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Efficacy and Safety of Praziquantel Against Light Infections of *Opisthorchis viverrini*: A Randomized Parallel Single-Blind Dose-Ranging Trial

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Background. The liver fluke *Opisthorchis viverrini*, highly prevalent in Southeast Asia, is an important public health burden, including a risk factor for developing an aggressive bile duct cancer, cholangiocarcinoma, in chronically infected patients. Praziquantel, administered at a single 40 mg/kg dose in preventive chemotherapy programs and 3 × 25 mg/kg for individual treatment, is the drug of choice, yet information on the nature of the dose-response relationship is lacking.

Methods. We performed a randomized, parallel, single-blind dose-ranging phase 2 trial in the Lao People's Democratic Republic in *O. viverrini*–infected adults. Patients were randomly assigned to 30 mg/kg, 40 mg/kg, 50 mg/kg, or 3 × 25 mg/kg praziquantel or placebo. Adverse events were recorded at baseline, 3 hours, and 24 hours posttreatment. Cure rates (CRs) and egg reduction rates (ERRs) were estimated 3 weeks after drug administration using available case analysis. Dose-response curves were predicted using E_{max} models.

Results. Two-hundred seventeen *O. viverrini*–infected patients were assigned to the 5 treatment arms. The majority (94.3%) of patients harbored light infections. The E_{max} model predicted a high efficacy among the observed dose range. We observed CRs ranging from 92.7% to 95.5% and ERRs >99.5% for all praziquantel treatment groups. Adverse events were mild but higher in the standard treatment group (3 × 25 mg/kg) than in the single-dose treatment arms.

Conclusions. Single-dose praziquantel appears to be as efficacious as the standard 3 × 25 mg/kg regimen for the treatment of *O. viverrini* infections, while presenting fewer adverse events. Further studies are necessary in moderate and heavy *O. viverrini* infections.

Clinical Trials Registration. Randomized Controlled Trials (ISRCTN77186750).

Keywords. praziquantel; opisthorchiasis; food-borne trematodiases; dose-ranging.

The trematode *Opisthorchis viverrini* is a significant public health problem in Southeast Asia. Opisthorchiasis affects >8 million people, primarily around the lower Mekong basin in Thailand, Lao People's Democratic Republic (PDR), Cambodia, and Vietnam [1]. This foodborne trematodiasis is acquired by the consumption of raw, fermented, or marinated fish dishes, harboring *O. viverrini* metacercariae [2–5]. Due to its location in the bile ducts, the parasite causes chronic inflammation of the biliary epithelium, leading to cholangiocyte hyperplasia and periductal fibrosis [6, 7]. Periductal fibrosis predisposes individuals to develop ascending cholangitis. The chronic inflammation and oncogenic properties associated with prolonged *O. viverrini* infection also predisposes individuals to develop cholangiocarcinoma, a malignant bile duct cancer that occurs in about 10% of infected individuals [8, 9].

The standard treatment for *O. viverrini* is praziquantel, a broad-spectrum anthelmintic pyrazino-isoquinoline, effective against almost all flatworm species [10]. The standard dosing scheme to treat opisthorchiasis is 3 time-separated doses of 25 mg/kg body weight administered orally within 24 hours for 2 consecutive days [11, 12]. In morbidity control programs, a single dose of 40 mg/kg is commonly used [12]. The Lao national recommendation is to use either a single 40 mg/kg or 75 mg/kg divided in 3 doses for 1 day [13]. Dose-response relation studies of praziquantel with opisthorchiasis patients are, however, lacking, which might simplify and optimize the administration strategy for large-scale deworming campaigns. Three dose-comparison studies were performed in Thailand in the early 1980s among adults with opisthorchiasis. The first trial compared a 3 × 25 mg/kg treatment schedule administered in 1 day

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compared to a 6 × 25 mg/kg schedule given over 2 days, both of which yielded a high cure rate (CR) of 100% [14]. The second study focused on lower doses of 1 × 25 mg/kg, 2 × 25 mg/kg, and 40 mg/kg and observed CRs of 44%, 89%, and 91%, respectively [15]. In the third trial, doses of 40 mg/kg and 50 mg/kg were investigated, resulting in CRs of 96% and 97%, respectively [16]. In a recent trial in Lao PDR comparing doses of 40 mg/kg and 50 + 25 mg/kg in infected children, the observed CRs were 71% and 97%, respectively [17]. However, none of the trials investigated the effect of single oral doses compared with the standard triple 25 mg/kg dose in a homogenous trial design. Determining whether—and which—single oral doses are equivalent to triple dosing could have important implications both for individual therapy as well as preventive chemotherapy campaigns.

