Atovaquone-Proguanil Compared with Chloroquine and Chloroquine-Sulfadoxine-Pyrimethamine for Treatment of Acute Plasmodium falciparum Malaria in the Philippines

Dorina G. Bustos, Craig J. Canfield, Editha Canete-Miguel, and David B. A. Hutchinson

This randomized, open-label clinical trial compared a fixed-dose combination of atovaquone and proguanil (n = 55) with chloroquine (n = 23) or a combination of chloroquine, sulfadoxine, and pyrimethamine (n = 32) for treatment of acute falciparum malaria in the Philippines. Patients were hospitalized for 28 days to ensure medication compliance and prevent reinfection. Atovaquone-proguanil produced a significantly higher cure rate (100%) compared with that for chloroquine (30.4%; P < .0001) or chloroquine-sulfadoxine-pyrimethamine (87.5%; P < .05). Treatments did not differ significantly with respect to parasite clearance time (mean: 46.7 h for atovaquone-proguanil, 60.0 h for chloroquine, and 42.8 h for chloroquine-sulfadoxine-pyrimethamine) or fever clearance time (mean: 38.8, 46.8, and 34.5 h, respectively). Adverse events were typical of malaria symptoms; the most frequently reported events were vomiting (18% for atovaquone-proguanil, 17% for chloroquine, and 9% for chloroquine-sulfadoxine-pyrimethamine), abdominal pain (15%, 17%, and 3%, respectively), anorexia (11%, 13%, and 0%, respectively), and headache (6%, 17%, and 3%, respectively). Atovaquone-proguanil was well tolerated and more effective than chloroquine or chloroquine-sulfadoxine-pyrimethamine for treatment of multidrug-resistant falciparum malaria in the Philippines.

Received 7 October 1998; revised 8 February 1999.

Malaria is the most frequently encountered parasitic infection in the world [1]. Each year, malaria accounts for 300–500 million clinical episodes and 1.5–2.7 million deaths (4% of all reported fatalities) [2]. A resurgence of Plasmodium falciparum malaria has been seen in the Philippines, where the development and spread of multidrug-resistant falciparum malaria was first reported in the early 1970s [3]. As of 1996, between 23% and 39% of all cases of falciparum malaria in the Palawan region of the Philippines were resistant to chloroquine [4]. Despite resistance, chloroquine remains the treatment of choice in most parts of the Philippines because of its low cost, low incidence of high-level resistance, and resistance to other antimalarial drugs.

Atovaquone, a hydroxynaphthoquinone that inhibits plasmodial mitochondrial electron transport [5], and proguanil, an isopropylbiguanide that inhibits plasmodial dihydrofolate reductase (primarily via its metabolite cycloguanil) [6], act synergistically to kill blood-stage schizonts [7]. In clinical trials, treatment of falciparum malaria with a combination of atovaquone and proguanil hydrochloride was significantly more effective than treatment with either drug alone [8] or with amoquin in Gabon [9] or mefloquine in Thailand [10], and it was equivalent to a quinine-tetracycline combination in Brazil [11]. The atovaquone-proguanil combination has been generally well tolerated [12].

The objective of the present study was to evaluate the efficacy and safety of atovaquone and proguanil hydrochloride compared with that of chloroquine or a chloroquine-sulfadoxine-pyrimethamine combination in patients with acute falciparum malaria in the Philippines.

Patients and Methods

Patient populations. All subjects were treated at the Palawan Provincial Hospital in Puerto Princesa, Palawan, Philippines, between October 1994 and February 1995. Patients were eligible for enrollment if they had acute, uncomplicated falciparum malaria with parasite counts between 1000 and 200,000/µL, were 12–65 years of age, and weighed >20 kg. Exclusion criteria were as previously described [8–11].

Study design. The study began as a randomized, open-label comparison of atovaquone-proguanil versus chloroquine. However, after 40 patients had been entered into the trial, the cure rate with...
chloroquine was <35%, and, for ethical reasons, further treatment with chloroquine alone was considered imprudent. The protocol was amended so that patients subsequently randomized to receive chloroquine also received a sulfadoxine-pyrimethamine combination. Thus, the trial became a randomized, open-label comparison of three treatment regimens. Patients were sequentially admitted to the study, hospitalized on the medical service during the acute stage of illness, and transferred to a convalescent wing during a 28-day follow-up period.

Treatment assignment. Patients assigned to atovaquone-proguanil received 3 doses of each component at 24-h intervals for 3 days, supplied as 250-mg tablets of atovaquone and 100-mg tablets of proguanil hydrochloride. Patients weighing >40 kg received 4 tablets of each drug daily, and patients weighing 30–40 kg received 3 tablets of each drug daily. Chloroquine was supplied as a 150-mg (base) tablet. Patients weighing >40 kg received 1500 mg (base) during 3 days. After an initial dose of 4 tablets, 2 additional tablets were administered 6, 24, and 48 h later. Patients weighing 30–40 kg were treated with an initial dose of 10 mg/kg followed by 5 mg/kg 6, 24, and 48 h later. Sulfadoxine-pyrimethamine was supplied as tablets, each containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.

