RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ORAL ARTEMETHER FOR THE PREVENTION OF PATENT SCHISTOSOMA HAEMATOBIUM INFECTIONS

ELIÉZER K. N’GORAN, JÜRGIN UTZINGER, HENRI N. GNACA, AHOA YAPI, NICAISE A. N’GUESSAN, SILÉU D. KIGBAFORI, CHRISTIAN LENGELER, JACQUES CHOLLET, XIAO SHUHUA, AND MARCEL TANNER

Laboratoire de Biologie Animale, Université de Cocody, Abidjan, Côte d’Ivoire; Centre Suisse de Recherches Scientifiques, Abidjan, Côte d’Ivoire; Office of Population Research, Princeton University, Princeton, N.J.; Grandes Endémies de Tiassalé, Tiassalé, Côte d’Ivoire; Swiss Tropical Institute, Basel, Switzerland; Institute of Parasitic Diseases, Chinese Centre for Disease Control and Prevention, Shanghai, China

Abstract. Artemether is an efficacious antimalarial drug that also displays antischistosomal properties. Laboratory studies have found that artemether curtails the development of adult worms of Schistosoma japonicum, S. mansoni, and S. haematobium, and thus prevents morbidity. These findings have been confirmed in clinical trials for the former two parasites; administered orally once every 2–3 weeks, artemether significantly reduced the incidence and intensity of patent infections. Here, we present the first randomized, double-blind, placebo-controlled trial of artemether against S. haematobium, done in a highly endemic area of Côte d’Ivoire. Urine specimens from 440 schoolchildren were examined over 4 consecutive days, followed by two systematic praziquantel treatments 4 weeks apart. S. haematobium-negative children were randomized to receive 6 mg/kg artemether (N = 161) or placebo (N = 161). Medication was administered orally for a total of six doses once every 4 weeks. Adverse events were assessed 72 hours after medication, and perceived illness episodes were monitored throughout the study period. Incidence and intensity of S. haematobium infections, and microhematuria and macrohematuria were assessed 3 weeks after the final dosing. We also monitored malaria parasitemia and treated positive cases with sulfadoxine-pyrimethamine (SP). Oral artemether was well tolerated. The incidence of patent S. haematobium infections in artemether recipients was significantly lower than in placebo recipients (49% versus 65%, protective efficacy: 0.25, 95% CI: 0.08–0.38, P = 0.007). The geometric mean infection intensity in the artemether group was less than half that of the placebo recipients (3.4 versus 7.4 eggs/10 mL urine, P < 0.001). Heavy S. haematobium infections, microhematuria and macrohematuria, and the incidence of malaria parasitemia were all significantly lower in artemether recipients. In conclusion, previous findings of efficacy of artemether against S. japonicum and S. mansoni were confirmed for S. haematobium, although the protective efficacy was considerably lower. These findings enlarge the scope and potential of artemether and further contribute to discussions of its role as an additional tool for integrated schistosomiasis control.

INTRODUCTION

Schistosomiasis is a chronic and debilitating disease that remains one of the most prevalent parasitic infections in the humid tropics, with an estimated 650 million people at risk of infection and 200 million actually infected. Three species—Schistosoma haematobium, S. japonicum, and S. mansoni—cause the bulk of an estimated global burden of 4.5 million disability-adjusted life years, 85% of them concentrated in sub-Saharan Africa. Awareness is growing that the burden of schistosomiasis is largely underestimated and requires revision, as it might actually rank close to that of malaria. It is encouraging that significant progress in the control of schistosomiasis is largely underestimated and requires revision, as it might actually rank close to that of malaria. On the other hand, praziquantel is virtually the only antischistosomal drug readily available for treatment. Metrifonate (which is active against S. haematobium) has recently been withdrawn from the market, and oxamniquine (widely and effectively used against S. mansoni in Brazil) is being replaced by praziquantel. Therefore, research and development of novel antischistosomal drugs is a pressing need, which has recently been acknowledged by WHO/TDR.

Compounds exhibiting activity against the young developmental stages of the schistosome parasites also are relevant, as praziquantel is largely ineffective in this period. Artemether, a derivative of the antimalarial artemisinin, has recently been identified with exactly these characteristics. Detailed laboratory studies have revealed that schistosomula of S. japonicum, S. mansoni, and S. haematobium are significantly more susceptible to artemether than adult worms. These laboratory findings have been confirmed for S. japonicum and S. mansoni in eight randomized controlled clinical trials with >5,000 study participants (for review, see Utzinger et al.19). Administered orally once every 2–3 weeks for up to 20 weeks at a dose of 6 mg/kg, artemether was safe, prevented acute cases of schistosomiasis japonica, and showed significant effects on the incidence and intensity of patent infections.

The efficacy of artemether for prevention of patent S. haematobium infections in a human population has not been investigated. Our detailed laboratory investigations—demonstrating in vitro and in vivo activity of artemether against this schistosome species—formed a sound basis for carrying out the first randomized, double-blind, placebo-controlled trial. Our study was done in an area highly endemic.
for *S. haematobium* in Côte d’Ivoire and followed a protocol similar to that of our previous trial with artemether for prevention of patent *S. mansoni* infections.  

