abdominal pain as well as hepatomegaly and splenomegaly (Table 2). No significant differences were observed between groups. The intensities of *S. japonicum* infection (geometric mean eggs per gram of faeces, epg) in study participants within the treatment regimens are shown in Table 3. These intensities were similar except for group B, which was 81.7 epg (95% confidence inverval, CI: 58.4–114.3). Six patients (2.9%) were shown to be co-infected with *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm) and/or *Fasciolopsis buski* (giant intestinal fluke). Patients who had fever above 39 °C (146; 71.2%) received short-term oral prednisone (0.5–1mg/kg/day for 2–3 days) to reduce fever during hospitalization.

Treatment efficacy

Efficacies for the four treatment regimens are shown in Table 3. All groups had similarly high treatment efficacies ranging from 95.7% (group D) to 98% (group A). Comparisons of group A with group B and group C with group D for the determination of the additive effect of AM showed that there were higher, not statistically significant ($P = 0.947$), treatment efficacies in the regimes that included AM. The two different dosages of PZQ (group A with C and group B with D) provided the same level of efficacy.

Treatment efficacy in terms of reduction of fever – the main symptom of acute schistosomiasis – and length of stay in hospital are shown in Table 4. Fever subsided in 3.9, 5.1, 6.4 and 5.2 days post-AM treatment in groups A, B, C and D, respectively ($P = 0.027$). Combined AM/PZQ (60 mg/kg) treatment was the most effective for fever clearance. Patients in groups A to D remained in hospital on average 6.4, 8.0, 9.4 and 8.9 days, respectively; the hospital stay of patients in group A was significantly shorter than in the other groups ($P = 0.023$).

Prior to treatment, sinus tachycardia was evident in 85.7%, 82.2%, 68.6% and 75.5% of cases from groups A, B, C and D respectively ($P = 0.156$); and sinus dysrhythmia was evident in 11.3%, 14.3%, 8.9% and 7.8% cases from groups A, B, C and D respectively ($P = 0.715$). There was no additional adverse effect on ECG parameters observed during medication time or 10 days post-treatment. All ECG changes observed before treatment returned to normal for all study subjects post-treatment in our study. Chest X-ray revealed diffuse, nodular or patchy bilateral infiltrates in the lungs of 53 patients (22.6%, 21.4%, 31.15% and 29.4% from groups A, B, C and D respectively; $P = 0.129$). All abnormalities were recovered before discharge from hospital. Prior to treatment, all patients showed widened echogenic dots but no network in liver parenchyma on ultrasound examination. In addition, hepatomegaly and splenomegaly were observed in 41.5% and 13.7% of patients, respectively, by ultrasonographic examination with no significant difference between groups

Table 3. **Infection intensity, treatment efficacy and blood biochemistry of subjects in various treatment groups**

Parameters[a]	Group A (n = 51)	Group B (n = 55)	Group C (n = 44)	Group D (n = 46)	P-value
Cases positive: baseline	51	55	44	46	
Mean epg baseline (95% CI)	54.6 (35.7–83.5)	81.7 (58.4–114.3)	51.5 (33.1–80)	50.6 (34.2–74.8)	0.265
Cases positive: follow-up	1	2	1	2	
Treatment efficacy in %	98	96.4	97.7	95.7	0.947
Mean ALT_0, μ/l (SD) (n = 205)	54.3 (41.0)	66.2 (50.2)	48.9 (20.5)	57.9 (41.1)	0.531
Mean ALT_{10}, μ/l (SD)	69.6 (55.2)	77.4 (44.2)	54.7 (31.0)	66.9 (65.5)	0.527
Mean ALT_{20}, μ/l (SD)	53.7 (35.6)	49.2 (15.8)	35.7 (11.8)	34.6 (21.4)	0.358
Mean BUN_0, mmol/L (SD)	3.5 (1.2)	3.6 (0.9)	3.0 (1.1)	3.1 (1.1)	0.852
Mean BUN_{20}, mmol/L (SD)	3.4 (1.6)	3.4 (1.6)	3.4 (1.2)	3.1 (1.0)	0.776
Mean blood $creatinine_0$, mmol/L (SD)	75.2 (25.2)	70.5 (15.6)	77.7 (18.5)	80.4 (21.9)	0.729
Mean blood $creatinine_{20}$, μmol/L (SD)	72.6 (21.2)	73.7 (19.1)	78.5 (13.5)	74.5 (18.5)	0.458
Mean $haemoglobin_0$, g/dl (SD)	119.9 (18.5)	120.1 (11.9)	126.3 (13.7)	121.4 (13.1)	0.794
Mean $haemoglobin_{20}$, g/dl, (SD)	129.0 (15.4)	119.3 (16.1)	123.6 (16.8)	122.1 (14.7)	0.625
Mean $eosinophils_0$, % (SD)	33.8 (33.5)	31.2 (21.9)	25.5 (15.2)	36.0 (27.9)	0.595
Mean $eosinophils_{20}$, % (SD)	33.3 (22.4)	31.7 (20.5)	24.0 (12.6)	32.9 (11.9)	0.434

