

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Hou, XY; McManus, DP; Gray, DJ; Balen, J; Luo, XS; He, YK; Ellis, M; Williams, GM; LI, YS; (2008) A randomized, double-blind, placebo-controlled trial of safety and efficacy of combined praziquantel and artemether treatment for acute schistosomiasis japonica in China. Bulletin of the World Health Organization, 86 (10). pp. 788-95. ISSN 0042-9686 DOI: <https://doi.org/10.2471/BLT.08.053041>

Downloaded from: <http://researchonline.lshtm.ac.uk/3074/>

DOI: <https://doi.org/10.2471/BLT.08.053041>

Usage Guidelines:

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

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

Xun-Ya Hou,^a Donald P McManus,^b Darren J Gray,^b Julie Balen,^b Xin-Song Luo,^a Yong-Kang He,^a Magda Ellis,^b Gail M Williams^c & Yue-Sheng Li^b

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 regimens: 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).

Bulletin of the World Health Organization 2008;86:788–795.

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-

^a Hunan Institute of Parasitic Diseases, WHO Collaborating Centre for Research and Control on Schistosomiasis in Lake Region, Yueyang, China.

^b Molecular Parasitology Laboratory, Queensland Institute of Medical Research, 300 Herston Road, Herston, Brisbane, Qld., Australia.

^c School of Population Health, University of Queensland, Brisbane, Qld., Australia.

Correspondence to Yue-Sheng Li (e-mail: yuesheng.li@qimr.edu.au).

doi:10.2471/BLT.08.053041

(Submitted: 16 March 2008 – Revised version received: 4 June 2008 – Accepted: 5 June 2008 – Published online: 25 August 2008)

Xun-Ya Hou et al.

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 China¹³: (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 $\geq 15\%$ 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

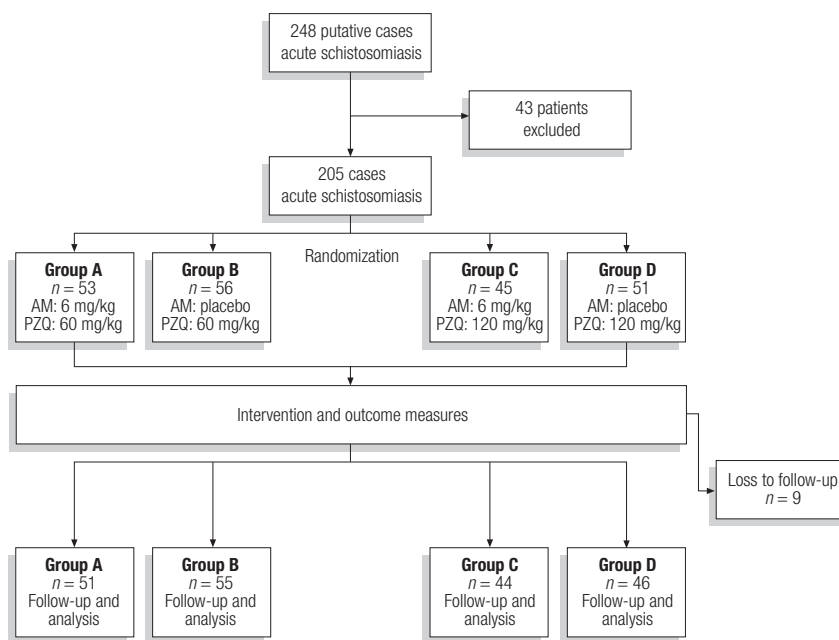
Clinical evaluations were carried out throughout the treatment and hospitalization period. Patients were observed for clinical improvement, drug side-effects and any serious or unexpected adverse events. At days 10 and 20, liver and renal functions and haematological status were assessed for any abnormality. 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 interval, 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 (0.5–1 mg/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 egg 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 , µl (SD) (n = 205) | 54.3 (41.0) | 66.2 (50.2) | 48.9 (20.5) | 57.9 (41.1) | 0.531 |
| Mean ALT ₁₀ , µl (SD) | 69.6 (55.2) | 77.4 (44.2) | 54.7 (31.0) | 66.9 (65.5) | 0.527 |
| Mean ALT ₂₀ , µl (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; egg, 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, vomit-

ing 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 administered 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 non-specific 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.

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

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.

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, 20 mg/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. ■

Acknowledgements

We thank all patients who participated in the trial and all the physicians and staff involved in the study.

Funding: This work was supported by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) (grant no. A20041) and a Wellcome Trust (UK)-National Health and Medical Research Council (Australia) International Collaborative Research Grants Scheme Award (WT071657-MA).