The aim of this study is to determine the nature of the dose-response relationship of praziquantel in the treatment of opisthorchiasis in adult patients using single oral doses of 30 mg/kg, 40 mg/kg, and 50 mg/kg, with placebo and the standard dose of 3 × 25 mg/kg as comparators.

METHODS

Setting and Participants

The study was conducted between August and October 2014 in 2 villages (Maisivilay and Namsaitha) of Champasack province, southern Lao PDR, an area that is highly endemic for *O. viverrini* infection [18, 19].

We included all patients between 15 and 76 years of age with a diagnosed *O. viverrini* infection, not suffering from major systemic, acute, and/or chronic illnesses or psychiatric and neurological disorders. In addition, we excluded patients who were pregnant or had an anthelmintic treatment within the last 3 months.

The study was approved by the National Ethics Committee for Health Research, Ministry of Health of Lao PDR (reference no. 033/2014) and the Ethics Committee of Northern and Central Switzerland (reference no. 163/2014) The study is registered at Randomized Controlled Trials (ISRCTN77186750).

Randomization and Blinding

Using a computerized block randomization procedure (variable block size of 5 and 10), we assigned participants to different dosages of praziquantel (30, 40, 50 mg/kg or 3 × 25 mg/kg) or placebo. Praziquantel (Distocide; 600 mg) was purchased from Shin Poong, Korea. Placebo tablets of similar shape and color were purchased from Fagron, Germany. Tablets were administered in 150-mg increments. For the 3 × 25 mg/kg treatment, each praziquantel dose was administered in 4-hour intervals. Participants, investigators, and laboratory technicians were blinded to group assignment. The investigator responsible for treatment might have been aware of the dose due to the number of tablets administered, but he was not involved in adverse events (AEs) or parasitological assessment. The blinding was maintained throughout the trial until data entry and processing were completed and the data had been verified.

Procedures

We invited village inhabitants to join an information meeting in Lao language about the objectives, procedures, potential risks, and benefits of the study. Potential participants were given adequate information about the research process by the local co–principal investigator and trained health personnel and were allowed to ask questions. Following the meeting, eligible villagers were invited to participate and written informed consent was obtained from each study participant. In case of illiteracy of the villagers, the informed consent was presented orally. Two stool samples were collected from each participant within a maximum of 5 days and analyzed using the Kato-Katz method [20] and the quantitative formalin-ether concentration technique (FECT) [21] for the detection of minute intestinal flukes, such as *Haplorchis taichui* and *Phaneropsolus bonnei* [22, 23]. Two Kato-Katz thick smears (41.7 mg) were prepared from each stool sample and exactly 1 g of stool was preserved in 10% of formalin for the FECT analysis, following the methods used by Sayasone and colleagues [24]. The duplicate Kato-Katz thick smears were examined under a light microscope by 2 different experienced technicians. Ten percent of the negative slides were randomly chosen for quality control reexamination.

Study participants with parasitologically confirmed *O. viverrini* infection underwent a full clinical examination to assess the presence of any acute and chronic diseases. Height (using a measuring stick to the nearest point 1 cm), weight (using an electronic balance to the nearest 1 kg), blood pressure (using a sphygmomanometer to the nearest 0.1 mmHg), and axillary temperature (using battery-powered thermometers to the nearest 0.1°C) were recorded. A urine sample was collected from female participants for pregnancy testing (Orchid+, www.truelinemed.com). Before treatment, participants obtained a local meal (rice with vegetables). Study participants were observed for 3 hours following treatment (following the first dose in the 3 × 25 mg/kg group) by the physician team for documentation of possible AEs. For participants reporting any symptoms, the study physicians performed a full clinical examination and, if needed, patients were treated accordingly. For the occurrence of AEs at 24 hours posttreatment (post–first dosing for the 3 × 25 mg/kg patients), patients were interviewed by home visits and followed up at 48 hours by phone interviews (results not shown). At 19–25 days posttreatment, another 2 stool samples were collected for assessing treatment efficacy. Study participants testing positive for intestinal parasites were treated according to national guidelines [13].

