

## MAJOR ARTICLE

# Efficacy and Safety of Tribendimidine Against *Clonorchis sinensis*

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**Background.** Clonorchiasis is of considerable public health importance, particularly in the People's Republic of China (PR China), where most of the 15 million individuals infected with *Clonorchis sinensis* are currently concentrated. Praziquantel is the drug of choice, but tribendimidine might be an alternative.

**Methods.** We performed a randomized open-label trial in Guangxi, PR China, to assess the efficacy and safety of 400 mg tribendimidine once, 400 mg tribendimidine daily for 3 days, and 75 mg/kg praziquantel in 1 day divided in 3 doses against parasitological-confirmed *C. sinensis* infections. Cure and egg reduction rates were determined 3 weeks posttreatment using available case analysis. Clinical symptoms were documented at baseline, and adverse events were recorded and graded 3 and 24 hours after each dose.

**Results.** A total of 74 patients were included in the final analysis. Single-dose tribendimidine achieved a cure rate of 44%, whereas cure rates of 58% and 56% were obtained for tribendimidine administered for 3 days and praziquantel, respectively. High egg reduction rates (97.6%–98.8%) were observed for all treatment regimens. Single-dose tribendimidine was the best-tolerated treatment scheme. Patients treated with praziquantel experienced significantly more adverse events than did tribendimidine recipients ( $P < .05$ ).

**Conclusions.** Tribendimidine has an efficacy comparable to praziquantel in the treatment of *C. sinensis* infection and resulted in fewer adverse events compared to praziquantel. Larger clinical trials are warranted among *C. sinensis*-infected patients to determine the potential of tribendimidine against clonorchiasis and other helminthiasis.

**Clinical Trials Registration.** Controlled-Trials.com, ISRCTN80829842.

**Keywords.** tribendimidine; praziquantel; *Clonorchis sinensis*; clonorchiasis; People's Republic of China.

## INTRODUCTION

An estimated 15 million people, most of them living in the People's Republic of China (PR China), are

infected with the liver fluke *Clonorchis sinensis*, resulting in a global burden of at least 275 370 disability-adjusted life-years (DALYs) [1]. The consumption of raw freshwater fish is a popular tradition not just in PR China but also in Vietnam and South Korea. Infections occur when raw freshwater fish, harboring infective metacercariae, are consumed. Pathological changes caused by *C. sinensis* infection are largely confined to the bile duct, liver, and gallbladder. Individuals with heavy infections often suffer from unspecific symptoms, such as fever, fatigue, weakness, nausea, or abdominal pain, but more severe consequences, namely obstructive jaundice and biliary colic,

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might occur [2]. The most serious complication of *C. sinensis* infection is cancer of the bile ducts, cholangiocarcinoma [3].

Praziquantel, administered at 3 doses of 25 mg/kg each at 5-hour intervals, is the drug of choice against clonorchiasis [4]. This treatment schedule is highly efficacious, with an egg reduction rate (ERR) of 99% [5]. However, transient adverse events, such as dizziness, sleepiness, headache, and diarrhea, are commonly observed after praziquantel administration [4]. Effective alternative drugs with a good safety profile are not available.

The Chinese anthelmintic drug tribendimidine might be a potential new drug candidate for treating infections with *C. sinensis*. Tribendimidine was observed to be highly effective in *C. sinensis*-infected rats [6] and in vitro [7]. In a randomized open-label trial in Lao People's Democratic Republic (Lao PDR), tribendimidine administered as a single oral dose of 200 mg (subjects <14 years of age) or 400 mg (subjects aged  $\geq 14$  years) to patients with parasitologically confirmed *Opisthorchis viverrini* infections, a related liver fluke, was found to be as efficacious as praziquantel (75 mg/kg given in 2 doses) [8]. Clinical trials with tribendimidine have therefore been suggested to determine the efficacy and safety of this drug in patients infected with *C. sinensis* [4, 9]. Tribendimidine is registered for human use for the treatment of infections with soil-transmitted helminths in PR China. A consortium composed of Chinese, Swiss, and US partners are currently seeking regulatory approval for the use of tribendimidine outside PR China [10], as studies in PR China have demonstrated that the drug is safe and efficacious against hookworm and *Ascaris lumbricoides* infections [11, 12].