**MATERIALS AND METHODS**

**Study area and participants.** The study was carried out in the village of Taabo, in the district of Tiassalé, south-central Côte d’Ivoire, from November 2000 to July 2001. This village, located 150 km northwest of the financial and political capital, Abidjan, is next to the artificial Lake Taabo, along the Bandama River, at the western end of the embankment dam. The village has an estimated population of 1,500, including some fishermen from neighboring Mali and Burkina Faso who arrived shortly after completion of dam construction 20 years ago. Villagers are engaged mainly in subsistence farming of yams, manioc, and bananas, with a little cash crop production of coffee and cacao. There is a primary school with 12 classes that had 440 children registered in the 2000–2001 school year. Annual precipitation is approximately 1,100 mm, with most rain occurring from April to September. Taabo is highly endemic for *S. haematobium*. Our own previous work in the village revealed a prevalence of infection among schoolchildren > 90%, with high reinfection rates occurring shortly after successful chemotherapy with praziquantel. Malaria is also endemic. In a recent prospective study among 94 children, aged 6–15 years, *Plasmodium falciparum* parasites were found in the blood of 55% (N’Goran EK and others, unpublished data).

**Study design, sample size calculation, and ethical clearance.**

We designed a randomized, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of oral artemether for prevention of patent *S. haematobium* infections in schoolchildren aged 5–15 years. The primary endpoints were the incidence and intensity of patent *S. haematobium* infections 3 weeks after the final medication (6 months after systematic administration of praziquantel). *S. haematobium* infections were quantitatively assessed by screening urine specimens over 4 consecutive days. An estimated sample size of 252 children, assigned either oral artemether or a placebo, was required to detect a difference of 50% in the *S. haematobium* incidence rate with 90% power at a 5% significance level. Based on our earlier work in this village, it was reasonable to assume that at least 50% of the placebo recipients would become infected with *S. haematobium* within 6 months.

The study protocol was reviewed and approved by the Institutional Review Boards of the Swiss Tropical Institute (Basel, Switzerland) and the Center Suisse de Recherches Scientifiques (Abidjan, Côte d’Ivoire) and was granted ethical clearance by the Ministry of Public Health in Côte d’Ivoire. One month before the baseline survey, the objectives, procedures, and possible risks of the study were explained to the village authorities and schoolteachers at a meeting in Taabo. Teachers were then asked to prepare class lists with the name, sex, and age of the children. Written informed consent was obtained from the parents or legal guardians of all children enrolled in the school. Eligibility criteria were that study participants appeared healthy at enrollment, as assessed by the study physician; had no known hypersensitivity to praziquantel or artemether; and were not pregnant or lactating.

**Trial procedures.** Figure 1 shows the sequence of the trial procedures. At enrollment, height (to the nearest cm) and weight (to the nearest kg) of all children were recorded, followed by a full clinical examination carried out by the study physician and two assistants. This consisted of measurement of axillary temperature by an electronic thermometer, palpation for spleen and liver enlargement, and appraisal of anemia. The next day between 10 AM and noon, children were asked to provide urine specimens in 125-mL plastic containers for assessment of *S. haematobium* infections. The containers were labeled with unique identifiers before transfer to the nearby district hospital laboratory. Urine collection procedures were repeated over 4 consecutive days. During this baseline survey, children also provided a small portion of their morning stool. Plastic containers issued the previous day were collected early in the morning, labeled, and transferred to the nearby laboratory where stool specimens were screened for geohelminths and *S. mansoni*.

In the afternoon of the last urine collection, all children were treated with praziquantel at a single oral dose of 40 mg/kg. Four weeks later, praziquantel was systematically administered to all children for a second time at the same dose without prior urine collection. Three weeks after the second treatment of praziquantel, urine specimens were collected again over 4 consecutive days. In addition, all children provided finger-prick blood samples for preparation of thick and thin blood films for determination of malaria infections, and the packed cell volume (PCV) of blood collected in heparinized microcapillary tubes was appraised.

**Drugs and randomization.** Artemether, formulated as 40-mg capsules, and indistinguishable capsules of placebo containing starch were a gift from the Kunming Pharmaceutical Corp. (Kunming, China). The products were manufactured according to international Good Manufacturing Practice standards and fully licensed for human use. Product specifications and sterility were confirmed by routine laboratory tests (bacteria, mycoses, and *Bacillus coli*). The capsules were packed in 32 tin containers identified only by letters, each containing 500 capsules (artemether 16 tins, placebo 16 tins). Children who were treated twice with praziquantel, had at least three urine specimens analyzed 3 weeks after the second treatment round, and excreted no *S. haematobium* eggs in their urine were eligible for randomization. They were stratified by school grade and randomized in blocks of 32 to a tin by an independent statistician, who kept two copies of the code in sealed envelopes and was the only person to know the code. Capsules were prepacked by the study pharmacist according to subject weights and kept in sealed envelopes, with extra capsules in case of vomiting.