Outcome and Sample Size Determination

CR, defined as the conversion from a positive diagnostic Kato-Katz test pretreatment to a negative test posttreatment, was the

primary endpoint in our study. A previous dose range trial [25] showed that 40 individuals per group would result in a median precision (defined as one-half length of the 95% confidence interval [CI]) of the dose-response curve of 5–10 percentage points.

Statistical Analysis

Data were digitally collected on tablets using CommCare ODK, version 2.8. The questionnaires and forms were developed in the CommCare server (www.commcarehq.org). A hard copy of the forms was also completed during the data collection and was used to cross-check 10% of the electronically collected data. Validated data were transferred to Stata software, version 14 (StataCorp, College Station, Texas), and R (R Foundation for Statistical Computing, Vienna, Austria) version 3.2.4, for statistical analyses.

Infection intensity, expressed as eggs per gram of stool (EPG), was determined for each individual by adding egg counts of the 4 examined Kato-Katz smears and multiplying by 6. *Opisthorchis viverrini* infections were classified into low (1–999 EPG), moderate (1000–9999 EPG), and heavy (≥10 000 EPG) infection intensities [26]. Egg reduction rates (ERRs) were determined based on arithmetic and geometric mean egg counts. The arithmetic ERR is the relative difference expressed as percentage between the posttreatment mean egg count and the pretreatment mean egg count (1– post mean egg count/pre mean egg count) including all patients. For the geometric mean ERR, a log transformation log (x + 1) was first calculated prior to determining the relative difference, expressed in percentage between the posttreatment mean egg count and the pretreatment mean egg count. Ordinary nonparametric bootstrap resampling within each trial group (2000 replicates) was used to determine 95% CIs for the ERRs.

We performed an available case analysis including all patients with primary endpoint data. An intention-to-treat (ITT) analysis is presented in Supplementary Table 1. For the ITT analysis, 2 approaches were conducted to impute missing data—that is, all treatment success (all individuals with no endpoint data were assumed to be free of infection) and all treatment failure scenarios (all individuals with no endpoint data were assumed to have the same egg counts as before infection).

We evaluated dose-response curves by fitting nonlinear E_{max} models for CRs and ERRs for the placebo, 30 mg/kg, 40 mg/kg, and 50 mg/kg groups. For ERRs, we separately modeled population arithmetic and geometric mean reductions, using the DoseFinding package in R [27]. For individual ERRs, we modeled residual egg proportion (final egg count/initial egg count) using a Tweedie compound Poisson-gamma distribution, an exponential dispersion model with a positive mass at zero. We used the Tweedie package [28] for maximum likelihood estimation of the index parameter and Statmod package [29] for Tweedie Family generalized linear model, and then predicted individual egg reduction as a function of dose.

RESULTS

Participant Flow and Baseline Characteristics

The study flowchart is presented in Figure 1. We recruited 634 adults, of whom 21 did not consent to follow the trial. An *O. viverrini* infection was diagnosed in 231 patients of the 443 patients who provided 2 stool samples, and no minute intestinal flukes were observed, as confirmed by FECT analysis. Fourteen patients were excluded from the trials due to chronic diseases (ie, chronic cardiovascular, diabetes, chronic kidney failure, and chronic hepatitis). In total, 217 participants were assigned to the 5 treatment arms. Five patients were absent at the follow-up examination (2.3% loss), and 1 patient from the 40 mg/kg treatment group was wrongly dosed receiving a 54 mg/kg dose. Table 1 summarizes the demographic and parasitological baseline characteristics. Baseline *O. viverrini* infection intensity, coinfection with other helminths, sex, age, weight, and height were well balanced among treatment groups. More than 90% of the patients harbored a light infection (median EPG in study arms ranging from 54 to 78).

Efficacy of Praziquantel

The range of the actual mean doses administered were 28–33, 39–42 (plus the wrongly dosed patient at 54 mg/kg) and 49–65 mg/kg praziquantel in the single-dose 30 mg/kg, 40 mg/kg, and 50 mg/kg groups, and triple doses of 23–33 mg/kg praziquantel in the 3 × 25 mg/kg group.

