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Efficacy and Safety of Mefloquine, Artesunate, Mefloquine-Artesunate, and Praziquantel against *Schistosoma haematobium*: Randomized, Exploratory Open-Label Trial

Jennifer Keiser,[1] Nicaise A. N'Guessan,[4] Koffi D. Adoubryn,[5] Kigbafori D. Silué,[4,6] Penelope Vounatsou,[2] Christoph Hatz,[3] Jürg Utzinger,[2] and Eliézer K. N'Goran[4,6]

[1]Department of Medical Parasitology and Infection Biology, [2]Department of Public Health and Epidemiology, and [3]Medical Department, Swiss Tropical Institute, Basel, Switzerland; [4]Laboratoire de Zoologie et Biologie Animale, Unité de Formation et de Recherche Biosciences, and [5]UFR des Sciences Médicales, Université de Cocody-Abidjan, and [6]Centre Suisse de Recherches Scientifiques, Abidjan, Côte d'Ivoire

(See the editorial commentary by Bergquist, on pages 1214–1215.)

Background. Morbidity control of schistosomiasis relies on a single drug, praziquantel. The antimalarial drug mefloquine possesses interesting antischistosomal properties, yet no clinical studies have been performed.

Methods. We conducted a randomized, exploratory open-label trial to assess the efficacy and safety of mefloquine (25 mg/kg), artesunate (3 doses of 4 mg/kg), mefloquine-artesunate (3 doses of 100 mg artesunate plus 250 mg mefloquine), and praziquantel (40 mg/kg) against *Schistosoma haematobium*. The effects on *Schistosoma mansoni*, malaria parasitemia, soil-transmitted helminths, and intestinal protozoa were also determined.

Results. A total of 83 *S. haematobium*–infected schoolchildren were included in the study. Cure rates of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against *S. haematobium* at day 26 after treatment were 21%, 25%, 61%, and 88%, respectively. Both mefloquine-artesunate and praziquantel resulted in egg reduction rates >95%. Significantly lower egg reduction rates were seen in the artesunate (85%) and mefloquine groups (74%). In children coinfected with *S. mansoni*, praziquantel and mefloquine-artesunate, but not mefloquine and artesunate alone, resulted in high cure rates and egg reduction rates. Mefloquine, artesunate, and mefloquine-artesunate completely cured infections due to *Plasmodium falciparum*. No effects were found against soil-transmitted helminths and intestinal protozoa. Abdominal pain was the most frequent adverse event, with a higher incidence among children treated with mefloquine (89%), mefloquine-artesunate (83%), and artesunate (60%) than among children treated with praziquantel (46%).

Conclusions. The high efficacy of mefloquine-artesunate against *S. haematobium* warrants further investigation. Individuals coinfected with *Plasmodium* and *Schistosoma* who were treated with a mefloquine-artesunate combination against malaria might have a dual benefit: clearance of malaria parasitemia and reduction of schistosomiasis-related morbidity.

Clinical trials registration. Current Controlled Trials identifier: ISRCTN06498763.

Blood-dwelling flukes of the genus *Schistosoma* are the causative agent of schistosomiasis, a chronic and debilitating disease [1]. In terms of public health and economic impact, *Schistosoma haematobium*, *Schistosoma mansoni*, and *Schistosoma japonicum* are the most important species [2]. More than 200 million individuals are infected, 97% of whom are concentrated in Africa [3, 4]. The global strategy for schistosomiasis control is morbidity control, relying on a single drug, praziquantel. Although no clinically relevant resistance to praziquantel has been described to date, development of drug-resistance remains a growing threat, particularly in view of mounting praziquantel pressure [5, 6].

Adult schistosomes feed on blood and, similar to *Plasmodium* protozoa causing malaria, hemoglobin is degraded into hemozoin [7]. The formation of he-

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Reprints or correspondence: Dr Jennifer Keiser, Dept of Medical Parasitology and Infection Biology, Swiss Tropical Institute, PO Box, CH-4002 Basel, Switzerland (jennifer.keiser@unibas.ch).

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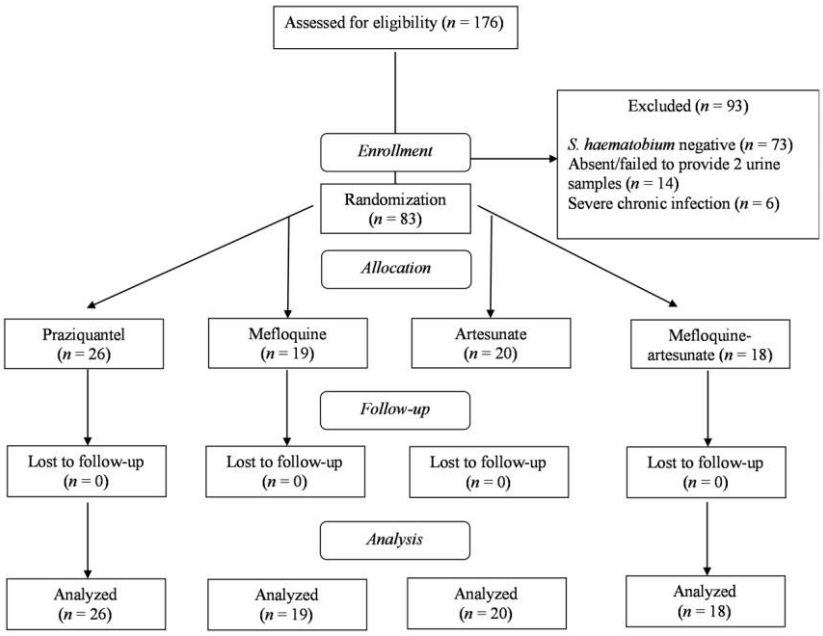