Artemether, at a dose of 6 mg/kg, or placebo was administered orally under direct supervision of the study physician. The first dose was given 3 days after the final urine collection 3 weeks after the second praziquantel treatment, and the children remained under medical surveillance for 1 hour to ensure retention of the drugs and appraisal of immediate adverse events. The dose was repeated if vomiting occurred. Treatment at the same dose and surveillance period was repeated for a total of 6 times, once every 4 weeks (Figure 1).

Those children who were infected with malaria parasites of any density were treated with a single oral dose of SP (25 mg/kg sulfadoxine and 0.75 mg/kg pyrimethamine) 3 days after the first artemether/placebo dosing, just after the study
physician's first appraisal of adverse events. When our trial was launched, SP was highly efficacious in this part of Côte d'Ivoire, according to the Ministry of Public Health and the Institut Pierre Richet (Bouaké, Côte d'Ivoire). Malaria parasitemia was monitored throughout the study period, i.e., before each follow-up dosing of artemether or placebo, finger-pricks were done for all children and thick and thin blood films examined for the presence of P. falciparum, P. Malariae, and P. ovale. Positive cases received SP shortly after the appraisal of adverse events 72 hrs post-administration of artemether or placebo.

**Adverse events, perceived illness episodes, and reported water contact patterns.** Seventy-two hrs after each artemether/placebo dosing, the study physician assessed the incidence of acute adverse events. Children were interviewed with a questionnaire that had been used successfully in our previous clinical trial of artemether against S. mansoni.21 Children reporting adverse events were examined carefully, and, if required, the study physician acted, following routine primary health care procedures of Côte d'Ivoire.

The incidence of perceived illness episodes and the frequency of water contacts in the adjacent Lake Taabo were assessed throughout the study period. Teachers interviewed children with a standardized questionnaire with a recall period of 1 week. The first interviews were conducted 1 week after the first artemether/placebo dosing and were continued for 22 weeks. Because of the teachers' workloads and school holidays, no interviews were conducted on 11 of the 22 weeks. Once every week, the study physician reviewed the accuracy of questionnaire responses while treating children and confirming ailments they reported.

**End of study.** Three weeks after the final dose of artemether or placebo, detailed parasitologic examinations were carried out. Urine specimens were collected over 4 consecutive days, and children provided a stool specimen. Finger-pricks were done for thick and thin blood smears and assessment of the PCV (Figure 1).

**Laboratory procedures.** Urine, stool, and blood specimens were brought to the nearby district hospital laboratory. The first urine specimen collected during each of the three surveys was analyzed macroscopically, distinguishing between three categories: 1) clear, 2) cloudy, and 3) visible blood (gross hematuria). The specimen was then semi-quantitatively tested for hematuria, leucocyturia, and proteinuria, using reagent strips (Nephur6–Test®, Roche Diagnostics, Mannheim, Germany), and the results were recorded according to the manufacturer's instructions. All urine specimens were quantitatively examined for S. haematobium eggs. Specimens were thoroughly mixed and 10 mL were passed through 13-mm diameter Nytrel filters, according to a standard procedure.26 Filters were placed on microscope slides and stained with a drop of Lugol solution, and eggs were counted under a light microscope (Wild, Heerbrugg, Switzerland) at a magnification of x100 by four experienced technicians. A random sample of 10% of the slides were re-examined by the senior microscopist for quality control purposes.

From each stool specimen, a single 42-mg Kato-Katz thick smear was prepared and quantitatively examined for Ascaris lumbricoides, hookworm, S. mansoni, and Trichuris trichiura following standard, quality-controlled procedures.21 Thick and thin blood films were stained with Giemsa. At the beginning of the study, the species-specific densities of malaria parasites were determined. This information is crucial for understanding the epidemiology and control strategies for each parasite species.
parasites were estimated under a light microscope with an x50 oil immersion lens and x10 eyepieces by counting the number of parasites per 200 white blood cells (WBC). If fewer than 10 parasites were found, the reading was continued up to 500 WBC. Parasite counts were expressed as count/mL, assuming a standard WBC count of 8,000/mL. The PCV was directly measured in microcapillary tubes after centrifugation in a microhematocrit centrifuge.

Data management and statistical analyses. Double data entry and validation was done in EpiInfo software (version 6.04; Centers for Disease Control and Prevention, Atlanta, GA). After a series of range and internal consistency checks, the cleaned data set was locked and handed over to the independent statistician in exchange for the code. The final statistical analyses included those children who had been randomized, received all six doses of artemether/placebo, and provided at least three urine specimens at the end of the study. Analyses were done with EpiInfo and STATA software (version 7.0, Stata Corp., College Station, TX).