The aim of this trial was to study and compare the efficacy and safety of tribendimidine, given as a single-dose or 3-day regimen, the latter already tested for the treatment of *Trichuris trichiura* infection [13], with the standard treatment of praziquantel in *C. sinensis*-infected individuals.

## PATIENTS AND METHODS

### Ethics Statement

The study was approved by the ethics committees in Basel, Switzerland (EKBB; reference nos. 209/09 and 375/11), the Liverpool School of Tropical Medicine (reference no. 12.02RS), and the National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention (reference no. 2012-02).

### Drugs

Tribendimidine (200 mg enteric-coated tablets) was purchased from Shandong Xinhua Pharmaceutical Co, Ltd (Zibo, PR China). Praziquantel (200 mg film-coated tablets) was the

product of Nanjing Pharmaceutical Factory Co, Ltd (Nanjing, PR China).

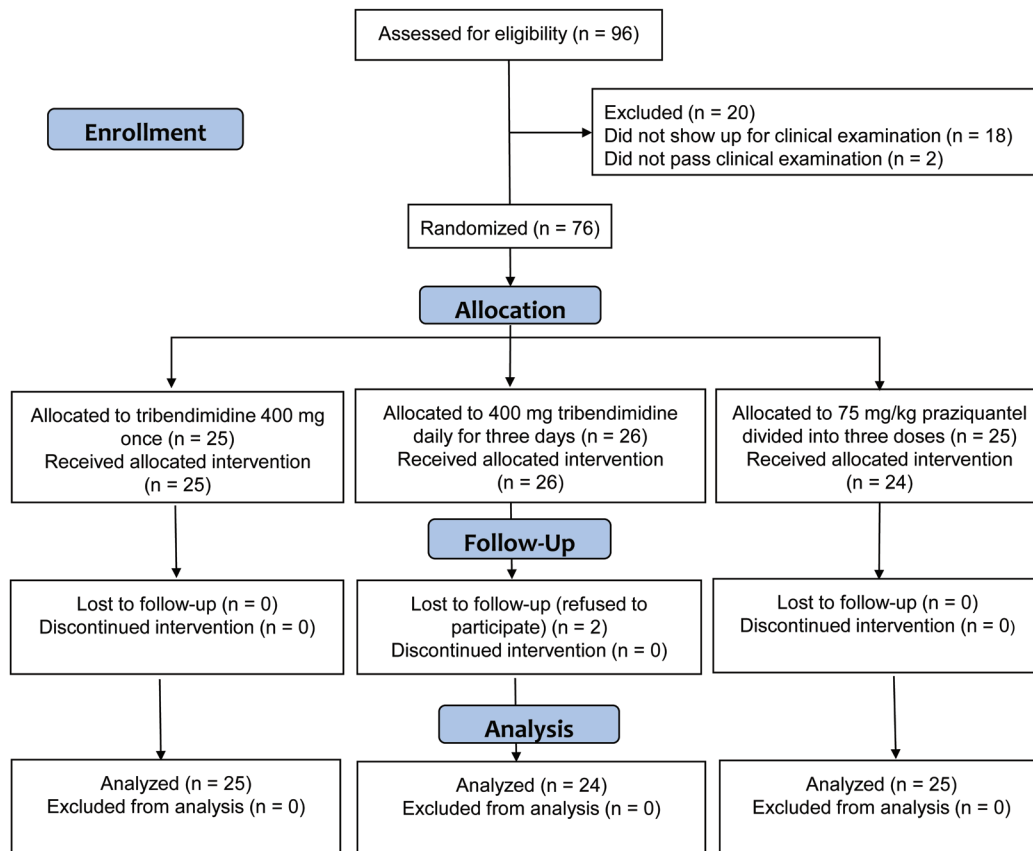
### Study Area and Participants

The study was conducted from June to July 2012 in a *C. sinensis*-endemic village (Hezhuang) located under the township of Gantang, Binyang county, Guangxi Zhuang Autonomous Region, PR China. Most villagers belong to the Zhuang ethnic group and are farmers. Living standards are relatively low as compared to the more developed regions of the country but literacy rate is high, with all villagers having received at least primary-school education.