Figure 1. Flow diagram of the randomized, exploratory open-label trial of the efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against *Schistosoma haematobium.*

mozoin is a key target in malaria chemotherapy; indeed, many antimalarial drugs affect heme-detoxification mechanisms (eg, chloroquine, mefloquine, and quinine) [8]. The formation of hemozoin in schistosomes might also represent a suitable target to develop novel antischistosomal drugs. We have recently shown that several quinoline antimalarials possess antischistosomal properties in vitro and in the mouse model, with the highest worm burden reductions observed with mefloquine [9, 10]. The artemisinins are another group of antimalarials that have been studied for their antischistosomal properties [11–13].

To our knowledge, mefloquine used alone or in combination with artesunate—commonly employed drugs in the prophylaxis and treatment of malaria—have not been evaluated for their effect against *Schistosoma* infection. The aim of this study was to investigate the efficacy and safety of mefloquine, artesunate, and mefloquine-artesunate—with mefloquine and mefloquine-artesunate administered according to currently used malaria treatment schemes—against *S. haematobium.* Praziquantel was also included, because it is the current drug of choice against schistosomiasis [14].

PATIENTS AND METHODS

Study site and population. The study was performed in the village of Guéssiguié in the district of Agboville, south Côte d'Ivoire (located at 5°44′15″ N latitude, 4°14′9″ W longitude, and with a population of 6451) in November and December 2008. In the 4 primary schools, a total of 1044 children were registered during 2008–2009. *S. haematobium* is highly endemic in the district of Agboville [15].

Design, outcome measures, and sample size. The study was designed as a randomized, exploratory open-label trial to assess the efficacy and safety of mefloquine, artesunate, and mefloquine-artesunate against parasitologically confirmed *S. haematobium* infections in schoolchildren 8–16 years of age. A fourth group was treated with praziquantel.

Cure rate (CR; defined as the percentage of children excreting no *S. haematobium* eggs 26 days after treatment among children with confirmed parasites at baseline) and egg reduction rate (ERR; defined as reduction of geometric mean [GM] egg count among *S. haematobium*–positive children after treatment, compared with the respective GM pretreatment) against *S. haematobium* infection were used as efficacy outcome measures. The incidence of adverse events was monitored up to 96 h after the first dosing.

We adhered to recommendations for pilot studies, which suggest sample sizes of at least 12 individuals per group [16]. To allow for a study drop-out rate of 25%, we aimed at a minimum of 15 individuals per treatment arm (60 individuals in total). On the assumption of an overall prevalence of *S. haematobium* among schoolchildren of 30%–40%, we aimed at 180 children for the baseline screening.

Study procedures. The trial flow is presented in Figure 1. Village authorities and teachers were informed about the objectives, procedures, and potential risks and benefits. Subsequently, all schoolchildren who attended grades 2–4 (176 chil-

dren) in 1 of the 4 schools were invited to participate and were asked to provide a urine specimen (collected between 10 AM and 2 PM), which was examined for the presence and number of *S. haematobium* eggs.

Children with a parasitologically confirmed *S. haematobium* infection were invited to provide a second urine specimen, a stool specimen, and a finger-prick blood sample. Thick and thin blood films were prepared on microscope slides, labeled, and air dried. The weight (nearest 0.1 kg, determined using an electronic balance) and axillary temperature (to the nearest 0.01°C, determined using battery-powered thermometers) of each child were recorded. Next, children were subjected to a full clinical examination. The following exclusion criteria were employed: presence of clinical malaria (ie, axillary temperature $\geqslant$37.5°C plus parasitemia); being in the first trimester of pregnancy, assessed verbally; the presence of any abnormal medical conditions; history of acute or severe chronic disease, including hepato-splenic schistosomiasis, macrohematuria, and bloody stools; psychiatric disorders, such as epilepsy; use of artesunate, artemether, any artemisinin-based combination therapy (ACT), mefloquine, or praziquantel within the previous month; and weight <20 kg. *S. haematobium*–infected children who were excluded from the study were offered praziquantel (40 mg/kg).

Consenting children who met our inclusion criteria were assigned to treatment. Treatment efficacy was assessed 26 days after the last treatment dose. Two urine specimens and a single stool specimen were collected, and a finger-prick blood sample was obtained. At the end of the trial, all children who were still infected with *S. haematobium* (or *S. mansoni*) were treated with praziquantel (40 mg/kg), and all children were given albendazole (400 mg) in accordance with World Health Organization (WHO) recommendations [14].

Drugs, randomization, and adverse events. Mefloquine (mephaquine), formulated as 250-mg lactabs, and mefloquine-artesunate (artequin) were products of Mepha. Artesunate (arinate), formulated as 50-mg tablets, was supplied by Dafra Pharma. Praziquantel (600-mg tablets) was purchased from Inresa. Children received 1 of the following 4 dosing regimens: (1) mefloquine administered as a single 25-mg/kg dose (for patients with a body weight <28 kg) or as a split dose spaced by 6 h (for patients with body weight $\geqslant$28kg); (b) mefloquine-artesunate administered as 1 tablet of artesunate (100 mg) plus 1 lactab of mefloquine (250 mg) once daily for 3 consecutive days; (c) artesunate administered at a dosage of 4 mg/kg once daily for 3 consecutive days; and (d) a single 40-mg/kg dose of praziquantel. Mefloquine, artesunate, and praziquantel were given to the nearest half-tablet according to the calculated dose per kg of body weight. Children received a food item before drug administration to enhance bioavailability [17].