The E_{max} model predicted a high efficacy in terms of on CRs (Figure 2) and ERRs based on geometric means (Figure 3) among the observed dose range. There was no indication that higher single doses or a triple-dose regimen improves the efficacy markedly. Similarly high CRs were observed for all praziquantel treatment groups (92.7%–95.5%). For the placebo treatment, we observed a CR of 29.3% (Table 2). The corresponding ERRs for the treated groups were 99.5%–99.7% based on geometric mean and 94.7%–98.9% based on arithmetic mean. ERRs of placebo were 70.1% (geometric mean) and –8.6% (arithmetic mean).

Adverse Events

Before treatment, 34.9% of the patients treated with praziquantel and 28.6% of the placebo group reported mild clinical symptoms, such as vertigo or headache (Table 3). Three hours posttreatment, the placebo-treated group displayed a similar number of mild AEs (26.2%) compared with the baseline levels, with only 1 patient with moderate symptoms. In the praziquantel-treated groups, a total of 54.9% and 13.1% of the patients suffered from mild and moderate AEs, respectively. The most common AEs among praziquantel-treated patients were mild vertigo (53.8%; Table 4), mild headache (22.2%), and mild nausea (17.0%). The highest numbers of mild vertigo events were observed in the 40 mg/kg and 50 mg/kg treatment groups (62.2% and 61.4%, respectively).

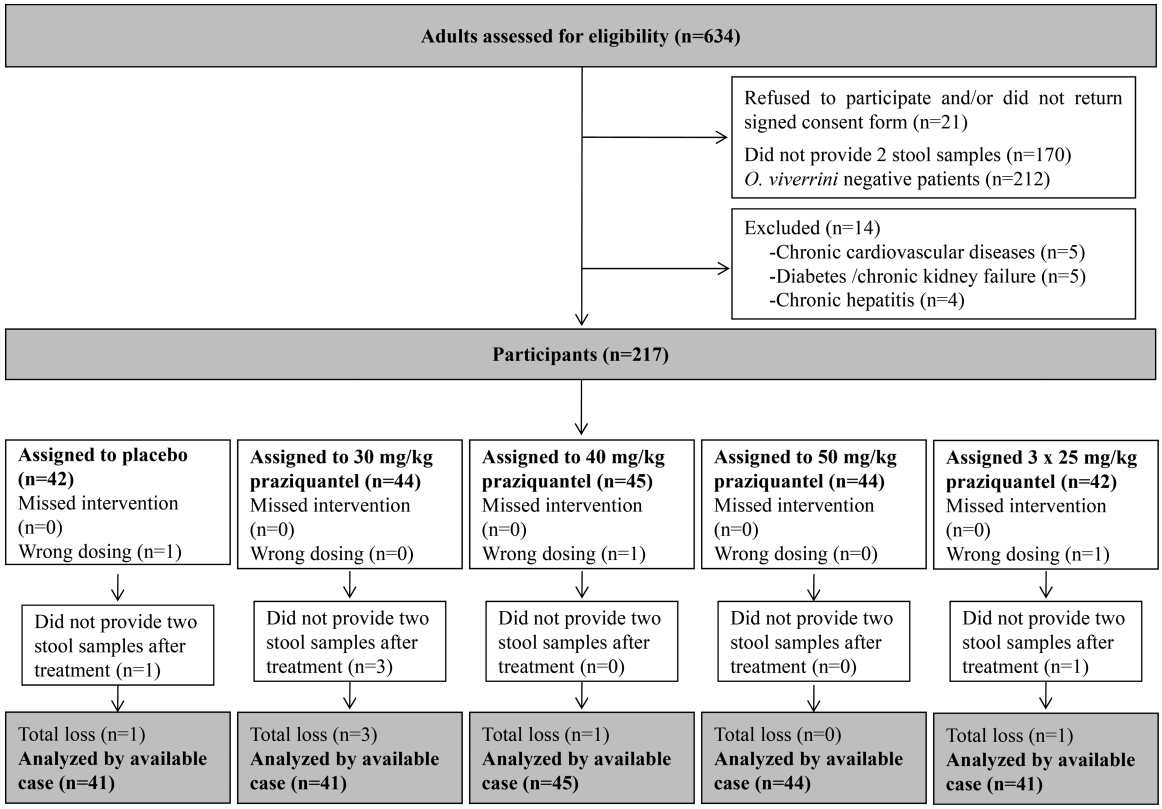

Figure 1. Trial profile.