The primary efficacy analyses were performed on the incidence of patent *S. haematobium* infections within 5 months and the geometric mean infection intensity among positive children, comparing artemether and placebo recipients. The protective effect of artemether, expressed in percent, was estimated as 100 (1 – relative risk). Proportions were tested using a Yates-corrected $\chi^2$ test. At the end of the study, we calculated the arithmetic mean egg counts for all positive children and compared the geometric means between the artemether and placebo groups by a t-test. For comparison of the incidence of acute adverse events within 72 hours after administration of praziquantel, and 11 children provided fewer than three urine specimens before the first artemether/placebo dosing. From the remaining 365 children, another 43 were excluded because they continued to excrete *S. haematobium* eggs in their urine (viable eggs: $N = 21$; dead eggs: $N = 22$). Consequently, 322 children were randomly assigned artemether ($N = 161$) or placebo ($N = 161$). Twelve children who missed one of the six medications given once every 4 weeks, mainly because they had moved elsewhere, also were excluded (7 placebo, 5 artemether). Four children—all placebo recipients—provided fewer than three urine samples at study end. Thus, the final cohort consisted of 306 children (156 artemether, 150 placebo), and all subsequent analyses were performed on this cohort.

Comparison of groups. The two groups were well balanced with regard to baseline demographics, anthropometrics, and clinical characteristics (Table 1). The baseline prevalence of *S. haematobium* infections was considerably higher in the artemether group than in the placebo recipients: 79.5% versus

TABLE 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 150)</th>
<th>Artemether (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–7</td>
<td>51 (34.0%)</td>
<td>51 (32.7%)</td>
</tr>
<tr>
<td>8–11</td>
<td>63 (42.0%)</td>
<td>60 (38.5%)</td>
</tr>
<tr>
<td>12–15</td>
<td>36 (24.0%)</td>
<td>45 (28.8%)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.3 (2.8)</td>
<td>9.4 (2.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69 (46.0%)</td>
<td>67 (42.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>81 (54.0%)</td>
<td>89 (57.1%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>132 (14)</td>
<td>132 (14)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>131 (105–171)</td>
<td>132 (99–167)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>131 (105–171)</td>
<td>132 (99–167)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.2 (8.8)</td>
<td>26.5 (7.8)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>25 (15–57)</td>
<td>25 (15–55)</td>
</tr>
<tr>
<td>Children with axillary temperature $\leq$ 37.5°C</td>
<td>19 (12.7%)</td>
<td>12 (7.7%)</td>
</tr>
<tr>
<td>Children with enlarged spleen</td>
<td>14 (9.3%)</td>
<td>10 (6.4%)</td>
</tr>
<tr>
<td>Children with signs of anemia</td>
<td>5 (3.3%)</td>
<td>5 (3.2%)</td>
</tr>
<tr>
<td>Children with enlarged liver</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Effect of praziquantel and repeated artemether administration on the prevalence and intensity of *Schistosoma haematobium* infections, microscopic urine presentation, hematuria, leucocyturia, and proteinuria (placebo: *n* = 150; artemether: *n* = 156)

<table>
<thead>
<tr>
<th>S. haematobium (eggs/10 mL urine)</th>
<th>Placebo</th>
<th>Artemether</th>
<th>Placebo</th>
<th>Artemether</th>
<th>Placebo</th>
<th>Artemether</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (0)</td>
<td>46 (30.7%)</td>
<td>32 (20.5%)</td>
<td>150 (100%)</td>
<td>156 (100%)</td>
<td>53 (35.3%)</td>
<td>80 (51.3%)</td>
</tr>
<tr>
<td>Light infection (&lt; 50)</td>
<td>66 (44.0%)</td>
<td>92 (59.0%)</td>
<td>0</td>
<td>0</td>
<td>76 (50.7%)</td>
<td>71 (45.5%)</td>
</tr>
<tr>
<td>Heavy infection (≥ 50)</td>
<td>38 (25.3%)</td>
<td>32 (20.5%)</td>
<td>0</td>
<td>0</td>
<td>21 (14.0%)</td>
<td>5 (3.2%)</td>
</tr>
<tr>
<td>All infections*</td>
<td>104 (69.3%)</td>
<td>124 (79.5%)</td>
<td>0</td>
<td>0</td>
<td>97 (64.7%)</td>
<td>76 (48.7%)**</td>
</tr>
<tr>
<td>Geometric mean egg count/10 mL</td>
<td>17.0 (11.5–25.2)</td>
<td>18.8 (13.8–25.6)</td>
<td>0</td>
<td>0</td>
<td>7.4 (4.8–11.5)</td>
<td>3.4 (2.3–5.1)***</td>
</tr>
</tbody>
</table>

**Macroscopic urine analysis†**

- Clear: 82 (56.2%) vs 83 (54.6%), 128 (94.1%) vs 131 (95.6%), 108 (74.0%) vs 130 (85.0%)
- Cloudy: 59 (40.4%) vs 61 (40.1%), 8 (5.9%) vs 6 (4.4%), 29 (19.9%) vs 21 (13.7%)
- Visible blood*: 5 (3.4%) vs 8 (5.3%), 0 vs 0, 9 (6.2%) vs 2 (1.3%)*