After the protocol amendment, patients randomized to receive chloroquine also received sulfadoxine-pyrimethamine. Patients weighing >50 kg received 3 tablets, and those weighing ≤50 kg received 2 tablets as a single dose. Because pharmacokinetic studies have shown that ingestion of food increases the bioavailability of atovaquone, the atovaquone-proguanil regimen was administered 45 min after ingestion of a liquid meal. All antimalarial drugs were administered under supervision of the investigators and readministered if vomiting occurred within 20 min after drug intake.

Clinical assessments and efficacy end points. Clinical examinations were performed at least once daily for 7 days and weekly thereafter. At each examination, patients were queried from a standard list of 16 symptoms commonly associated with malaria infections and also asked an open-ended question about other symptoms.

Response to treatment was evaluated on the basis of the World Health Organization (WHO) classification system (S = sensitive; R = resistant): S = parasite clearance within 7 days without recrudescence up to day 28; R1 = parasite clearance within 7 days, followed by recrudescence within 28 days; R2 = marked reduction of parasitemia but without clearance in 7 days; R3 = no significant reduction of parasitemia during the first 48 h [13]. The primary efficacy end point (the 28-day cure rate) and secondary end points (parasite clearance time [PCT] and fever clearance time [FCT]) were determined as previously described [8–11]. Parasite counts were also expressed as a percentage of the baseline count for graphical presentation of data and evaluation of the proportion of patients in each treatment group who had an increase in parasite counts after starting treatment.

Laboratory assessments. Thick and thin blood films were prepared every 6 h for determination of parasite counts until 3 films were negative. Thereafter, blood films were prepared daily until day 28. The films were stained with Giemsa stain, and parasite levels were determined by counting the number of asexual parasites per 1000 white blood cells on a thin film or per 200 white blood cells on a thick film and expressing the results in counts per microliter of peripheral blood. A blood slide was considered negative only if examination of 200 oil-immersion fields on a thick film showed no parasites.

Blood was obtained for routine hematology and clinical chemistry studies prior to treatment and on study days 3, 7, 14, and 28. Blood was obtained prior to treatment and immediately tested by in vitro culture for drug sensitivity by use of a modification of the radioisotopic method of Desjardins et al. [14].

Safety analysis. Data from all study participants were used in the safety analysis. Adverse experiences were defined as any clinical finding that first occurred or increased in intensity within 10 days of treatment initiation.

Statistical analysis. Yates’s corrected $\chi^2$ analysis was used to compare differences between treatment groups in cure rates and to calculate 95% confidence intervals. The Kruskal-Wallis test was used to calculate differences in medians (with 95% confidence intervals) for the FCT and PCT and in median hematology and biochemistry test results at each time period. $P < .05$ was considered statistically significant.

Results

Patient characteristics. A total of 110 Filipino patients with acute uncomplicated falciparum malaria were randomly assigned to treatment with atovaquone-proguanil ($n = 55$), chloroquine ($n = 23$), or chloroquine-sulfadoxine-pyrimethamine ($n = 32$). Treatment groups did not differ significantly with respect to baseline demographic, clinical, or laboratory characteristics. One patient responded promptly to treatment with atovaquone-proguanil and remained aparasitemic for 28 days but was considered unevaluable because he received a disallowed drug (cotrimoxazole for a urinary tract infection) on day 8. All other patients were evaluable. In vitro sensitivity testing, using a battery of antimalarial drugs, was attempted with fresh blood samples from 87 patients. Satisfactory growth occurred with at least 30 of these isolates for each drug tested. All isolates were sensitive to atovaquone, but there was in vitro resistance to chloroquine (41%), quinine (32%), mefloquine (29%), and halofantrine (48%).

Efficacy. The 28-day cure rate was significantly higher in the atovaquone-proguanil group (100%) than in the chloroquine group (30.4%, $P < .001$) or the chloroquine-sulfadoxine-pyrimethamine group (87.5%, $P < .05$; table 1). Among the 16 patients who were not cured with chloroquine alone, the pattern of resistance was R1 in 11, R2 in 3, and R3 in 2. All 4 patients who were not cured with chloroquine-sulfadoxine-pyrimethamine had an R1 response. The 95% confidence interval of the difference in cure rates between atovaquone-proguanil and the comparator drug was 49.8%–89.4% for chloroquine and 3.3%–21.7% for chloroquine-sulfadoxine-pyrimethamine. No significant differences were observed between treatment groups with respect to PCT or FCT (table 1). Patients who were cured were generally free of malaria symptoms within 72 h of treatment initiation in all groups.