Twenty-four hours posttreatment, a higher number of patients treated with the triple praziquantel dose compared with single doses reported mild (45.2% vs 22.7%–31.8%) and moderate (16.7% vs 0–2.3%) AEs (Table 3). Placebo-treated patients revealed a low number of mild AEs (7.1%) 24 hours posttreatment. The most common reported AE 24 hours posttreatment was mild vertigo (22.8% of all praziquantel-treated patients), which was mainly observed among participants assigned to the standard triple dose (48%) (Table 4).

DISCUSSION

Praziquantel has been widely used for several decades for the treatment of infections with the liver flukes *O. viverrini*, *O. felineus*, and *Clonorchis sinensis*. Apart from triclabendazole, used

Table 1. Baseline Characteristics of *Opisthorchis viverrini*–Infected Patients Stratified by Treatment Group

Characteristic	Placebo (n = 41)	Praziquantel			
		30 mg/kg (n = 41)	40 mg/kg (n = 45)	50 mg/kg (n = 44)	3 × 25 mg/kg (n = 41)
Female sex, %	43.9	51.2	46.7	47.7	53.7
Age, y, median (IQR)	44 (31–56)	45 (30–55)	43 (29–53)	48 (33–57)	47 (35–59)
Weight, kg, median (IQR)	57 (50–65)	55 (51–62)	59 (53–65)	55 (50–60)	57 (50–61)
Height, cm, median (IQR)	160 (155–163)	159 (152–165)	159 (155–164)	159 (152–161)	158 (150–162)
EPG, median (IQR)	60 (27–198)	54 (30–240)	54 (18–144)	75 (30–176)	78 (21–207)
Opisthorchis viverrini infection intensity, % (No.)					
Low	95.1 (39)	92.7 (38)	93.3 (42)	95.4 (42)	95.1 (39)
Moderate	4.9 (2)	7.3 (3)	6.7 (3)	4.6 (2)	4.9 (2)
Heavy	0	0	0	0	0
Coinfections, % (No.)					
Hookworms	56.1 (23)	53.7 (22)	71.1 (32)	50.0 (22)	61.0 (25)
Taenia species	9.8 (4)	12.2 (5)	15.6 (7)	11.4 (5)	4.9 (2)
Trichuris trichiura	0	4.9 (2)	0	4.6 (2)	0
Ascaris lumbricoides	0	0	0	2.3 (1)	0

Abbreviations: EPG, eggs per gram; IQR, interquartile range.

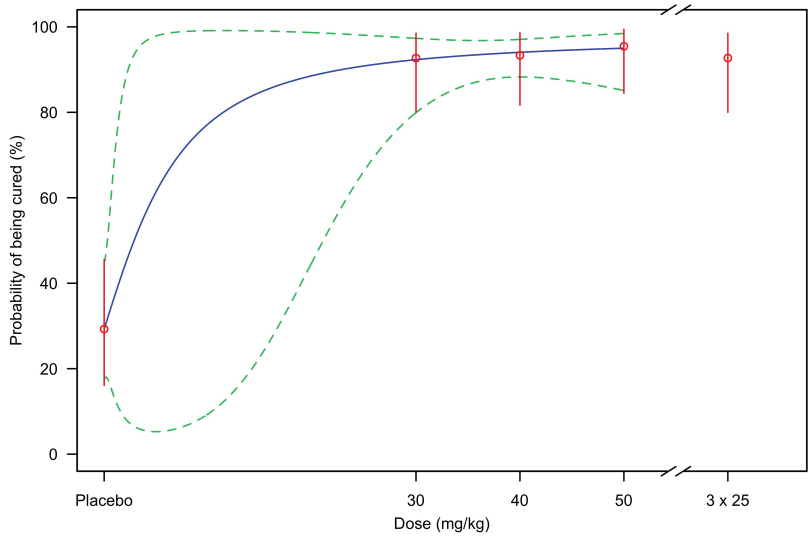

Figure 2. E_{max} model for the cure rates (CRs) of placebo and 4 doses of praziquantel against *Opisthorchis viverrini* infections. Circles show observed CRs with 95% confidence intervals (CIs; vertical lines). The solid line represent the estimated dose-response curve and the dashed lines the corresponding 95% CIs predicted by the E_{max} models.

for the treatment of infections with *Fasciola* species [30], praziquantel is the mainstay for the treatment of most foodborne trematode infections. In 2015, an estimated 600 000 individuals were reported to be treated for foodborne trematodiases worldwide [31]. However, proper dose-response relationship studies have not been conducted to date, which is reflected into the various dosing strategies currently applied. Our study aimed to close this knowledge gap and inform treatment recommendations as well as preventive chemotherapy guidelines.