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 Évaluer 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 antibióticoterapia 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 مُعشاة مزدوجة التعمية مُضَبَّطَة بِالْغُفْلِ حَوْلَ سَلَامَةِ وَكِفَاءَةِ الْمَعَالِجَةِ الْمَشْتَرَكَةِ بِالْبِرَازُكُونْتِيلِ وَالْأَرْتِيمِيثِيرِ لِدَاءِ الْبِلَهَارَسِيَّاتِ الْيَابَانِيَّةِ الْحَادِ فِي الصِّينِ

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 مُعشاة مزدوجة التعمية مُضَبَّطَة بِالْغُفْلِ لتقييم المعالجة الكيميائية بتوليفة تضم الأرتيميثير بجرعتين مختلفتين هما 60 ملغ/كغ و120 ملغ/كغ مع البرازكوانتيل لمعالجة داء البلهارسيات اليابانية الحاد في الصين. ولم يؤد الجمع بين الأرتيميثير وإعطاء 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 يُعطى فيها 120 ملغ/كغ من البرازكوانتيل مُقسماً على ستة أيام بمقدار 20 ملغ/كغ كل يوم مقسمة على ثلاث جرعات يفصل بينها 4-5 ساعات.

الهدف: تقييم سلامة وكفاءة المعالجة المشتركة بالبرازكوانتيل والأرتيميثير في نُظْمِ المعالجة المختلفة لمعالجة داء البلهارسيات اليابانية الحاد في الصين. **الطريقة:** أجرينا دراسة مُعشاة مزدوجة التعمية مُضَبَّطَة بِالْغُفْلِ 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 توزع المشاركون في الدراسة توزيعاً عشوائياً في أربع مجموعات من حيث النُظْمِ العلاجية: بحيث يتلقى مَنْ كان منهم في المجموعة A، 60 ملغ/كغ من البرازكوانتيل و6 ملغ من الأرتيميثير، ويتلقى مَنْ كان منهم في المجموعة B، 60 ملغ/كغ من البرازكوانتيل وُغُفْلاً عوضاً عن الأرتيميثير، ويتلقى مَنْ كان منهم في المجموعة C، 120 ملغ/كغ من البرازكوانتيل و6 ملغ/كغ من الأرتيميثير، ويتلقى مَنْ كان منهم في المجموعة D، 120 ملغ/كغ من البرازكوانتيل وُغُفْلاً عوضاً عن الأرتيميثير. 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 تتضمن مراقبة مستويات الهيموغلوبين وإنزيم ناقلة أمين الألائن مع مرور الزمن.