Eligible individuals were adults of both sexes, aged  $\geq 18$  years. During the clinical examination by physicians, villagers who had no major systemic, acute, or chronic illnesses, no known or reported psychiatric or neurological disorders, or hypersensitivity to tribendimidine or praziquantel, and were not pregnant, were invited to join the study. Individuals were excluded from trial participation if they had used any anthelmintic within the past month or were attending other clinical trials during the same period. Only participants with written informed consent, who provided 2 stool samples at baseline, and were willing to provide another 2 stool samples 3 weeks posttreatment were finally included in the study.

### Study Flow, Sample Size, and Randomization

Our study was a randomized, open-label trial aiming to recruit 20–25 patients per treatment arm [14], similar to our earlier study focusing on *O. viverrini* [8]. Villagers were invited to provide a fresh morning stool sample in a container labeled with a unique identifier. Stool samples were transferred to the laboratory of Binyang Center for Disease Control and Prevention (CDC) and examined for the presence of *C. sinensis* eggs. Patients with a parasitologically confirmed *C. sinensis* infection were asked to provide another stool sample over the next 5 days. Written informed consent was obtained from *C. sinensis*-infected patients, and only consenting individuals were examined clinically, which included a physical examination and the measurement of height, weight, axillary temperature, blood pressure, and pulse. Study participants were randomly allocated, using a computer-generated randomization code prepared by an independent statistician, into 3 treatment arms: (i) tribendimidine 400 mg once, (ii) tribendimidine 400 mg daily for 3 days, and (iii) praziquantel 75 mg/kg divided into 3 doses administered within a day (Figure 1). All patients were treated on the same day. Three and 24 hours after each dosing, each patient was asked open-ended questions for the presence and severity of adverse events. In a next step, the physicians asked for specific adverse events. Adverse events were graded (ie, mild, moderate, severe, and life threatening) [15], recorded in the case report forms (CRFs), and remedial measures were taken if necessary. For



**Figure 1.** Trial flow diagram demonstrating patient compliance in a randomized open-label trial assessing the efficacy and safety of tribendimidine against *C. sinensis* in Guangxi, PR China, from June to July 2012.

each patient, the same physician performed the clinical examination and collected adverse events throughout all follow-ups.

### Laboratory Procedure

From each stool sample, triplicate Kato-Katz thick smears, using 41.7 mg templates, were prepared [16] and quantitatively examined for *C. sinensis* eggs under a microscope by experienced technicians, who were blinded to treatment allocation. The number of *A. lumbricoides*, *T. trichiura*, hookworm, and other helminth eggs were recorded separately. For quality control, the 3 slides were independently read by different technicians, and the results compared. Slides were reread if inconsistencies were detected.

### Outcome Measures and Statistics

Statistical analyses were performed with Stata version 10.0 (StataCorp, College Station, Texas). Available case analysis was employed and thus, only those patients who had primary outcome data were used for analysis. Cure rate (CR) was defined as the proportion of *C. sinensis* egg-positive patients at baseline, who became egg-negative 3 weeks after treatment. CRs represented as odds ratio (OR) between different treatment arms and

calculated from logistic regressions were also determined. Fecal egg counts, as expressed as eggs per gram of stool (EPG), were calculated by multiplying the sum of the egg counts from the 6 Kato-Katz thick smears by a factor of 4. Infection intensity of *C. sinensis* was categorized as light (1–999 EPG), moderate (1000–9999 EPG), and heavy ( $\geq 10\,000$  EPG) according to Yu and colleagues [17]. ERRs for each treatment group were determined based on the geometric mean (GM) fecal egg counts before and 3 weeks after treatment. The 95% confidence intervals (CIs) of ERR were calculated with bootstrap resampling. The average dose (mg/kg) of tribendimidine was also determined and analyzed with a logistic regression to assess whether the dose of treatment had an influence on the CR. Other test statistics included  $\chi^2$  test, Fisher exact test, and analysis of variance, as appropriate.