All doses of praziquantel used in our study were highly effective, showing a flat dose-response curve and achieving similar CRs of 93–95%. Hence, our study is not able to define a no-effect dose range. Our findings are in contrast to an earlier study [15], which guided the selection of the doses used in our study. This trial in Thailand reported a complete cure of all the patients treated with 3 × 25 mg/kg, while a low CR of 44% was detected for a single 25 mg/kg praziquantel dose. In a nearby setting, in southern Laos PDR, CRs were 96.6% after 50 + 25 mg/kg praziquantel and 71.4% after a single 40 mg/kg dose of praziquantel in *O. viverrini*–infected children, as observed by Lovis and colleagues [17]. The high efficacy observed in the present study, with doses as low as 30–40 mg/kg could be explained with the low infection intensities of patients, in contrast to Thai participants who suffered from moderate to high infection intensities [15]. The relationship between praziquantel efficacy and infection intensities (ie,

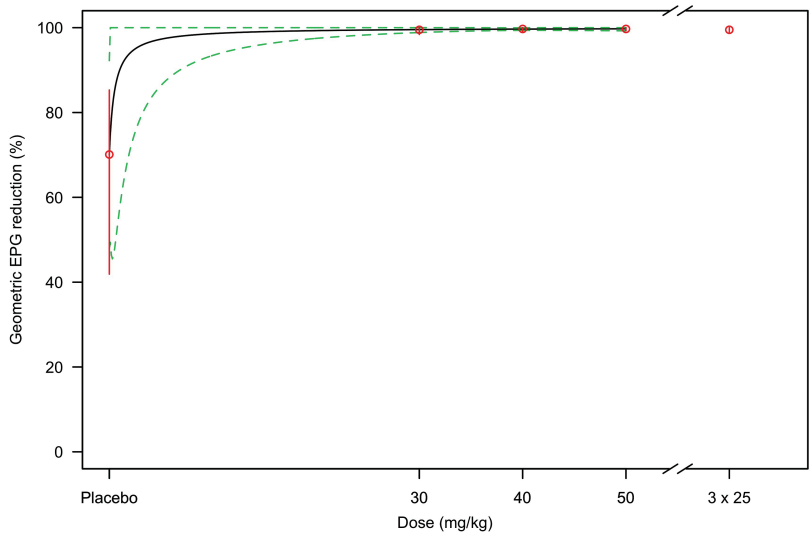

Figure 3. E_{max} model for egg reduction rates (ERRs) of placebo and 4 doses of praziquantel against *Opisthorchis viverrini* infections based on population geometric means. Circles show observed cure rates with 95% confidence intervals (CIs; vertical lines). The solid line represent the estimated dose-response curve and the dashed lines the corresponding 95% CIs predicted by the E_{max} models. Abbreviations: EPG, eggs per gram.

Table 2. Cure and Egg Reduction Rates of Different Praziquantel Dosages Against *Opisthorchis viverrini* Infections

Efficacy Measure	Placebo (n = 41)	Praziquantel			
		30 mg/kg (n = 41)	40 mg/kg (n = 45)	50 mg/kg (n = 44)	3 × 25 mg/kg (n = 41)
CR					
Patients positive before treatment, No.	41	41	45	44	41
Patients positive after treatment, No. (%)	29 (70.7)	3 (7.3)	3 (6.7)	2 (4.5)	3 (7.3)
CR, % (95% CI)	29.3 (16.1–45.5)	92.7 (80.0–98.5)	93.3 (81.7–98.6)	95.5 (81.3–98.6)	92.7 (80.0–98.5)
Geometric mean EPG					
Before treatment	77.0	80.2	70.6	72.4	65.4
After treatment	23.0	0.4	0.2	0.2	0.3
ERR, % (95% CI)	70.1 (41.9–85.3)	99.5 (98.4–100.0)	99.7 (99.0–100.0)	99.7 (99.3–100.0)	99.5 (98.8–100.0)
Arithmetic mean EPG					
Before treatment	227.9	257.6	336.4	172.8	230.5
After treatment	247.5	13.6	3.6	2.3	4.2
ERR, % (95% CI)	–8.6 (–110.5 to 38.2)	94.7 (83.7–99.5)	98.9 (93.6–99.8)	98.7 (95.4–99.5)	98.2 (90.7–99.7)