**Reagent strip testing§**

- > 5 erythrocytes/mL urine: 85 (57.0%) vs 102 (66.7%), 7 (4.9%) vs 19 (12.4%), 57 (38.5%) vs 40 (26.0%)*
- > 10 leukocytes/mL urine: 78 (52.3%) vs 91 (59.5%), 43 (29.9%) vs 53 (34.6%), 89 (60.1%) vs 78 (50.6%)
- > 30 mg protein/dL urine: 36 (24.2%) vs 32 (20.5%), 1 (0.7%) vs 3 (2.0%), 29 (19.6%) vs 19 (12.3%)
- Negative (0): 46 (30.7%) vs 32 (20.5%), 150 (100%) vs 156 (100%), 53 (35.3%) vs 80 (51.3%)
- Light infection (< 50): 66 (44.0%) vs 92 (59.0%), 0 vs 0, 76 (50.7%) vs 71 (45.5%)
- Heavy infection (≥ 50): 38 (25.3%) vs 32 (20.5%), 0 vs 0, 21 (14.0%) vs 5 (3.2%)
- All infections*: 104 (69.3%) vs 124 (79.5%), 0 vs 0, 97 (64.7%) vs 76 (48.7%)**

*For comparison of placebo vs artemether at the end of study: Yates corrected χ² test.

† For comparison of placebo vs artemether at the end of study: t-test.

* *P < 0.05; ** P < 0.01; ***; P < 0.001.

Table 2

Table 3

Number of children (percentage) infected with intestinal nematodes and malaria parasites at baseline/beginning of study and at end of study, where applicable. Geometric mean density of *Plasmodia* and packed cell volume (PCV) are also given.

<table>
<thead>
<tr>
<th>Stool examination (1 Kato-Katz)*</th>
<th>Placebo</th>
<th>Artemether</th>
<th>Placebo</th>
<th>Artemether</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hookworm</td>
<td>58 (39.7%)</td>
<td>52 (34.4%)</td>
<td>70 (48.3%)</td>
<td>81 (54.0%)</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td>11 (7.5%)</td>
<td>6 (4.0%)</td>
<td>8 (5.5%)</td>
<td>5 (3.3%)</td>
</tr>
<tr>
<td>Ascaris lumbricoides</td>
<td>1 (0.7%)</td>
<td>0</td>
<td>0</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Schistosoma mansoni</td>
<td>0</td>
<td>1 (0.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malariometric indices†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>68 (47.2%)</td>
<td>67 (45.3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Plasmodium malaria</td>
<td>11 (7.6%)</td>
<td>13 (8.8%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Plasmodium ovale</td>
<td>1 (0.7%)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Geometric mean density/mL</td>
<td>535 (436–705)</td>
<td>484 (383–613)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PCV (SD)¶</td>
<td>35.8 (2.9)</td>
<td>35.8 (3.5)</td>
<td>37.8 (3.3)</td>
<td>38.2 (3.5)</td>
</tr>
</tbody>
</table>

* Cohort: Baseline (146 placebo, 152 artemether), end of study (146 placebo, 150 artemether).

† Cohort: Beginning of study (144 placebo, 148 artemether).

‡ Cohort: Beginning of study (144 placebo, 143 artemether), end of study (144 placebo, 149 artemether).

For comparison of placebo vs artemether at the end of study: t-test.

For comparison of placebo vs artemether at the end of study: χ² test.

* *P < 0.05; ** P < 0.01; ***; P < 0.001.

Table 3

69.3% (χ² = 3.63, *P* = 0.057, Table 2). The baseline geometric mean egg count among *S. haematobium*-positive children in the artemether group was 18.8 eggs/10 mL urine (95% CI: 13.8–25.6), which was similar to the geometric mean egg count of positive children receiving a placebo (17.0 eggs/10 mL urine, 95% CI: 11.5–25.2; Table 2). Macroscopic urine examinations revealed similar characteristics between the two groups. At baseline, 13 children had gross hematuria (Table 2). Furthermore, 187 children had > 5 erythrocytes/mL urine as detected by reagent strips, with a considerably higher prevalence in the artemether group (66.7% versus 57.0% in placebo recipients). However, the difference was not significant (χ² = 2.96, *P* = 0.085). There were no differences for baseline prevalences of leucocyturia and proteinuria (Table 2). The two groups also were similar in terms of hookworm, *T. trichiura*, *P. falciparum*, and *P. malariae* infection prevalences before the first dosing of artemether or placebo (Table 3). Finally, no differences were measured in the geometric mean density of malaria parasites and the PCV before the first dose of artemether or placebo (Table 3).

**Effects of oral artemether on *S. haematobium*.** At the end of our trial—6 months after all study participants were microscopically confirmed to be free of *S. haematobium* eggs and 3 weeks after the final artemether/placebo dosing—a significant difference was found in the incidence of patent *S. haematobium* infections: artemether 76/156 versus placebo 97/150 (protective efficacy: 0.25 (95% CI: 0.08–0.38), χ² = 7.28, *P* = 0.007, Table 2). The geometric mean egg count of those children who had received six doses of artemether and who were egg-positive at study end (3.4 eggs/10 mL urine, 95% CI: 2.3–5.1) was less than half that of the egg-positive children in the placebo group (7.4 eggs/10 mL urine, 95% CI: 4.8–11.5, t-test = 3.97, *P* < 0.001, Table 2). At study end, 26 children were found with a heavy *S. haematobium* infection (≥ 50 eggs/10 mL urine), the large majority of whom had received placebo (*N* = 21) rather than artemether (*N* = 5, *N’GORAN AND OTHERS 28*).
Efficacy of Artemether Against S. haematobium

χ² = 11.46, P < 0.001, Table 2). Administration of artemether also showed significant effects on microhematuria and macrohematuria. Reagent strip testing at study end found 97 children with > 5 erythrocytes/mL urine (40 artemether, 57 placebo, χ² = 5.44, P = 0.020, Table 2), and macroscopic urine examination found 11 children with gross hematuria (two artemether, nine placebo, χ² = 4.97, P = 0.026, Table 2). The prevalences of leucocyturia and proteinuria at the end of the study were lower in the artemether group than among placebo recipients; however, the differences were not statistically significant at the 5% level.