## RESULTS

### Adherence and Baseline Characteristics

From a recruitment pool of 96 individuals assessed for eligibility, 20 patients were excluded because they did not participate

**Table 1. Demographic and Laboratory Baseline Characteristics of *Clonorchis sinensis*-Infected Patients in Guangxi, PR China, From June to July 2012 (N = 74)**

Parameter	Treatment Group		
	Tribendimidine 400 mg Once (n = 25)	Tribendimidine 400 mg Once Daily for 3 d (n = 24)	Praziquantel 75 mg/kg Divided in 3 Doses (n = 25)
Males/females (no.)	19/6	15/9	23/2
Mean (SD) age, years	51.2 (8.8)	49.9 (10.1)	50.5 (10.0)
Mean (SD) weight, kg	61.9 (10.8)	58.3 (7.6)	60.4 (12.3)
Mean (SD) height, cm	157 (6)	156 (8)	162 (8)
<i>C. sinensis</i> infection intensity			
Overall GM fecal egg counts, EPG	3387	2816	4051
Fecal egg counts (range), EPG	(124–29 624)	(184–18 772)	(212–31 244)
No. of light infections (1–999 EPG)	5	4	4
No. of moderate infections (1000–9999 EPG)	11	17	13
No. of heavy infections ( $\geq 10\,000$ EPG)	9	3	8

Abbreviations: EPG, eggs per gram of stool; GM, geometric mean; SD, standard deviation.

at the clinical examination (n = 18) or presented with chronic or severe illnesses (n = 2). In total, 76 participants were randomized to the 3 treatment arms. One patient discontinued praziquantel treatment after 2 doses due to adverse events and 2 patients were lost to follow-up, giving an overall compliance with treatment and follow-up of 96% (73/76).

Stool samples of the patient who discontinued praziquantel treatment were collected at the follow-up, and hence this patient was included in the available case analysis. Demographic and laboratory baseline characteristics of the 74 patients are summarized in Table 1. Fifty-seven participants (77.0%) were male and 17 were female. Only 2 women were randomized to the praziquantel treatment group. The mean age in the 3 treatment arms ranged from 49.9 to 51.2 years.

The height ranged from 156 to 162 cm. Most of the patients (n = 41) harbored a moderate *C. sinensis* infection (1000–9999 EPG). Fecal egg counts ranged from 124 to 31 244 EPG with a GM of 2816 to 4051 EPG according to treatment arms. Overall, 12, 2, and 1 patients were concurrently infected with hookworm, *T. trichiura*, and *A. lumbricoides*, respectively. Given the small number of soil-transmitted helminth infections, these were not considered further.

#### Efficacy Against *C. sinensis*

Single-dose tribendimidine (400 mg) achieved a CR of 44%, while CRs of 58% and 56% were obtained for 400 mg tribendimidine administered for 3 days and praziquantel, respectively (Table 2). All patients harboring a light *C. sinensis* infection

**Table 2. Effect of Tribendimidine Single and Triple Dosages and Praziquantel in Patients Infected With *Clonorchis sinensis* in Guangxi, PR China, From June to July 2012 (N = 74)**

Parameter	Treatment Group		
	Tribendimidine 400 mg Once (n = 25)	Tribendimidine 400 mg Once Daily for 3 d (n = 24)	Praziquantel 75 mg/kg Divided in 3 Doses (n = 25)
No. of patients cured (%)	11 (44)	14 (58)	14 (56)
No. of patients cured of light infection (%)	5 (100)	4 (100)	4 (100)
No. of patients cured of moderate infection (%)	6 (54)	10 (59)	7 (54)
No. of patients cured of heavy infection (%)	0	0	3 (38)
<i>C. sinensis</i> infection intensity			
Overall GM fecal egg counts, EPG	80.0	35.1	50.0
Fecal egg counts (range), EPG	(0–3636)	(0–1296)	(0–1876)
Egg reduction rate (%) (95% CI)	97.6 (93.0–98.6)	98.8 (96.9–99.6)	98.8 (97.0–99.6)

Abbreviations: CI, confidence interval; EPG, eggs per gram of stool; GM, geometric mean.