The drugs were dispensed by the 2 physicians using a computer-generated randomization code. A maximum of 76 children (4 groups of 19 children each) were randomized to 1 of the 4 drug regimens. If more individuals met the inclusion criteria, they were assigned to the praziquantel group. All drugs were administered under medical observation, and the exact time of drug intake was recorded. After ingestion of the medication, children were observed for 1 h to ensure retention of the drugs. If vomiting occurred within 1 h after treatment, a second treatment was administered.

Children were observed for at least 3 h after treatment for acute adverse events. In cases in which adverse events occurred, a full clinical examination was performed. Twenty-four, 48, 72, and 96 h after the first dosing, children were interviewed with a standardized questionnaire, and those who reported adverse events were clinically examined. Adverse events were graded (as mild, moderate, severe, or life threatening), and appropriate mitigation measures taken if needed.

Laboratory procedures. Urine, stool, and blood samples collected at baseline and at follow-up 26-days after treatment were brought to the laboratory. Urine specimens were vigorously shaken, and 10 mL was filtered through a 13-mm filter with an aperture of 25 μm. The filters were placed on microscope slides, a drop of Lugol's iodine was added, and the slides were read independently by 1 of 2 experienced laboratory technicians under a microscope at a $\times$100 magnification. The number of *S. haematobium* eggs was recorded [18]. Ten percent of the slides were reexamined for quality control. Urine specimens from children with results positive for *S. haematobium* eggs were subjected to a Combur 9 reagent strip (Roche Diagnostics) and the pH, hematuria, leucocyturia, and proteinuria were recorded.

From each stool specimen, duplicate Kato-Katz thick smears (41.7 mg each) were prepared [19] and quantitatively examined under a microscope. The number of *S. mansoni, Ascaris lumbricoides, Trichuris trichiura,* and hookworm eggs were counted and recorded separately. In addition, a small portion of stool (1–2 g) was preserved in sodium acetate-acetic acid-formalin and processed with an ether-concentration method adhering to a standard operating procedure [20]. Samples were examined microscopically at a $\times$100 magnification for helminths and at $\times$400 magnification for intestinal protozoa.

Blood films were stained with Giemsa, rinsed in water, dried, and examined under a microscope by experienced technicians at $\times$500 magnification using oil immersion. The species-specific densities of *Plasmodium* were recorded, and parasitemia was expressed as the number of *Plasmodium* parasites per μL of blood. Malaria slides collected at the end of the study were reexamined by experienced technicians at the Swiss Tropical Institute.

Ethical approval, trial registration, and informed consent. Ethical clearance was obtained from the Ministry of Health and Public Hygiene in Côte d'Ivoire (no. 2868) and the Ethics Com-

Table 1. Demographic, Clinical, and Laboratory Baseline Characteristics of Schoolchildren Infected with *Schistosoma haematobium* Included in the Study

Characteristic	Drug			
	Mefloquine (n = 19)	Artesunate (n = 20)	Mefloquine-artesunate (n = 18)	Praziquantel (n = 26)
Male/female	7/12	9/11	7/11	14/12
Age, mean years (±SD)	9.2 (2.0)	9.5 (1.6)	9.4 (2.1)	9.5 (2.3)
Weight, mean kg (±SD)	26.0 (4.6)	24.7 (7.9)	27.4 (5.4)	25.9 (7.0)
Range of actual total dose, mg/kg	21.0–24.9	9.7–12.3	20.2–37.0/7.3–15.0	30.0–40.7
Schistosoma haematobium				
GM eggs per 10 mL of urine (range)	30.1 (1–2039)	40.2 (2–562)	42.0 (1–688)	32.0 (1–457)
Light infection (<50 eggs per 10 mL of urine)	11	10	10	17
Heavy infection (≥50 eggs per 10 mL of urine)	8	10	8	9
Malariometric indices				
Plasmodium infection	18 (94.7)	19 (95.0)	17 (100)[a]	14 (73.7)[b]
Parasitemia (mean parasites per μL of blood)	765	308	477	172
Coinfection				
With *Schistosoma mansoni*	8 (42.1)	6 (35.3)[c]	10 (62.5)[d]	7 (30.4)[e]
GM *S. mansoni* EPG (range)	63.9 (12–798)	49.8 (12–204)	62.6 (12–786)	54.5 (24–120)
Soil-transmitted helminths				
Ascaris lumbricoides	10 (52.6)	8 (47.1)[c]	10 (62.5)[d]	14 (60.7)[e]
Trichuris trichiura	15 (78.9)	9 (52.9)[c]	12 (75.0)[d]	19 (82.6)[e]
Hookworm	3 (20.0)[f]	3 (23.1)[f]	2 (12.5)[g]	6 (33.3)[h]
Intestinal protozoa				
Endolimax nana	11 (73.3)[i]	11 (84.6)[f]	11 (68.8)[g]	14 (77.8)[h]
Entamoeba coli	10 (66.6)[i]	11 (84.6)[f]	10 (62.5)[g]	10 (55.5)[h]
Giardia intestinalis	3 (20.0)[i]	2 (15.4)[f]	2 (12.5)[g]	2 (11.1)[h]
Chilomastrix mesnili	1 (6.7)[i]	2 (15.4)[f]	0	3 (16.7)[h]
Blastocystis hominis	2 (13.3)[i]	1 (7.6)[f]	1 (6.3)[g]	2 (11.1)[h]
Entamoeba histolytica/*Entamoeba dispar*	0	1 (7.6)[f]	0	1 (5.5)[h]
Jodamoeba bütschlii	0	0	1 (6.3)[g]	1 (5.5)[h]
Hymenolepis nana	0	0	1 (6.3)[g]	0
Urinary analysis				
>10 leucocytes/μL	4 (21.1)	2 (10.0)	2 (11.1)	4 (15.4)
>30 mg/dL protein	12 (63.2)	13 (65.0)	13 (72.2)	15 (57.7)
>5 erythrocytes/μL	17 (89.5)	20 (100.0)	16 (88.9)	21 (80.8)