References

- Minggang C, Zheng F. Schistosomiasis control in China. *Parasitol Int* 1999;48:11-9. PMID:11269321 doi:10.1016/S1383-5769(99)00004-5
- Zhou XN, Wang LY, Chen MG, Wu XH, Jiang QW, Chen XY, et al. The public health significance and control of schistosomiasis in China - then and now. *Acta Trop* 2005;96:97-105. PMID:16125655 doi:10.1016/j.actatropica.2005.07.005
- Balen J, Zhao ZY, Williams GM, McManus DP, Raso G, Utzinger J, et al. Prevalence, intensity and associated morbidity of *Schistosoma japonicum* infection in the Dongting Lake region, China. *Bull World Health Organ* 2007;85:519-526. PMID:17768500 doi:10.2471/BLT.06.034033
- Yuan H, Guo JG, Bergquist R, Tanner M, Chen XY, Wang HZ. The 1992-1999 World Bank schistosomiasis research initiative in China: outcome and perspectives. *Parasitol Int* 2000;49:195-207. PMID:11426575 doi:10.1016/S1383-5769(00)00045-3
- Qing-Wu J, Li-Ying W, Jia-Gang G, Ming-Gang C, Xiao-Nong Z, Engels D. Morbidity control of schistosomiasis in China. *Acta Trop* 2002;82:115-25. PMID:12020884 doi:10.1016/S0001-706X(02)00006-2
- Ross AGP, Sleight AC, Li YS, Davis GM, Williams GM, Zheng J, et al. Schistosomiasis in the People's Republic of China: prospects and challenges for the 21st century. *Clin Microbiol Rev* 2001;14:270-95. PMID:11292639 doi:10.1128/CMR.14.2.270-295.2001
- Utzinger J, Zhou XN, Chen MG, Bergquist R. Conquering schistosomiasis in China: the long march. *Acta Trop* 2005;96:69-96. PMID:16312039 doi:10.1016/j.actatropica.2005.08.004
- Li YS, Raso G, Zhao ZY, He YK, Ellis MK, McManus DP. Large water management project and schistosomiasis control, Dongting Lake region, China. *Emerg Infect Dis* 2007;13:973-9. PMID:18214167
- Li YS, Sleight AC, Ross AGP, Li Y, Williams GM, Forsyth SJ, et al. A 2-year prospective study in China provides epidemiological evidence for resistance in humans to re-infection with *Schistosoma japonicum*. *Ann Trop Med Parasitol* 1999;93:629-42. PMID:10707108 doi:10.1080/00034989958131
- McManus DP, Bartley PB. A vaccine against Asian schistosomiasis. *Parasitol Int* 2004;53:163-73. PMID:15081948 doi:10.1016/j.parint.2004.01.006
- Finkelstein JL, Schleinitz MD, Carabin H, McGarvey ST. Decision-model estimation of the age-specific disability weight for schistosomiasis japonica: a systematic review of the literature. *PLoS Negl Trop Dis* 2008;2:e158. PMID:18320018 doi:10.1371/journal.pntd.0000158
- Ross AGP, Vickers D, Olds GR, Shah SM, McManus DP. Katayama syndrome. *Lancet Infect Dis* 2007;7:218-24. PMID:17317603 doi:10.1016/S1473-3099(07)70053-1
- Ministry of Public Health of China. *Manual for schistosomiasis control* [in Chinese]. 3rd ed. Shanghai: Publishing House for Science and Technology; 2001. pp. 58-61.
- Chen MG. Use of praziquantel for clinical treatment and morbidity control of schistosomiasis japonica in China: a review of 30 years' experience. *Acta Trop* 2005;96:168-76. PMID:16125657 doi:10.1016/j.actatropica.2005.07.011
- Xiao SH, Yue WJ, Yang YQ, You JQ. Susceptibility of *Schistosoma japonicum* of different developmental stages to praziquantel. *Chin Med J (Engl)* 1987;100:759-68. PMID:3127152
- Wang SR, Shi W, Zhou ZW. Treatment of schistosomiasis with praziquantel: report of 93 cases [in Chinese]. *Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi* 2004;16:264-8.
- Le WJ, You JQ, Yang YQ, Mei JY, Guo HF, Yang HZ, et al. Studies on the efficacy of artemether in experimental schistosomiasis [in Chinese]. *Yao Xue Xue Bao* 1982;17:187-93. PMID:7115549
- Xiao SH, Catto BA. In vitro and in vivo studies of the effect of artemether on *Schistosoma mansoni*. *Antimicrob Agents Chemother* 1989;33:1557-62. PMID:2510595
- Xiao SH, You JQ, Yang Y, Wang CZ. Experimental studies on early treatment of schistosomal infection with artemether. *Southeast Asian J Trop Med Public Health* 1995;26:306-18. PMID:8629066
- Utzinger J, Xiao SH, Keiser J, Chen MG, Zheng J, Tanner M. Current progress in the development and use of artemether for chemoprophylaxis of major human schistosome parasites. *Curr Med Chem* 2001;8:1841-60. PMID:11772354
- Xiao S, Tanner M, N'Goran EK, Utzinger J, Chollet J, Bergquist R, et al. Recent investigations of artemether, a novel agent for the prevention of schistosomiasis japonica, mansoni and haematobia. *Acta Trop* 2002;82:175-81. PMID:12020890 doi:10.1016/S0001-706X(02)00009-8
- Xiao S, Shi ZG, Zhuo SJ, Wang CZ, Zhang ZG, Chu B, et al. Field studies on the preventive effect of oral artemether against schistosomal infection. *Chin Med J (Engl)* 1996;109:272-5. PMID:8758286
- Tian ZY, Xiao SH, Xiao JW, Zhou YC, Liu DS, Zheng J, et al. Reduction of *Schistosoma japonicum* infection in an endemic area in islet with embankment after prophylaxis with oral artemether throughout the transmission season [in Chinese]. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Bing Bing Za Zhi* 1997;15:208-11.
- Wang JL, Xiao SH, Yang Z, Wang MK, Yang H, Liu YH, et al. Effect of oral artemether in controlling schistosomiasis in Yunnan mountainous endemic area [in Chinese]. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Bing Bing Za Zhi* 1997;15:138-43.
- Utzinger J, N'Goran EK, N'Dri A, Lengeler C, Xiao SH, Tanner M. Oral artemether for prevention of *Schistosoma mansoni* infection: randomized controlled trial. *Lancet* 2000;355:1320-5. PMID:10776745 doi:10.1016/S0140-6736(00)02114-0
- N'Goran EK, Utzinger J, Gnaka HN, Yapi A, N'Guessan NA, Kigbafori SD, et al. Randomized, double-blind, placebo-controlled trial of oral artemether for the prevention of patent *Schistosoma haematobium* infections. *Am J Trop Med Hyg* 2003;68:24-32. PMID:12556143
- Li YS, Chen HG, He HB, Hou XY, Ellis M, McManus DP. A double-blind field trial on the effects of artemether on *Schistosoma japonicum* infection in a highly endemic focus in southern China. *Acta Trop* 2005;96:184-90. PMID:16112071 doi:10.1016/j.actatropica.2005.07.013
- ShuHua X, Jiqing Y, Jinying JM, Huifang G, Peiyang J, Tanner M. Effect of praziquantel together with artemether on *Schistosoma japonicum* parasites of different ages in rabbits. *Parasitol Int* 2000;49:25-30. PMID:10729714 doi:10.1016/S1383-5769(00)00029-5
- Utzinger J, Chollet J, You JQ, Mei JY, Tanner M, Xiao SH. Effect of combined treatment with praziquantel and artemether on *Schistosoma japonicum* and *Schistosoma mansoni* in experimentally infected animals. *Acta Trop* 2001;80:9-18. PMID:11495639 doi:10.1016/S0001-706X(01)00138-3
- Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in schistosomiasis mansoni. *Rev Inst Med Trop Sao Paulo* 1972;14:397-400. PMID:4675644
- Utzinger J, Xiao SH, Tanner M, Keiser J. Artemisinins for schistosomiasis and beyond. *Curr Opin Investig Drugs* 2007;8:105-16. PMID:17328226