Abbreviations: CI, confidence interval; CR, cure rate; ERR, egg reduction rate; EPG, eggs per gram.

higher CRs among patients with low infection intensities) has been described for the treatment of *Schistosoma* patients [32, 33]. However, in the study by Lovis and colleagues, patients harboring light infection intensities demonstrated only a moderate CR of 75% [17]. Another explanation could be the influence of food administered with the treatment [34, 35]. Lovis et al provided a single spoon of rice together with the medication, while in our study the patients received a breakfast prior to treatment, which most likely increased bioavailability and consequently efficacy. It has been well studied that the administration of food increases maximum plasma levels of praziquantel [36]. In the other studies, no information on concomitant food was reported. The relatively important CRs observed in the placebo group (29.3%) can be explained by the light infection intensities observed among our patients, which play with the limits of detection of microscopic diagnostics.

Our study was unable to discriminate the effect of escalating treatment dosages and a triple dose on ERRs estimated based on geometric means. However, calculating mean individual ERRs brings out a different result, with noticeable differences between treatment arms (Supplementary Figure 1). A model of individual ERRs displays a higher variability in ERRs and a lower mean ERR among the 30 mg/kg group compared to the other doses (Supplementary Figures 2 and 3) that could be translated into a more important outcome difference among patients harboring high infection intensities. To be noted, in the 30 mg/kg group, there was 1 patient with a tremendous increase in egg burden (>600%), which is weighting on the mean individual-based ERRs.

Table 3. Clinical Symptoms Observed Prior to Treatment and 3 and 24 Hours After Treatment With Different Praziquantel Dosages Against *Opisthorchis viverrini* Infections[a]

Observed Symptoms	Placebo (n = 41)	Praziquantel				
		30 mg/kg (n = 41)	40 mg/kg (n = 45)	50 mg/kg (n = 44)	3 × 25 mg/kg[b] (n = 41)	Overall (N = 171)
Before treatment						
None	71.4 (30)	75.0 (33)	57.8 (26)	70.5 (31)	57.1 (24)	65.1 (114)
Mild	28.6 (12)	25.0 (11)	42.2 (19)	29.5 (13)	42.9 (18)	34.9 (61)
Moderate	0	0	0	0	0	0
3 h posttreatment						
None	71.4 (30)	36.4 (16)	20.0 (9)	22.7 (10)	50.0 (21)	32.0 (56)
Mild	26.2 (11)	54.6 (24)	60.0 (27)	61.4 (27)	42.9 (18)	54.9 (96)
Moderate	2.4 (1)	9.0 (4)	20.0 (9)	15.9 (7)	7.1 (3)	13.1 (23)
24 h posttreatment						
None	92.9 (39)	75.0 (33)	77.8 (35)	68.2 (30)	38.1 (16)	65.1 (114)
Mild	7.1 (3)	22.7 (10)	22.2 (10)	31.8 (14)	45.2 (19)	30.3 (53)
Moderate	0	2.3 (1)	0	0	16.7 (7)	4.6 (8)

[a]Data are shown as percentage (No.).

[b]The first dose is the reference time for adverse event reporting.

Table 4. Adverse Events Among *Opisthorchis viverrini*–Infected Patients Assessed 3 and 24 Hours After Treatment by Praziquantel Dosage[a]