NOTE. Data are no. (%) of subjects, unless otherwise indicated. GM, geometric mean; SAF, sodium acetate-acetic acid-formalin; SD, standard deviation.

[a] Seventeen malaria slides.
[b] Nineteen malaria slides.
[c] Based on Kato-Katz thick smear results available from 17 children and ether-concentration method from SAF-preserved stool samples from 13 children.
[d] Based on Kato-Katz thick smear results and ether-concentration method from SAF-preserved stool samples from 16 children.
[e] Based on Kato-Katz thick smear results available from 23 children and ether-concentration method from SAF-preserved stool samples from 18 children.
[f] Ether-concentration method from SAF-preserved stool samples from 13 children.
[g] Ether-concentration method from SAF-preserved stool samples from 16 children.
[h] Ether-concentration method from SAF-preserved stool samples from 18 children.
[i] Ether-concentration method from SAF-preserved stool samples from 15 children.

mittee of Basel, Switzerland (no. 70/08). The trial was registered with Current Controlled Trials (ISRCTN06498763). Written informed consent was obtained from parents or legal guardians of children and oral informed consent was obtained from children with a parasitologically confirmed *S. haematobium* infection. Participation was voluntary, and children could withdraw from the trial at any time.

Statistical analysis. Data were entered into an Excel spreadsheet and transferred to Stata software, version 10.0 (Stata Corp). After internal consistency checks, all statistical analyses were performed in Stata.

S. haematobium egg counts before and after treatment were averaged for each child (arithmetic mean), and the GM egg count for each treatment group was calculated. Because egg

Table 2. Effect of Mefloquine, Artesunate, Mefloquine-Artesunate, and Praziquantel in Schoolchildren Infected with *Schistosoma haematobium*.

Characteristic after treatment	Drug			
	Mefloquine (n = 19)	Artesunate (n = 20)	Mefloquine-artesunate (n = 18)	Praziquantel (n = 26)
Children with cure	4 (21)	5 (25)	11 (61)	23 (88)
GM *Schistosoma haematobium* eggs per 10 mL of urine (range)	7.9 (1–694)	6.2 (1–267)	1.7 (1–73)	1.1 (1–5)
ERR, %	74	85	96	97
Malariometric indices				
Children with *Plasmodium* infection	0	0	0	19 (73.1)
Parasitemia (mean parasites per μL of blood)	0	0	0	450
Schistosoma mansoni				
Children with infection	8[a] (42.1)[b]	6[c] (31.6)[d]	4[c] (25.0)[e]	2[f] (12.5)[g]
Children with cure	3 (37.5)	2 (33.3)	6 (75)[h]	5 (83.3)[i]
GM *S. mansoni* EPG	44.2	11.3	2.7	1.5
ERR, %	31	77	96	97
Coinfection				
With soil-transmitted helminths				
Ascaris lumbricoides	11 (57.9)[b]	10 (52.6)[d]	9 (56.3)[e]	14 (58.3)[g]
Trichuris trichiura	17 (89.5)[b]	10 (52.6)[d]	10 (62.5)[e]	19 (79.1)[g]
Hookworm	3 (15.8)[b]	2 (13.3)[j]	1 (7.7)[k]	6 (25.0)[g]
With intestinal protozoa				
Endolimax nana	9 (60.0)[j]	9 (60.0)[j]	9 (69.2)[k]	14 (87.5)[l]
Entamoeba coli	8 (53.3)[j]	9 (60.0)[j]	9 (69.2)[k]	13 (81.3)[l]
Giardia intestinalis	3 (20.0)[j]	3 (20.0)[j]	2 (15.4)[k]	3 (18.8)[l]
Entamoeba histolytica/Entamoeba dispar	2 (13.3)[j]	1 (6.7)[j]	1 (7.7)[k]	3 (18.8)[l]
Blastocystis hominis	2 (13.3)[j]	1 (6.7)[j]	1 (7.7)[k]	2 (12.5)[l]
Chilomastrix mesnili	1 (6.7)[j]	0	1 (7.7)[k]	1 (6.3)[l]
Jodamoeba bütschlii	0	2 (13.3)[j]	0	0
Hymenolepsis nana	0	1 (6.7)[j]	0	0

NOTE. Data are no. (%) of subjects, unless otherwise indicated. EPG, eggs per g of stool; ERR, egg reduction rate; GM, geometric mean; SAF, sodium acetate-acetic acid-formalin.