Adverse events. Orally administered artemether at a dose of 6 mg/kg was well tolerated. There were no serious or severe adverse events within 1 hour after medication, and no child required immediate medical care throughout the study. The compliance rate for reporting adverse events within 72 hours after medication was excellent (1.813/1.836). Overall, study participants reported 284 adverse events, of which 128 (45.1%) occurred among artemether recipients. No symptoms were reported significantly more often by artemether recipients than placebo recipients (Table 4).

Perceived illness episodes and reported water contact patterns. Weekly interviews of children about perceived illness episodes and reported water contact patterns yielded a total of 3,519 child-weeks at risk. The percentage of children absent during the interviews was 5.4%, hence a total of 3,334 child-weeks of observations were made (artemether 1,696, placebo 1,638). There were a total of 1,228 perceived illness episodes, similarly distributed among artemether (N = 612) and placebo (N = 616) recipients. Headache was the most frequently perceived illness episode (N = 324), followed by abdominal pain (N = 266) and cough (N = 197). Artemether recipients were significantly less likely to report dizziness (RR = 0.18, 95% CI: 0.04–0.79, P = 0.022), as well as to suffer from malaria (RR = 0.32, 95% CI: 0.12–0.88, P = 0.036). All other perceived illness episodes showed virtually identical frequencies between the two groups.

The total number of children who reported having had water contacts in the week before being interviewed was 1,364, with similar distributions among those receiving artemether or placebo. These high frequencies of reported water contacts indicate that approximately 41% of the children had at least one water contact in the adjacent Lake Taabo over the course of 1 week. Further data about the number of water contacts revealed that 44% of the children reported having had more than three water contacts within 1 week.

Effects on other parasites. Artemether showed no efficacy against hookworm or T. trichiura infections (Table 3). Since infection prevalences of A. lumbricoides and S. mansoni were virtually zero among study participants, appraisal of the potential effect of artemether against these parasites was not feasible (Table 3). Malaria parasitemia was monitored once every 4 weeks throughout the study period, with prompt SP treatment of all positive children. Over the course of the study, 1,768 slides were microscopically examined (artemether 905, placebo 863), and 260 positive cases were identified (artemether 117, placebo 143, RR = 0.78 (95% CI: 0.62–0.98, χ² = 4.39, P = 0.036). The PCV among both artemether and placebo recipients was considerably higher at study end than at the beginning; however, there were no differences between the two groups at either time point (Table 3).

**DISCUSSION**

This study found that artemether, administered orally at a dose of 6 mg/kg, is safe, well tolerated, and efficacious in the prevention of patent S. haematobium infections. The incidence of S. haematobium infections in artemether recipients was 25% lower (95% CI: 8–38%) than in individuals receiving a placebo. Even more important are the findings that the mean infection intensity and proportion of heavy infections, as well as macrohematuria and microhematuria, were all significantly lower in those children who received artemether rather than placebo. In fact, the geometric mean infection intensity among positive children in the artemether group was less than half that of the placebo recipients (3.4 versus 7.4 eggs/10 mL urine). In the artemether group, heavy S. haematobium infections and gross hematuria were found in five and two children, respectively, as opposed to 21 and 9 children, respectively, in the placebo group. Since the severity of morbidity and subsequent sequelae are generally correlated with infection intensities—indirectly assessed by egg output and/or hematuria⁷—our findings are of considerable public health importance in S. haematobium endemic settings.

Our findings that artemether is efficacious in preventing patent S. haematobium infections confirm previous findings with S. japonicum and S. mansoni. Administration of oral artemether, also at a dose of 6 mg/kg, once every 2 weeks for up to 11 doses in different S. japonicum-endemic areas of China resulted in incidence reductions of 60–100%, and infections were of lower intensities.⁸ In an area highly endemic for S. mansoni in Côte d’Ivoire, six doses of artemether given at the same dose but spaced by 3-week intervals showed an incidence reduction of 50%, and the geometric mean egg output was reduced from 32 to 19 eggs/g stool.⁹

The incidence reduction of S. haematobium found in the present study was considerably lower than those previously reported for S. japonicum and S. mansoni. However, it is important to note that this trial was carried out in an area that is one of the most intense S. haematobium foci in Côte d’Ivoire and probably elsewhere in sub-Saharan Africa. In our earlier work in Taabo, commencing in 1997, we screened > 200 schoolchildren and found eggs of S. haematobium in 94% of them and a geometric mean egg count among positive subjects of 24.6 eggs/10 mL urine.¹₀ Subsequent treatment