ALT, alanine aminotransferase; BUN, blood urea nitrogen; CI, confidence interval; epg, eggs per gram; SD, standard deviation.
[a] Numbers in subscript indicate days post-treatment with artemether.

($P > 0.05$; Table 2). Significant improvement was not observed over the course of the trial and follow-up period (data not shown).

Little change in haemoglobin levels of patients was observed over the course of the trial and there were no significant differences between the groups both pre- and post-treatment. Eosinophilia was high before treatment and remained high over the course of the trial. Renal functions were not influenced by the drug treatment. In total, 34 cases had an elevated ALT level before treatment, of which 24 returned to normal at day 20 post-AM treatment. Although the mean levels of ALT at day 10 post-AM treatment were increased by 7.8% (group A), 8.6% (group B), 8.9% (group C) and 8.7% (group D), there were no statistically significant differences between the groups, and the mean levels of ALT at 20 days post-AM treatment dropped to normal levels (Table 3). The general condition of patients was improved before their discharge from hospital.

Drug safety

AM was well-tolerated with excellent compliance. Only 13 (6.3%) minor adverse events (allergy, nausea, vomiting and abdominal discomfort) were reported and/or observed within 4 hours of AM administration; and there were no serious or unexpected adverse events observed or reported during the trial period. Some patients (54; 26.3%) suffered pain in the upper abdominal region after PZQ treatment (first or second dose), and this was usually accompanied with one to two episodes of diarrhoea. Other side-effects included headache (11.7%), nausea (10.7%), lower abdominal discomfort (7.8%) and fatigue (7.3%). Our study did not reveal any additional side-effects caused by possible interactions of PZQ and AM when the drugs were administrated approximately 12 hours apart.

Discussion

Acute schistosomiasis is a clinical manifestation that occurs several weeks post-schistosomal infection.[12] Because of this temporal delay and its nonspecific presentation, accurate diagnosis is problematic and can often be delayed on average up to 2 weeks. Patients are often misdiagnosed as having the common cold or other infections. Once the patient is correctly diagnosed and offered treatment, schistosome worms can be cleared rapidly and all symptoms disappear.

Here we evaluated the efficacy and safety of combined PZQ and AM chemotherapy for acute schistosomiasis japonica in 196 Chinese patients, all with a history of fever (an average of 12 days) before hospitalization. High treatment efficacies for acute schistosomiasis resulted following PZQ chemotherapy with or without the addition of AM (Table 3). Animal model experiments had shown previously that combination treatment with PZQ plus AM, given 1 or 3 days apart, was more effective than each drug given separately.[28,29] In contrast, the additive effect of AM (Table 3; $P = 0.947$) could not be quantified in the current trial due to the treatment efficacies in the control groups (PZQ/placebo) being too high and above those predicted.