[a] Three new infections.
[b] Based on Kato-Katz thick smear results available from all children and ether-concentration method from SAF-preserved stool samples from 15 children.
[c] Two new infections.
[d] Based on Kato-Katz thick smear results available from 19 children and ether-concentration method from SAF-preserved stool samples from 15 children.
[e] Based on Kato-Katz thick smear results available from 16 children and ether-concentration method from SAF-preserved stool samples from 13 children.
[f] One new infection.
[g] Based on Kato-Katz thick smear results available from 24 children and ether-concentration method from SAF-preserved stool samples from 16 children.
[h] Based on 8 stool samples.
[i] Based on 6 stool samples.
[j] Ether-concentration method from SAF-preserved stool samples from 15 children.
[k] Ether-concentration method from SAF-preserved stool samples from 13 children.
[l] Ether-concentration method from SAF-preserved stool samples from 16 children.

counts are overdispersed, they were logarithmically transformed (log [count +1]), and the GM was expressed as the antilogarithm of the mean. The ERR was calculated as (1−[GM egg count after treatment/GM egg counts at enrollment] × 100).

Pearson's χ^2 test was used to compare baseline binary characteristics and the proportion of reported adverse events between treatment arms. Logistic regression models were applied to assess CRs against *S. haematobium, S. mansoni,* malaria, soil-transmitted helminths, and intestinal protozoa between treatment arms. Statistical significance was estimated using a likelihood ratio test. Negative binominal models were fitted to compare the number of adverse events between the different treatment arms.

RESULTS

Adherence and baseline characteristics. Of the 176 schoolchildren invited for baseline screening, 173 provided a urine specimen, and 103 (59.5%) had results that were positive for *S. haematobium.* Twenty children were excluded from the study

Table 3. Comparison of Treatment Outcomes Between Groups

Outcome	Mefloquine vs praziquantel	*P*	Artesunate vs praziquantel	*P*	Mefloquine-artesunate vs praziquantel	*P*
Schistosoma haematobium infection						
CR	28.8 (5.6–147.1)	<.001	23.0 (4.8–110.8)	<.001	4.9 (1.1–22.6)	.043
ERR	21.1 (5.6–80.1)[a]	<.001	12.8 (3.5–47.8)[a]	<.001	3.0 (0.7–12.5)[a]	.130
Plasmodium species	NA (CR = 100%)		NA (CR = 100%)		NA (CR = 100%)	
Schistosoma mansoni infection						
CR	10.0 (0.8–128.8)	.077	12 (0.8–181.0)	.073	1.5 (0.1–20.6)	.762
ERR	2.5 (0.4–17.0)[a]	.354	4.0 (0.57–27.3)[a]	.164	1.2 (0.2–8.1)[a]	.885
Ascaris lumbricoides infection CR	1.6 (0.1–21.1)	.706			0.4 (0.05–2.8)	.333
Trichuris trichiura infection CR	NA (CR = 0%)		0.2 (0.02–2.8)	.244	0.3 (0.02–3.2)	.244
Hookworm infection CR	1.5 (0.05–40.6)	.810	1.5 (0.05–40.6)	.810	3.0 (0.08–107.4)	.547
Entamoeba coli CR	0.5 (0.06–4.9)	.579	0.9 (0.1–7.8)	.949	0.5 (0.06–4.9)	.579
Endolimax nana CR	0.2 (0.02–2.6)	.223	0.4 (0.03–5.9)	.534	0.3 (0.02–4.4)	.389

NOTE. Data are odds ratios (95% confidence intervals), unless otherwise indicated. CR, cure rate; ERR, egg reduction rate; NA, not applicable.
[a] Incidence rate ratio.

because they failed to provide a second urine specimen (14 children) or had a severe disease condition (6 children) (Figure 1). Eighty-three children (37 boys and 46 girls; mean age, 9.4 years) were included, and 76 children were randomly assigned to the 4 treatment groups (1 child was wrongly assigned to the artesunate group instead of the mefloquine-artesunate group). The remaining 7 children were given praziquantel.

Table 1 summarizes the baseline demographic, clinical, and laboratory characteristics of the 4 treatment groups, which were comparable. The 7 children who were additionally given praziquantel had similar baseline characteristics (data not shown). The baseline GM *S. haematobium* egg count among children in the 4 treatment groups ranged from 30 to 42 eggs per 10 mL of urine. Forty-eight children received a diagnosis of a light *S. haematobium* infection (<50 eggs per 10 mL of urine), whereas the remaining 35 children had heavy infections (⩾50 eggs per 10 mL of urine) [21]. Reagent strip tests revealed that 74 children had >5 erythrocytes/mL of urine. A high *P. falciparum* baseline prevalence was found (89.5%), with no difference among groups. The mean parasitemia was 172–765 *Plasmodium* parasites per μL of blood. Of the 75 individuals who had a stool sample examined, 31 (41%) were concurrently infected with *S. mansoni.* No difference was observed regarding *S. mansoni,* soil-transmitted helminths, and intestinal protozoa infections among treatment groups.

Baseline clinical symptoms of children participating in the study included headache (17 children), wind (18), and coughing (11).

***Efficacy against* S. haematobium.** No child was lost to follow-up on day 26 after treatment (Figure 1), and therefore data of all 83 children were included in the final analysis (intention-to-treat). CRs achieved with mefloquine, artesunate, and mefloquine-artesunate against *S. haematobium* were 21%, 25%, and 61%, respectively (Table 2). A significantly higher CR (88%) was observed with praziquantel. Comparison of treatment outcomes between groups are shown in Table 3. Both praziquantel and mefloquine-artesunate resulted in ERRs >95% with no statistically significant difference (incidence rate ratio, 3.0; $P = .130$). ERRs in the mefloquine and the artesunate groups were 74% and 85%, respectively, which were significantly lower than ERRs in the 2 other treatment groups (both $P < .001$).