---

**TABLE 4**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Placebo</th>
<th>Artemether</th>
<th>RR (95% CI)</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>59</td>
<td>48</td>
<td>0.73 (0.54–1.14)</td>
<td>0.239</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>56</td>
<td>52</td>
<td>0.90 (0.62–1.29)</td>
<td>0.631</td>
</tr>
<tr>
<td>Fever</td>
<td>9</td>
<td>6</td>
<td>0.64 (0.23–1.80)</td>
<td>0.558</td>
</tr>
<tr>
<td>Itching</td>
<td>8</td>
<td>4</td>
<td>0.48 (0.15–1.60)</td>
<td>0.353</td>
</tr>
<tr>
<td>Cough</td>
<td>6</td>
<td>3</td>
<td>0.48 (0.12–1.93)</td>
<td>0.472</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4</td>
<td>5</td>
<td>1.21 (0.33–4.38)</td>
<td>0.695</td>
</tr>
<tr>
<td>Chills</td>
<td>3</td>
<td>3</td>
<td>0.97 (0.20–4.78)</td>
<td>0.714</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>2</td>
<td>0.64 (0.11–3.85)</td>
<td>0.969</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>3</td>
<td>1.45 (0.24–8.65)</td>
<td>0.969</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>0</td>
<td>0.00</td>
<td>NA</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>2</td>
<td>0.97 (0.14–6.85)</td>
<td>0.641</td>
</tr>
</tbody>
</table>

* Denominator for adverse events: 891 observations for placebo recipients, 922 for artemether recipients.

² For comparison of placebo vs artemether: Yates corrected χ² test.
with praziquantel was efficacious. However, 6 and 12 months post-treatment, the infection prevalence again had reached very high levels of 63% and 85%, respectively.25 There is evidence that *S. haematobium* was introduced in Taabo and neighboring villages less than 2 decades ago, with construction of the lake there.24 In the present study, the baseline infection prevalence of those children who had complete data records was 75%, and the geometric mean egg output was 17.9 eggs/10 mL urine. Therefore, both prevalence and intensity of *S. haematobium* infections were somewhat lower than in 1997. This is probably due to systematic treatment of neighboring villages less than 2 decades ago, with construction of Taabo lake. 

Our finding that artemether showed a protective efficacy in this highly endemic setting of *S. haematobium* is encouraging, and its effect against this schistosome species might be further improved by reducing the treatment intervals from 4 to 2 or 3 weeks. In fact, preceding experiments in hamsters harboring juvenile *S. haematobium* have revealed considerably higher worm burden reductions when artemether was administered once every 2–3 weeks instead of using 4-week intervals.18 Laboratory studies have established that not only artemether but also artesunate and arteether—compounds that also are derived from artesinin—exhibit antischistosomal properties (for a review, see Utzinger et al.29). Analogues to artemether, the larval migratory stages of *S. japonicum* and *S. mansoni*, were found to be significantly more susceptible to artesunate than the adult worms.30,31 Interestingly, a first comparative appraisal between artemether and artesunate in *S. mansoni*-infected mice revealed that the former exhibited consistently higher activities, both on juvenile and adult worms.31 To the best of our knowledge, no data are available on artesunate susceptibility of different developmental stages of *S. haematobium*, but it is reasonable to assume that schistosomula are particularly susceptible.

Despite the lack of these laboratory data, a first randomized, double-blind, placebo-controlled trial has recently been completed among 296 *S. haematobium*-infected schoolchildren in Gabon.23 Infected children were assigned to artesunate plus placebo, praziquantel plus placebo, artesunate together with praziquantel, or placebo alone. Artesunate was administered over three consecutive days at daily doses of 4 mg/kg. The primary outcome measure was the parasitologic cure rate, assessed 8 weeks after drug administration by microscopic urine examinations on two consecutive days. The study found a cure rate of 27% in the artesunate-placebo group, which was not significantly higher than that obtained after placebo administration alone (cure rate 20%, *P* = 0.45). Hence, it was concluded that artemisinin derivatives are not efficacious against *S. haematobium*. A different conclusion was drawn from another recent study, also assessing the therapeutic efficacy of artesunate but carried out in 288 *S. haematobium*-infected schoolchildren from two villages in Senegal.33 Here, study participants were systematically allocated artesunate (total dose 400 mg administered over 5 consecutive days) or praziquantel, and cure rates were assessed 5, 12, and 24 weeks after medication by microscopic examination of two urine specimens. Five weeks post-treatment, parasitologic cure rates of 20% and 48% were found in artesunate recipients, and egg count reductions > 80% occurred among heavily infected children. It was concluded that artesunate is efficacious in the treatment of *S. haematobium* infections.