The results suggest that a 60 mg/kg (1 day, 3 × 20 mg/kg doses at 4–5 hour intervals) PZQ dosage may be as effective as a 120 mg/kg (1–6 days, 20 mg/kg for each day split into 3 doses at 4–5 hour intervals) dosage for treating acute schistosomiasis, even though the latter treatment regimen is currently recommended in China. A reduction in the dosage of PZQ could reduce the

costs and potential side-effects of treatment for acute schistosomiasis. Combined PZQ (60 mg/kg)/AM (6 mg/kg) treatment was better for clearance of fever ($P < 0.05$) and resulted in shorter hospitalization time ($P < 0.05$). This can probably be explained by both the effect of a shorter PZQ treatment regimen and quicker worm clearance by the combined drug treatment.

In field trials in China and Africa,[22,23,25] 2–11 doses of AM (6 mg/kg) given fortnightly were well-tolerated with no major adverse events observed, although there have been reports of minor symptoms that were transient and usually self-limiting.[31] Our study supports these findings with no serious or unexpected adverse effects observed. A single 6 mg/kg dose of AM therefore appears to be safe for treating acute schistosomiasis japonica, with subjects exhibiting only minor side-effects. AM and PZQ given 12 hours apart overnight did not induce any adverse effects and so combined chemotherapy also appears to be a safe treatment option.

Table 4. **Days of remaining fever and days of additional hospital stay following treatment in 205 patients with acute *S. japonicum* infection, according to treatment groups**

Group	*N*	Days of fever mean (SD)	Additional hospital days mean (SD)
A	53	3.9 (3.4)	6.4 (3.9)
B	56	5.1 (5.0)	8.0 (4.2)
C	45	6.4 (7.8)	9.4 (3.8)
D	51	5.2 (3.1)	8.9 (3.1)
Total	205	5.1 (5.1)	8.1 (3.9)

SD, standard deviation.

Conclusion

This is the first report of a randomized, double-blind, placebo-controlled trial for evaluating combined chemotherapy with AM and PZQ at two different dosages (60 mg/kg and 120 mg/kg) in the treatment of acute schistosomiasis japonica in China. The combination of AM and PZQ chemotherapy did not improve treatment efficacy compared with PZQ alone, and the trial had no influence on improving certain clinical manifestations as a result of acute schistosomiasis. PZQ given as a dosage of 60 mg/kg (1 day, 3 × 20 mg/kg doses at 4–5 hour intervals) may be as effective as the dosage of 120 mg/kg (6 days, 20mg/kg for each day split into 3 doses at 4–5 hour intervals) that is currently used for treating acute schistosomiasis in China. An additional study is now required to confirm these findings before any recommendations for policy changes regarding future schistosomiasis treatment in China. ■

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Competing interests: None declared.

Résumé

Essai contrôlé randomisé en double aveugle, portant sur l'innocuité et l'efficacité de l'association praziquantel/artéméther dans le traitement de la schistosomiase asiatique aiguë en Chine

Objectif Evaluer l'innocuité et l'efficacité de l'association artéméther (AM)/praziquantel (PZQ) dans le cadre de différents schémas thérapeutiques contre la schistosomiase asiatique aiguë.

Méthodes Nous avons entrepris un essai contrôlé randomisé en double aveugle dans quatre hôpitaux spécialisés dans la schistosomiase de la région du lac de Dongting, dans la province du Hunan, en Chine, entre mai 2003 et décembre 2005. Aux participants à l'étude, on a affecté au hasard l'un des quatre schémas thérapeutiques suivants : le groupe A a reçu 60 mg/kg de PZQ + 6 mg/kg d'AM ; le groupe B a reçu 60 mg/kg de PZQ + placebo de l'AM ; le groupe C a reçu 120 mg/kg de PZQ + 6 mg/kg d'AM ; et le groupe D a reçu 120 mg/kg de PZQ + placebo de l'AM. Tous les participants ont été suivis sur une période de 45 jours. La principale mesure de résultat pour l'essai était le statut infectieux des sujets (déterminé par le résultat de l'examen de selles). Parmi les mesures de résultat secondaires, figuraient des observations cliniques et des analyses biochimiques du sang, notamment la surveillance des taux d'hémoglobine et d'alanine aminotransférase au cours du temps.