Effect against other parasites. Praziquantel and mefloquine-artesunate resulted in high CRs against *S. mansoni* (83% and 75%, respectively) (Table 2). Only low CRs were observed with mefloquine and artesunate alone (38% and 33%, respectively). Praziquantel, mefloquine-artesunate, artesunate, and mefloquine achieved ERRs against *S. mansoni* of 97%, 96%, 77%, and 31%, respectively.

Mefloquine, artesunate, and mefloquine-artesunate completely cured *P. falciparum* infections, whereas the *P. falciparum* prevalence in the praziquantel treatment group was 73% (mean parasitemia, 450 *Plasmodium* parasites per μL of blood), similar to the baseline survey.

None of the treatments tested had an effect against any of the 3 soil-transmitted helminths or any of the 8 intestinal protozoa (Table 2). There was no statistically significant difference between praziquantel treatment and mefloquine, artesunate, or mefloquine-artesunate on soil-transmitted helminths and intestinal protozoa (Table 3).

Adverse events. Three hours after treatment, 6 children reported clinical symptoms. There were 4 cases of mild headache (2 in mefloquine group and 2 in praziquantel group) and 2 cases with moderate coughing (1 in artesunate group and 1 in

Table 4. Clinical Symptoms Reported 24–72 h after Treatment, Stratified by Treatment Group

	No. (%) of subjects with adverse event															
	Mefloquine, by time after treatment (n = 19)				Artesunate, by time after treatment (n = 20)				Mefloquine-artesunate, by time after treatment (n = 18)				Praziquantel, by time after treatment (n = 26)			
Adverse event, grade	24	48	72	At any time point	24	48	72	At any time point	24	48	72	At any time point	24	48	72	At any time point
Coughing																
Mild	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1 (3.8)
Moderate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Headache																
Mild	0	0	0	0	2	2	0	4 (20.0)	1	2	0	3 (16.7)	0	0	0	0
Moderate	3	1	1	3 (15.8)	0	1	2	3 (15.0)	0	1	0	1 (5.6)	0	2	2	3 (11.5)
Chill																
Mild	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1 (3.8)
Moderate	0	0	0	0	0	1	0	1 (5)	0	0	0	0	0	0	0	0
Vomiting																
Mild	2	0	0	2	0	1	0	1 (5.0)	0	1	0	1 (5.6)	0	1	0	1 (3.8)
Moderate	1	2	0	3	0	0	0	0	0	1	0	1 (5.6)	0	1	0	1 (3.8)
Abdominal pain																
Mild	3	2	0	4 (21.1)	1	2	2	4 (20.0)	3	3	1	6	2	7	0	9 (34.6)
Moderate	5	10	4	13 (68.4)[a]	3	6	2	8 (40)[b]	2	6	4	10 (55.6)[c]	2	3	0	4 (15.4)
Vertigo																
Mild	1	0	0	1 (5.2)	1	1	0	1 (5.0)	0	0	0	0	1	0	0	1 (3.8)
Moderate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhea																
Mild	0	0	0	0	0	0	0	0	2	0	0	2 (11.1)	0	0	0	0
Moderate	0	1	0	1 (5.2)	0	0	0	0	0	0	0	0	0	0	0	0

[a] Significantly different from praziquantel-treated children ($P < .001$).
[b] Significantly different from praziquantel-treated children ($P = .037$).
[c] Significantly different from praziquantel-treated children ($P = .008$).

mefloquine group). Both symptoms, however, were also reported before treatment.

Table 4 summarizes reported symptoms at different time points after treatment. There were 48 mild and 70 moderate adverse events recorded at the 24, 48, and 72 h after treatment examinations. At least 1 adverse event at any of the 3 assessment time points was reported by 61% of children who received praziquantel, 80% of those who received artesunate, 94% of those who received mefloquine-artesunate, and 100% of those who received mefloquine (χ^2, 13.44; $P = .004$). Abdominal pain was the predominant adverse event. The incidence of moderate abdominal pain was significantly higher for children treated with mefloquine (89%; $P < .001$), mefloquine-artesunate (83%; $P = .008$), and artesunate (60%; $P = .037$) than it was for those treated with praziquantel (46%). No statistically significant difference was observed between the 4 treatment groups, and the reported occurrence of headache, coughing, vomiting, vertigo, or chill. No serious or life-threatening adverse events were reported that would have necessitated referral to a hospital, and no neuropsychological adverse events were observed. None of the adverse events led to study discontinuation.

DISCUSSION

To our knowledge, this is the first clinical investigation documenting antischistosomal properties of mefloquine and mefloquine-artesunate administered according to current malaria treatment regimens. As a benchmark, a group of children was treated with praziquantel [14]. Finally, a fourth group of children was given artesunate alone to be able to test whether mefloquine combined with artesunate acts synergistically, additively, or antagonistically when compared with monotherapies. To defy the risk of resistance of *P. falciparum* to monotherapies, such as artesunate or mefloquine, and to improve treatment outcome, drug combinations have been recommended for the treatment of uncomplicated *P. falciparum* malaria [22, 23].