**Table 3. Number of Patients With Adverse Events Among the 3 Treatment Arms, as Assessed at Different Time Points, in a Randomized Open-Label Trial Assessing the Efficacy and Safety of Tribendimidine Against *Clonorchis sinensis* in Guangxi, PR China, From June to July 2012<sup>a</sup>**

Time Point	Treatment Group		
	Tribendimidine 400 mg Once	Tribendimidine 400 mg Once Daily for 3 d	Praziquantel 75 mg/kg Divided in 3 Doses
Related symptoms before treatment	3 (12)	1 (4)	4 (16)
No. of patients with adverse events (%)			
3 hours after first treatment	5 (20) <sup>b</sup>	9 (38)	12 (48)
24 hours after first treatment	7 (28)	10 (42)	NA
3 hours after second treatment	NA	2 (8) <sup>c</sup>	16 (64)
24 hours after second treatment	NA	4 (16)	NA
3 hours after third treatment	NA	3 (12.5)	NA <sup>d</sup>
24 hours after third treatment	NA	1 (4) <sup>c</sup>	17 (71)
Overall number of patients experiencing adverse events at any time point	11 (44) <sup>b</sup>	16 (67) <sup>b</sup>	23 (92)

Abbreviation: NA, not applicable.

<sup>a</sup> *P* values were calculated using  $\chi^2$  or Fisher exact test, as appropriate.

<sup>b</sup> Significantly different from praziquantel group (*P* < .05).

<sup>c</sup> Significantly different from praziquantel group (*P* < .001).

<sup>d</sup> The third treatment of praziquantel was administered in the evening and it was logistically impossible for the patients to report back 3 hours after treatment. Thus, adverse events were only recorded 24 hours after treatment.

(1–999 EPG) were cured regardless of the treatment administered. In all 3 treatment arms, CRs of 54%–59% were observed against moderate (1000–9999 EPG) infections. Praziquantel was able to cure 3 of 8 patients with a heavy *C. sinensis* infection ( $\geq 10\,000$  EPG), while tribendimidine failed to cure such heavy infections regardless of dose. High ERRs (97.6%–98.8%) were observed for all treatments. Tribendimidine administered once daily for 3 days had 10% higher odds of curing a *C. sinensis* infection than praziquantel. On the other hand, single-dose tribendimidine had 38% and 44% lower odds of curing *C. sinensis* infection than praziquantel and the 3-day tribendimidine regimen, respectively. However, no significant differences were observed for the treatment outcomes in the praziquantel treatment arm vs tribendimidine single-dose or given for 3 days, and between both tribendimidine regimens.

The actual dose of tribendimidine administered ranged from 4.9 to 9.1 mg/kg for the single-dose and 16.9–29.6 mg/kg for the 3-day regimen. No significant association between CRs and dose was observed.

### Adverse Events

No life-threatening adverse events were observed following treatment. One patient treated with praziquantel experienced severe vomiting and discontinued treatment (the patient did not take the third dose). Most adverse event episodes were mild (*n* = 121), with 9 moderate or heavy adverse events either at 3 hours (*n* = 2) or 24 hours (*n* = 7). Table 3 summarizes the

number of patients experiencing adverse events, stratified by treatment arm at the different examination time points, while [Supplementary Table 1](#) presents the number of adverse events reported at different time points after treatment.

Single-dose tribendimidine was the best-tolerated treatment scheme. Eleven patients treated with a single dose of tribendimidine complained of adverse events, with dizziness/faintness the predominant adverse event reported by 5 patients. However, this symptom was already stated by 3 patients before treatment. Adverse events were reported among 16 patients who were given tribendimidine daily for 3 days, dizziness/faintness being the most commonly reported symptom.

Patients treated with praziquantel experienced significantly more adverse events than patients given tribendimidine (*P* < .05). Dizziness/faintness was significantly more often reported by patients treated with praziquantel than in patients treated with tribendimidine (*P* < .05). Praziquantel-treated patients also experienced abdominal pain, vomiting, and nausea. Adverse events labeled as “others” that were commonly reported by praziquantel-treated and tribendimidine-treated patients were bloatedness and dry mouth, respectively.