Parasite counts appeared to fall at a slower rate in the ato-
Atovaquone-proguanil group than in the chloroquine-sulfadoxine-pyrimethamine treatment groups, but maximum reduction was achieved at approximately the same time (within 48 h). Patients treated with chloroquine alone had an intermediate response (figure 1). There were 25 patients who had a >50% increase in parasite counts within 6–18 h after starting treatment, including 14 (25%) of 55 treated with atovaquone-proguanil, 4 (17%) of 23 treated with chloroquine, and 7 (22%) of 32 treated with chloroquine-sulfadoxine-pyrimethamine. Parasite counts more than doubled within the first 24 h after starting treatment in 10 patients treated with atovaquone-proguanil (range, 2.2–5.5 times baseline), in 1 patient treated with chloroquine, and in no patients treated with chloroquine-sulfadoxine-pyrimethamine. By 48 h after the start of treatment, parasite counts had decreased to <10% of baseline counts in all but 6 patients. Two of these patients treated with chloroquine had an R3 response, 1 patient treated with chloroquine had a 48-h count that was 85% of baseline and had an R1 response, and 1 patient treated with chloroquine had a 48-h count that was 149% of baseline and was cured. Two patients treated with atovaquone-proguanil had 48-h counts that were 11% and 29% of baseline and were cured.

Safety. Adverse events were typical of malaria symptoms and did not differ significantly among treatment groups. The most frequently reported events in patients treated with atovaquone-proguanil, chloroquine, or chloroquine-sulfadoxine-pyrimethamine were vomiting (18%, 17%, and 9%, respectively), abdominal pain (15%, 17%, and 3%), anorexia (11%, 13%, and 0%), and headache (6%, 17%, and 3%). There were no clinically important changes in laboratory tests.

Discussion

In this study, the combination of atovaquone and proguanil hydrochloride once daily for 3 days was significantly more effective than either chloroquine or a chloroquine-sulfadoxine-pyrimethamine combination for treatment of falciparum malaria in an area where multidrug resistance is common. Atovaquone-proguanil, which achieved a cure rate of 100%, constitutes an important therapeutic advance not only in the Philippines but also in other parts of the world where chloroquine and sulfadoxine-pyrimethamine resistance continues to increase.

Although chloroquine-resistant strains of P. falciparum were expected at the outset of the study, the magnitude of resistance was not. A previous study reported the frequency of chloroquine resistance to be 23%–39% and predominantly of the R1 category [4]. When it became apparent that chloroquine monotherapy was associated with an unacceptably low cure rate, the study was amended to provide treatment with chloroquine plus sulfadoxine-pyrimethamine. Initially, sulfadoxine-pyrimethamine was given at the end of chloroquine treatment, but later this was changed to concurrent treatment with the triple combination. Both approaches achieved high cure rates (81%–91%).

Although chloroquine-sulfadoxine-pyrimethamine appeared
to reduce parasitemia somewhat faster than atovaquone-proguanil in this study (figure 1), maximum reduction was achieved at approximately the same time. The rapidity of reduction in parasitemia did not correlate with the cure rate (which was significantly higher with atovaquone-proguanil) or with the onset of symptom relief (which occurred at about the same time in all treatment groups). The transient rise in parasitemia observed in a subset of patients during the first day after initiation of treatment presumably reflects the maturation of schizonts that were sequestered from the peripheral circulation when the baseline blood film was prepared. A similar transient increase in parasitemia has been observed during treatment with other antimalarial drugs, and its prognostic significance is not always unfavorable [15].

Results in several patients highlighted the fact that WHO definitions for sensitive and resistant parasitologic responses are not mutually exclusive. For example, 1 patient with a baseline parasite count of 1394/μL had counts at 48, 54, and 60 h after starting treatment that were 85%, 24%, and 0% of baseline counts, respectively. Parasite counts remained undetectable until day 7. This patient thus met the criteria for both an R3 response (48 h count >25% of baseline count) and an R1 response (parasite clearance within 7 days, followed by recrudescence within 28 days). When patients met the literal criteria for an R3 response but were not treated with another antimalarial drug and subsequently met the criteria for an R1 or S response, we assigned them to the less resistant classification.

This study demonstrated that the combination of atovaquone and proguanil was well tolerated and more effective than chloroquine or chloroquine-sulfadoxine-pyrimethamine in the treatment of acute, uncomplicated, multidrug-resistant falciparum malaria in the Philippines. Atovaquone-proguanil is an important therapeutic option for malaria acquired in areas of the world where \textit{P. falciparum} is resistant to standard antimalarial drugs.

\textbf{Acknowledgments}

We thank the doctors, nurses, and laboratory staff at the Palawan Provincial Hospital who helped conduct this clinical trial.

\textbf{References}