We found that mefloquine-artesunate is efficacious in the treatment of *S. haematobium* infections. Eleven of 18 children

were free of *S. haematobium* eggs in their urine 26 days after treatment, owing to an observed CR of 61%. The ERR exceeded 95%. Our results are based on a reasonably sensitive diagnostic approach with 2 urine specimens examined before and after treatment. A third urine specimen obtained after treatment might have identified additional infections, mainly of low intensity, and therefore the true CR might be somewhat lower. This issue has been documented in a previous randomized controlled trial with oral artemether for prevention of patent *S. haematobium* infection [24]. It is also important to note that, among those children treated with mefloquine-artesunate, 16 had a stool specimen subjected to the Kato-Katz method before and after treatment. There were 8 individuals with a concurrent *S. mansoni* infection at baseline; after treatment, only 2 remained positive for *S. mansoni* eggs. Two new infections were recorded, but these were likely cases that were missed during the pretreatment baseline evaluation because of the imperfect sensitivity of the Kato-Katz method [25–27]. Results from another proof-of-concept trial with mefloquine, artesunate, and mefloquine-artesunate, focusing on *S. mansoni,* will be presented elsewhere.

To date, artesunate-sulfadoxine-pyrimethamine, artesunate-amodiaquine, and artesunate-sulfamethoxypyrazine plus pyrimethamine have been examined in *S. haematobium*–infected children [13, 28]. High CRs (87%–100%) and ERRs (92%–100%) have been observed with artesunate-sulfadoxine-pyrimethamine and artesunate-amodiaquine in a small number of preschool-aged children concurrently infected with *Plasmodium* and *S. haematobium* in Senegal [28]. A lower CR (43.9%) was obtained in a randomized controlled trial that tested the efficacy of artesunate-sulfamethoxypyrazine plus pyrimethamine in 384 *S. haematobium*–infected children [13]. Although our exploratory study does not substitute for a larger clinical trial, mefloquine-artesunate is likely to have the strongest antischistosomal properties, because both mefloquine and artesunate exhibit antischistosomal properties, whereas in other ACTs, it is only the artemisinin compound that does so.

In light of the considerable geographic overlap of malaria and schistosomiasis, it is conceivable that many people coinfected with *Plasmodium* and *S. haematobium* (or other schistosome species) who will be treated with mefloquine-artesunate (or any other ACT) will have a dual benefit: clearance of malaria parasitemia and reduction of schistosomiasis-related morbidity [12]. In view of scaling-up activities of ACTs for malaria control, there is an opportunity to monitor population-based effects against schistosomiasis.

Monotherapy with mefloquine and artesunate in *S. haematobium*–infected children yielded only low CRs (21% and 25%, respectively). Although the respective ERRs were considerably higher (74% and 85), these were significantly lower than ERRs observed among praziquantel and mefloquine-artesunate recipients. Therefore, the combination of mefloquine and artesunate seems to act additively or even synergistically when compared with each drug administered alone. The CR of artesunate observed in our study is in line with a previous investigation using the same treatment regimen with artesunate (3 doses of 4 mg/kg) in the treatment of *S. haematobium*–infected children in Gabon, which reported a CR of 27% [29]. In Nigerian children, a CR of 70% and an ERR of 86% were found using 2 doses of artesunate at 6 mg/kg given 2 weeks apart [30]. Finally, a 5-day treatment regimen with artesunate administered to schoolchildren in 2 Senegalese villages resulted in CRs of 20% and 48% and ERRs of 55% and 89%, respectively [31]. Therefore, it is too early to draw conclusions as to the efficacy of artesunate (or other artemisinins) or mefloquine used alone against schistosomiasis.

Additional work is required to deepen our understanding of therapeutic dose range and the dosage regimen of mefloquine in *S. haematobium*–infected patients. Moreover, and in contrast to praziquantel, mefloquine shows high activity against all stages of the schistosomes in the vertebrate host [9]. Therefore, the effect of mefloquine and mefloquine-artesunate against juvenile schistosomes should be studied. We speculate that mefloquine or mefloquine-artesunate might be of interest for travel medicine; tourists who travel to Africa and are exposed to *S. haematobium*–infected water might be treated with a single dose of mefloquine or mefloquine-artesunate, which might prevent the development of adult egg-producing worms.

All children treated with mefloquine and most of the children administered mefloquine-artesunate reported adverse events that were either mild or moderate. However, adverse events were transient and self-limiting, none required referral to a hospital, and some were also reported before drug administration. Gastrointestinal complaints, including abdominal pain, nausea, and vomiting, were the most frequent symptoms in clinical trials administering mefloquine to patients with malaria [32]. No cardiovascular and neuropsychological symptoms, which have previously been associated with mefloquine [33], were observed in the present study.

In conclusion, high CR and ERR were obtained with the standard single dose of praziquantel against *S. haematobium* infections in our study setting in southern Côte d'Ivoire, confirming previous results from Côte d'Ivoire and elsewhere [34, 35]. Mefloquine-artesunate, administered in accordance with the currently recommended malaria treatment schedule, showed promising results against *S. haematobium,* as well as against *S. mansoni* in those children concurrently infected with both schistosome species. Additional and coherent experimental, clinical, and epidemiological inquiry is therefore warranted.