Résultats L'efficacité du traitement par les quatre schémas thérapeutiques était respectivement de 98,0 %, 96,4 %, 97,7 % et 95,7 % pour les groupes A, B, C et D ($p > 0,05$). Le traitement du groupe B s'est révélé plus efficace (98 %) que celui du groupe D (95,7 %) ($p > 0,05$). Le traitement du groupe A a permis une meilleure élimination de la fièvre ($p < 0,05$) et une durée d'hospitalisation plus courte ($p < 0,05$).

Conclusion C'est la première fois qu'on rapporte un essai contrôlé randomisé en double aveugle visant à évaluer l'association médicamenteuse AM/PZQ et deux doses différentes (60 et 120 mg/kg) de PZQ dans le traitement de la schistosomiase asiatique aiguë en Chine. Le recours à l'association médicamenteuse AM/PZQ n'a pas amélioré l'efficacité du traitement par rapport à l'administration de PZQ seul. Le PZQ pourrait être aussi efficace à la dose de 60 mg/kg (sur une journée, 3 doses de 20 mg/kg à 4-5 heures d'intervalle) qu'à celle de 120 mg/kg (sur 6 jours, 20 mg/kg chaque jour, répartis en 3 doses à 4-5 heures d'intervalle).

Resumen

Ensayo aleatorizado a doble ciego controlado con placebo sobre la seguridad y eficacia del tratamiento combinado con prazicuantel y artemetero contra la esquistosomiasis japonesa aguda en China

Objetivo Evaluar la seguridad y eficacia de la combinación de artemetero (AM) y prazicuantel (PZQ) en diferentes posologías para tratar la esquistosomiasis japonesa aguda.

Métodos Entre mayo de 2003 y diciembre de 2005 se realizó un ensayo aleatorizado a doble ciego controlado con placebo en cuatro hospitales especializados en la esquistosomiasis de la región del lago Dongting, en la provincia china de Hunan. Los participantes en el estudio se repartieron aleatoriamente entre cuatro grupos sometidos a distintas pautas de tratamiento: el grupo A recibió 60 mg/kg PZQ + 6 mg/kg AM; el grupo B, 60 mg/kg PZQ + placebo de AM; el grupo C, 120 mg/kg PZQ + 6 mg/kg AM; y el grupo D, 120 mg/kg PZQ + placebo de AM. Todos los participantes fueron sometidos a seguimiento durante un periodo de 45 días. El criterio principal de valoración empleado en el ensayo fue la presencia de la infección (examen coproparasitoscópico positivo). Como criterios secundarios de valoración se emplearon los resultados de la exploración clínica y de los análisis bioquímicos sanguíneos, en particular la evolución de los niveles de hemoglobina y de alanina-aminotransferasa.

Resultados La eficacia de las cuatro pautas de tratamiento fue del 98,0%, 96,4%, 97,7% y 95,7% para los grupos A, B, C y D, respectivamente ($p > 0,05$). La eficacia fue mayor en el grupo B (98%) que en el D (95,7%) ($p > 0,05$). El tratamiento recibido por el grupo A eliminó más eficazmente la fiebre ($p < 0,05$) y acortó el tiempo de hospitalización ($p < 0,05$).

Conclusión Este es el primer trabajo publicado sobre un ensayo aleatorizado a doble ciego controlado con placebo destinado a evaluar la antibioticoterapia combinada con AM y dos posologías diferentes (60 mg/kg y 120 mg/kg) de PZQ como tratamiento de la esquistosomiasis japonesa aguda en China. La combinación de AM y PZQ no mejoró la eficacia del tratamiento en comparación con el uso aislado de PZQ. El PZQ administrado en dosis de 60 mg/kg (1 día, 3 tomas de 20 mg/kg a intervalos de 4-5 horas) puede ser tan eficaz como en dosis de 120 mg/kg (6 días, 20 mg/kg cada día repartidos en 3 tomas a intervalos de 4-5 horas).