### DISCUSSION

Clonorchiasis is a public health problem in PR China, yet only a single treatment—praziquantel—is currently available [18].

Repurposing existing medicines cuts drug development costs and might provide alternative treatments in a timely manner [19,20]. We studied tribendimidine, a Chinese broad-spectrum anthelmintic drug marketed for the treatment of soil-transmitted helminthiasis, against infections with the liver fluke *C. sinensis* in a randomized open-label trial.

We found that single-dose tribendimidine (400 mg) achieved a high ERR and moderate CR in patients infected with *C. sinensis*, an efficacy profile comparable to standard triple-dose praziquantel. Moreover, tribendimidine was better tolerated than triple-dose praziquantel. Indeed, and in line with findings from previous studies [21,22], praziquantel-treated patients commonly reported dizziness, abdominal pain, nausea, and vomiting. It is interesting to note that dizziness has also been reported previously in praziquantel-treated patients infected with *O. viverrini* [8] and *Hymenolepis nana* [23]. To our knowledge, it is not known why praziquantel causes dizziness. More investigation into this issue is warranted, as praziquantel is routinely used in preventive chemotherapy, and dizziness as a common adverse event is not desirable.

Our results confirm recent results obtained with single-dose tribendimidine in patients infected with *O. viverrini* in Lao PDR. Indeed, in that proof-of-concept study, 19 of 27 *O. viverrini*-infected-patients were cured (70%) and an ERR of over 99% was achieved. In line with our findings, tribendimidine was better tolerated than praziquantel [8].

Though our study was not designed as an equivalence trial, our findings hint that single-dose tribendimidine is equally efficacious as 3 doses of the drug. Note that in preventive chemotherapy programs, which aim to prevent morbidity due to helminthiasis using the available armamentarium of anthelmintics, drugs are administered as single doses to entire at risk-populations without prior diagnosis, often in remote rural areas where access to public services is a formidable challenge [24]. A clonorchicidal drug, which is effective as a single dose, would therefore greatly facilitate preventive chemotherapy programs.

In terms of CR, all 3 treatment regimens had an excellent efficacy against light infections and a reasonable efficacy against moderate infections, but a poor efficacy against heavy *C. sinensis* infections. The differing susceptibility to praziquantel depending on infection intensity of trematode infections is well known [22,25], and therefore different doses and treatment schedules have been proposed [22]. For example, praziquantel given at  $3 \times 25$  mg/kg was found to be superior to a single dose of 40 mg/kg, in particular for *C. sinensis* infection of heavy intensities [22]. It has been suggested that genetic polymorphism might be a reason for the low efficacy of praziquantel against heavy *C. sinensis* infection. For example, patients with a particular single-nucleotide polymorphism of their cytochrome P450 gene revealed lower CRs than

patients without [26]. In addition, genetic diversity of *C. sinensis* could also play a factor in the success of praziquantel treatment, with strains in Southeast Asia showing lower susceptibility to the drug than strains from East Asia [27,28].

Because soil-transmitted helminthiasis and clonorchiasis often overlap geographically [29], praziquantel and albendazole have been coadministered in areas where trematode (eg, *C. sinensis* and *O. viverrini*) and nematode infections (eg, soil-transmitted helminths) coexist [30]. Our findings point to an additional benefit of tribendimidine; because of the broad spectrum of activity of this drug, concurrent infections with soil-transmitted helminths and liver flukes could be targeted in one go. In the present setting, only few *C. sinensis*-infected patients were coinfecting, and hence the efficacy and safety of tribendimidine in patients infected with both soil-transmitted helminths and liver flukes remains to be investigated.

In conclusion, our results suggest that single-dose tribendimidine is comparable to triple-dose praziquantel, both in terms of efficacy and safety, in the treatment of *C. sinensis* infections. Larger clinical trials, which have been initiated with *O. viverrini*-infected patients in Lao PDR, should also be planned in *C. sinensis*-infected patients.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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**Potential conflicts of interests.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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