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References

1. Davis A. Schistosomiasis. In: Cook GC, Zumla AI, eds. Manson's Tropical Diseases, 22nd edition. London: Saunders, **2009**:1413–1456.
2. Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet **2006**; 368:1106–1118.
3. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect Dis **2006**; 6:411–425.
4. Utzinger J, Raso G, Brooker S, et al. Schistosomiasis and neglected tropical diseases: towards integrated and sustainable control and a word of caution. Parasitology **2009**; 136:1859–1874.
5. Doenhoff MJ, Cioli D, Utzinger J. Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. Curr Opin Infect Dis **2008**; 21:659–667.
6. Melman SD, Steinauer ML, Cunningham C, et al. Reduced susceptibility to praziquantel among naturally occurring Kenyan isolates of *Schistosoma mansoni*. PLoS Negl Trop Dis **2009**; 3:e504.
7. Oliveira MF, d'Avila JC, Torres CR, et al. Haemozoin in *Schistosoma mansoni*. Mol Biochem Parasitol **2000**; 111:217–221.
8. Kumar S, Guha M, Choubey V, Maity P, Bandyopadhyay U. Antimalarial drugs inhibiting hemozoin (beta-hematin) formation: a mechanistic update. Life Sci **2007**; 80:813–828.
9. Keiser J, Chollet J, Xiao SH, et al. Mefloquine–an aminoalcohol with promising antischistosomal properties in mice. PLoS Negl Trop Dis **2009**; 3:e350.
10. Manneck T, Haggenmüller Y, Keiser J. Morphological effects and tegumental alterations induced by mefloquine on schistosomula and adult flukes of *Schistosoma mansoni*. Parasitology **2010**; 137:85–98.
11. Utzinger J, Xiao SH, Tanner M, Keiser J. Artemisinins for schistosomiasis and beyond. Curr Opin Investig Drugs **2007**; 8:105–116.
12. Keiser J, Utzinger J. Artemisinins and synthetic trioxolanes in the treatment of helminth infections. Curr Opin Infect Dis **2007**; 20:605–612.
13. Sissoko MS, Dabo A, Traore H, et al. Efficacy of artesunate + sulfamethoxypyrazine/pyrimethamine versus praziquantel in the treatment of *Schistosoma haematobium* in children. PLoS One **2009**; 4:e6732.
14. World Health Organization. Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers. Geneva, Switzerland: World Health Organization, **2006**.
15. Adoubryn KD, Ouhon J, Yapo CG, Assoumou EY, Ago KML, Assoumou A. Profil épidémiologique des schistosomoses chez les enfants d'âge scolaire dans la région de l'Agnéby (sud-est de la Côte-d'Ivoire). Bull Soc Pathol Exot **2006**; 99:28–31.
16. Julious S. Sample size of 12 per group rule of thumb for a pilot study. Pharm Stat **2005**; 4:287–291.
17. Castro N, Medina R, Sotelo J, Jung H. Bioavailability of praziquantel increases with concomitant administration of food. Antimicrob Agents Chemother **2000**; 44:2903–2904.
18. Plouvier S, Leroy J-C, Colette J. A propos d'une technique simple de filtration des urines dans le diagnostic de la bilharziose urinaire en enquête de masse. Med Trop (Mars) **1975**; 35:229–230.
19. 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.
20. Utzinger J, Botero-Kleiven S, Castelli F, et al. Microscopic diagnosis of sodium acetate-acetic acid-formalin-fixed stool samples for helminths and intestinal protozoa: a comparison among European reference laboratories. Clin Microbiol Infect **2010**; 16:267–273.
21. World Health Organization (WHO). Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO expert committee. WHO Tech Rep Ser **2002**; 912:i–iv, 1–57.
22. White NJ, Nosten F, Looareesuwan S, et al. Averting a malaria disaster. Lancet **1999**; 353:1965–1967.
23. Olliaro P, Wells TN. The global portfolio of new antimalarial medicines under development. Clin Pharmacol Ther **2009**; 85:584–595.
24. N'Goran EK, Utzinger J, Gnaka HN, 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.
25. de Vlas SJ, Gryseels B. Underestimation of *Schistosoma mansoni* prevalences. Parasitol Today **1992**; 8:274–277.
26. Utzinger J, N'Goran EK, N'Dri A, Lengeler C, Xiao SH, Tanner M. Oral artemether for prevention of *Schistosoma mansoni* infection: randomised controlled trial. Lancet **2000**; 355:1320–1325.
27. Bergquist R, Johansen MV, Utzinger J. Diagnostic dilemmas in helminthology: what tools to use and when? Trends Parasitol **2009**; 25: 151–156.
28. Boulanger D, Dieng Y, Cisse B, et al. Antischistosomal efficacy of artesunate combination therapies administered as curative treatments for malaria attacks. Trans R Soc Trop Med Hyg **2007**; 101:113–116.
29. Borrmann S, Szlezák N, Faucher J-F, et al. Artesunate and praziquantel for the treatment of *Schistosoma haematobium* infections: a double-blind, randomized, placebo-controlled study. J Infect Dis **2001**; 184: 1363–1366.
30. Inyang-Etoh PC, Ejezie GC, Useh MF, Inyang-Etoh EC. Efficacy of artesunate in the treatment of urinary schistosomiasis in an endemic community in Nigeria. Ann Trop Med Parasitol **2004**; 98:491–499.
31. De Clercq D, Vercruysse J, Kongs A, Verlé P, Dompnier JP, Faye PC. Efficacy of artesunate and praziquantel in *Schistosoma haematobium* infected schoolchildren. Acta Trop **2002**; 82:61–66.
32. Karbwang J, White NJ. Clinical pharmacokinetics of mefloquine. Clin Pharmacokinet **1990**; 19:264–279.
33. Chen LH, Wilson ME, Schlagenhauf P. Controversies and misconceptions in malaria chemoprophylaxis for travelers. JAMA **2007**; 297: 2251–2263.
34. N'Goran EK, Gnaka HN, Tanner M, Utzinger J. Efficacy and side-effects of two praziquantel treatments against *Schistosoma haematobium* infection, among schoolchildren from Côte d'Ivoire. Ann Trop Med Parasitol **2003**; 97:37–51.
35. Danso-Appiah A, Utzinger J, Liu J, Olliaro P. Drugs for treating urinary schistosomiasis. Cochrane Database Syst Rev **2008**:CD000053.