ملخص

دراسة مُعَشَّاة مزدوجة التعمية مُضَبَّطَة بالغُفُل حول سلامة وكفاءة المعالجة المشتركة بالبرازكوانتيل والأرتيميثير لداء البلهارسيات اليابانية الحاد في الصين

الهدف: تقييم سلامة وكفاءة المعالجة المشتركة بالبرازكونتيل والأرتيمثير في نُظُم المعالجة المختلفة لمعالجة داء البلهارسيات اليابانية الحاد في الصين.

الطريقة: أجرينا دراسة مُعَشَّاة مزدوجة التعمية مُضَبَّطة بالغُفُل في المستشفيات المتخصصة لمعالجة داء البلهارسيات في منطقة بحيرة دونغتنج، بمقاطعة هونان في الصين، في الفترة من أيار/مايو 2003 وحتى كانون الأول/ديسمبر 2005. وقد توزَّع المشاركون في الدراسة توزيعاً عشوائياً في أربع مجموعات من حيث النُظُم العلاجية: بحيث يتلقَّى مَنْ كان منهم في المجموعة A، 60 ملغ/كغ من البرازكونتيل و6 ملغ من الأرتيميثر، ويتلقّى مَنْ كان منهم في المجموعة B، 60 ملغ/كغ من البرازكونتيل وغُفُلاً عوضاً عن الأرتيثيمير، ويتلقَّى مَنْ كان منهم في المجموعة C، 120 ملغ/كغ من البرازكونتيل و6 ملغ/كغ من الأرتيميثر، ويتلقّى مَنْ كان منهم في المجموعة D، 120 ملغ/كغ من البرازكونتيل وغُفُلاً عوضاً عن الأرتيميثر. وتابعنا جميع المشاركين لمدة 45 يوماً. واعتبرنا نقطة النهاية الأولية للدراسة وضع العدوى البشرية (كما تحددها إيجابية فحص البراز)، فيما اعتبرنا أن نقطة النهاية الثانوية تشتمل على الملاحظات السريرية (الإكلينيكية) ونتائج الاختبارات الكيميائية الحيوية للدم والتي تتضمَّن مراقبة مستويات الهيموغلوين وإنزيم ناقلة أمين الألاين مع مرور الزمن.

الموجودات: بلغت نجاعة المعالجة لدى المجموعة A، 98% ولدى المجموعة B، 96.4% ولدى المجموعة C، 97.7% ولدى المجموعة D، 95.7% (بقوة احتمال تزيد على 0.05). وكان لدى المجموعة B نجاعة معالجة (96.4%) تزيد على ما لدى المجموعة D (95.7%) (بقوة احتمال تزيد على 0.05). وكانت المعالجة لدى المجموعة A أفضل من حيث زوال الحمى (بقوة احتمال يقل عن 0.05) وأدت إلى فترة إقامة في المستشفى أقصر (بقوة احتمال أقل من 0.05).

الاستنتاج: يعد هذا التقرير الأول من نوعه حول دراسة مُعَشَّاة مزدوجة التعمية مُضَبَّطة بالغُفُل لتقييم المعالجة الكيميائية بتوليفة تضم الأرتيميثر بجرعتين مختلفتين هما 60 ملغ/كغ و120 ملغ/كغ مع البرازكوانتيل لمعالجة داء البلهارسيات اليابانية الحاد في الصين. ولم يؤد الجمع بين الأرتيميثر والبرازكوانتيل في المعالجة الكيميائية إلى تحسين نجاعة المعالجة بالمقارنة مع إعطاء البرازكوانتيل لوحده، كما أن إعطاء 60 مغ من البرازكوانتيل لمدة يوم واحد مقسماً على ثلاث جرعات في كل منها 20 مغ/كغ، تؤخذ بفواصل 4-5 ساعات) قد يكون نفس النجاعة الناتجة عن الجرعات التي يُعْطَى فيها 120 ملغ/كغ من البرازكوانتيل مُقَسَّماً على ستة أيام بمقدار 20 ملغ/كغ كل يوم مقسمة على ثلاث جرعات يفصل بينها 4-5 ساعات.

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