			Praziquantel									
	Placebo (n = 41)		30 mg/kg (n = 41)		40 mg/kg (n = 45)		50 mg/kg (n = 44)		3 × 25 mg/kg[b] (n = 41)		Overall (N = 171)	
Adverse Event	3 h	24 h	3 h	24 h	3 h	24 h	3 h	24 h	3 h	24 h	3 h	24 h
Headache												
Mild	0	0	12.2 (5)	0	26.7 (12)	0	34.1 (15)	4.6 (2)	14.6 (6)	19.5 (8)	22.2 (38)	5.9 (10)
Nausea												
Mild	4.8 (2)	2.4 (1)	17.1 (7)	2.4 (1)	17.8 (8)	4.4 (2)	15.9 (7)	4.6 (2)	17.1 (7)	19.5 (8)	17.0 (29)	7.6 (13)
Moderate	2.4 (1)	0	0	2.4 (1)	4.4 (2)	0	2.3 (1)	0	0	0	1.8 (3)	0
Vertigo												
Mild	24.4 (10)	2.4 (1)	46.3 (19)	9.8 (4)	62.2 (28)	13.3 (6)	61.4 (27)	20.5 (9)	43.9 (18)	48.8 (20)	53.8 (92)	22.8 (39)
Moderate	0	0	4.9 (2)	0	8.9 (4)	0	6.8 (3)	0	2.4 (1)	4.9 (2)	5.9 (10)	1.2 (2)
Abdominal cramp												
Mild	0	0	4.9 (2)	2.4 (1)	6.7 (3)	2.2 (1)	0	2.3 (1)	0	4.9 (2)	2.9 (5)	2.9 (5)
Fatigue												
Mild	0	0	19.5 (8)	9.8 (4)	11.1 (5)	8.9 (4)	11.4 (5)	4.6 (2)	0	7.3 (3)	10.5 (18)	7.6 (13)
Moderate	0	0	0	0	2.2 (1)	0	0	0	0	0	0.6 (1)	0
Allergy												
Mild pruritus without rash	0	0	0	0	2.2 (1)	0	0	0	0	0	0.6 (1)	0
Mild localized urticaria	0	0	0	0	2.2 (1)	0	0	0	0	0	0.6 (1)	0
Vomiting[c]												
Mild	0	0	2.4 (1)	0	8.9 (4)	2.2 (1)	4.6 (2)	2.3 (1)	0	7.3 (3)	4.1 (7)	2.9 (5)
Moderate	0	0	4.9 (2)	0	8.9 (4)	0	9.1 (4)	2.3 (1)	4.9 (2)	12.2 (5)	7.0 (12)	2.9 (5)
Diarrhea[d]												
Mild	2.4 (1)	0	0	2.4 (1)	2.2 (1)	2.2 (1)	6.8 (3)	0	2.4 (1)	7.3 (3)	2.9 (5)	3.5 (6)

[a]Data are shown as percentage (No.).
[b]The first dose is the reference time for adverse event reporting.
[c]Vomiting: mild, 1 episode; moderate, 2–5 episodes in 24 hours; severe, >6 episodes or intravenous fluids required; critical, hospitalization.
[d]Diarrhea: mild, 3–4 episodes; moderate, 5–7 episodes; severe, >7 episodes or bloody diarrhea and intravenous fluids required; critical, hypotensive shock or hospitalization.

Three hours after treatment, slightly more than half of the patients reported mild AEs, but no differences between dosages could be identified. This observation highlights that treatment with praziquantel, even at low doses, is inherently followed by mild AEs. At 24 hours, the triple standard dose seemed to have affected the patients more than following single doses, with a higher number of patients complaining about symptoms. The most frequent AE reported at 3 hours and 24 hours was vertigo. This is consistent with other trials in opisthorchiasis patients, where dizziness and headache were the most prominent symptoms [16, 36–38]. In studies involving schistosomiasis patients, on the other hand, the treatment is first associated with gastrointestinal problems [32, 39, 40]. Abdominal signs in schistosomiasis patients can be explained by the release of parasitic antigens in the mesenterial veins and liver, not only by dying worms but also by eggs, which hatch as a consequence of the treatment with praziquantel [41]. In opisthorchiasis patients, the immune reaction to parasitic antigens after treatment could in theory differ because of the parasite's location in the bile ducts. To note, the various AEs reported in trials are also subject to cultural or genetic differences of the target patients.

In conclusion, our study provides convincing data that single doses of praziquantel reveal a similar performance compared to the standard 3 × 25 mg/kg dose and were better tolerated over 24 hours posttreatment. Given the practicability of a single-dose regimen, recommendations for individual patient management might be adopted. Our data support the use of the recommended dose of 40 mg/kg in preventive chemotherapy programs. However, as most patients harbored light *O. viverrini* infections, further studies are necessary in moderate and heavy *O. viverrini* infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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