There are two important differences between these studies and our own work: First, we used artemether instead of artesunate, a choice justified by consistently higher worm burden reductions using the former rather than the latter compound, as established in preceding animal experiments.31 Second, the study designs in Gabon and Senegal assessed the therapeutic efficacies of artesunate against *S. haematobium*. The design of our study explicitly took into account the fact that artemether shows highest activity against the juvenile stages of *S. haematobium*. This was ascertained by first clearing all patent infections using praziquantel before the first dosing of artemether, which was then repeatedly administered once every 4 weeks. This treatment interval is much shorter than the 63–65 days that are required for *S. haematobium* worms to reach oviposition.54 Our current results further contribute to the ongoing strategic discussions of how to translate these findings into effective public health actions.19,29 The use of artemether or another artemisinin derivative together with praziquantel might considerably increase the worm burden reduction rates and hence significantly impact overall transmission. There is evidence from animal experiments that combination therapy with praziquantel plus artesunate results in higher percentage worm reductions in both *S. japonicum* and *S. mansoni*.35,36 Repetition of these studies in *S. haematobium* animal models is needed. A preliminary study in a human population confirmed the beneficial effect of combining praziquantel with artesunate for treatment of *S. mansoni* infections.37 Although the first randomized, controlled clinical trial with combination treatment of praziquantel and artesunate against *S. haematobium* infections failed to show a significantly higher parasitologic cure rate than praziquantel alone, there was a significant effect on the geometric mean egg count.32 Using artemether instead of artesunate in combination with praziquantel might further improve the treatment outcomes. This strategy might prove highly effective in epidemiologic settings where *S. haematobium* transmission has become highly focalized in both space and time. Combined treatment might significantly increase the chances of approaching the goal of disease elimination, particularly in North Africa and the Middle East.

In view of our findings, artemether can now also be recommended in settings where schistosomiasis is endemic but malaria is not, for the prevention of acute cases and the reduction of incidence infections. Interestingly, such areas are more common than generally appreciated and can be found in large parts of Brazil, China, the Middle East, and North Africa.3 For the time being, use of artemether and other artemisinin derivatives for prevention and cure of schistosomiasis should not be recommended in areas where malaria and schistosomiasis are co-endemic, owing to the possibility of resistance development in the malaria parasites.19 Although the risk appears to be low—primarily because of the very short half-life times of artemisinin derivatives and their proposed mechanism of action38,39—and there is no single case of resistance reported in a clinical setting despite large-scale use,15,40 further work is required, and resistance monitoring is paramount. The World Health Organization has recently recommended that when artemisinins are being used against ma-
Efficacy of artemether against S. haematobium

laria in places where schistosomiasis co-exists, the effect on schistosomes should be monitored concurrently. We conclude that this trial and the previous ones have established the fact that artemether is safe and efficacious for prevention of patent infections of S. japonicum, S. mansoni, and S. haematobium. Artemether represents an additional tool with considerable potential for integrated schistosomiasis control efforts.

Received March 6, 2002. Accepted for publication July 8, 2002.

Acknowledgments: The authors thank the population and authorities of Taabo, particularly the chief, the school director, and the teachers and schoolchildren for their dedication and excellent collaboration over the last several years. We are grateful to Dr. G. P. Brika, executive director of the national control program against onchocerciasis, trypanosomiasis, schistosomiasis, and dracunculiasis. Thanks are addressed to laboratory technicians K. L. Lohourignon, B. Sosthène, and M. Traoré for their skilled technical assistance, and to Mr. Dupont for help in the laboratory. We are indebted to Dr. T. A. Smith for help in the laboratory. We are indebted to Dr. T. A. Smith for the randomization and keeping of the code. Kunming Pharmaceutical Corp. kindly provided the study medications.

Financial support: This investigation received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases and the Swiss Tropical Institute. E. K. N’Goran was financially supported by the Swiss Academy of Natural Science and J. Utzinger by the Swiss National Science Foundation and the Centre for Health and Wellbeing at Princeton University.

Authors’ addresses: Eliézer K. N’Goran, Ahoa Yapi, Nicaise A. and the Centre for Health and Wellbeing at Princeton University. E. K. N’Goran was financially supported by the Swiss Academy of Natural Science and J. Utzinger by the Swiss National Science Foundation and the Centre for Health and Wellbeing at Princeton University.

Authors’ addresses: Eliézer K. N’Goran, Ahoa Yapi, Nicaise A. N’Guesso, and Silué D. Kigbafori, UFR Biosciences, Université de Cocody, 22 BP 770, Abidjan 22, Côte d’Ivoire; Jürg Utzinger, Office for Population Research, Princeton University, Princeton, N.J. 08544; Henri N. Gnaka, Grandes Endémies de Tiassalé, BP, Tiassalé, Côte d’Ivoire; Silué D. Kigbafori, Christian Lengeler, Jacques Chollet, and Marcel Tanner, Swiss Tropical Institute, P.O. Box, CH-4002 Basel, Switzerland; Xiao Shuhua, Institute of Parasitic Diseases, Chinese Centre for Disease Control and Prevention, Shanghai 200025, China.

Reprint requests: Prof. Marcel Tanner, Swiss Tropical Institute, P.O. Box, CH-4002 Basel, Switzerland, Telephone +41 61 284 8283, Fax: +41 27 179 75 51, E-mail: marcel.tanner@unibas.ch

REFERENCES


32. Bormann S, Szlezák N, Faucher J-F, Matsiegui P-B, Neubauer


