MAJOR ARTICLE

Atovaquone and Proguanil versus Amodiaquine for the Treatment of *Plasmodium falciparum* Malaria in African Infants and Young Children

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Malaria-related morbidity and mortality are greatest among young children in areas with high malaria transmission intensity. An open-label, randomized study was done to evaluate the efficacy and safety of the combination of atovaquone and proguanil formulated as pediatric-strength tablets (20 and 8 mg/kg of body weight, respectively, administered once daily for 3 days), compared with amodiaquine (10 mg/kg of body weight, once daily for 3 days), among children weighing ⩾5 and <11 kg in Gabon. Two hundred patients aged 3–43 months were recruited. Use of atovaquone/proguanil resulted in a cure rate on day 28 of 95% (87 of 92 children), compared with 53% (41 of 78 children) for amodiaquine (difference, 42%; 95% CI, 30%–54%; $P < .001$). The incidence of adverse events was similar in both groups, and no serious adverse events were attributed to the use of atovaquone/proguanil. Atovaquone/proguanil was found to be highly effective and safe for the treatment of *Plasmodium falciparum* malaria in infants and young children weighing 5–10 kg in Africa.

The combination of atovaquone, a hydroxynaphthoquinone, with the biguanid proguanil has demonstrated excellent cure rates in the treatment of uncomplicated *Plasmodium falciparum* malaria [1–3] and is highly effective in curing multidrug-resistant falciparum malaria [4]. Its efficacy and safety for malaria chemoprophylaxis are well established [5].

At the time of the start of the present study in 1999, the Malarone (atavaquone-proguanil) Donation Programme was still ongoing at pilot sites in Kenya and Uganda for adult patients, and an expansion to include pediatric patients was planned [6], but there have been only 2 pediatric malaria treatment studies that examined a fixed-dose combination of atovaquone and proguanil hydrochloride to treat children weighing ⩾11 kg [4, 7]. Therefore, additional information about use of the drug to treat infants and young children was required, because this target group may benefit most from this new antimalarial combination chemotherapy. Amodiaquine, a 4-aminoquinoline, was chosen as the comparator because it is a safe, cheap, and, in many African countries, efficacious drug for the treatment of uncomplicated falciparum malaria [8].

This study was designed to evaluate the efficacy and safety of the combination of atovaquone and proguanil, compared with amodiaquine, in the treatment of children weighing ⩾5 and <11 kg who have uncomplicated *P. falciparum* malaria.

METHODS

Area and population. The trial was performed from January 1999 through December 2000 in the Medical Research Unit at the Albert Schweitzer Hospital, Lambaréné, in the province Moyen-Ogooué, Gabon. The

Received 28 February 2003; accepted 30 June 2003; electronically published 29 October 2003.

Financial support: GlaxoSmithKline.

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Clinical Infectious Diseases 2003; 37:1441–7

1058-4838/2003/3711-0003$15.00

unit is fully integrated in the routine flow of patient care at the hospital. *P. falciparum* transmission is intense and perennial in the study area, with an average entomologic inoculation rate of ~50 infective bites per person per year [9]. *P. falciparum* is the predominant malaria-causing species [10].

Study design and sample size. The study was a phase 3, randomized, open-label, parallel-group comparative trial. Two hundred children were recruited into the study. Ethical clearance was obtained from the ethics committee of the International Foundation of the Albert Schweitzer Hospital. The inclusion criteria for patients who presented to the outpatient clinic with symptoms suggestive of malaria were (1) documented, uncomplicated *P. falciparum* infection with an asexual parasite density of 1000–200,000 parasites/μL, (2) weight of $\geq$5 and <11 kg, and (3) written or verbal informed consent from a parent or guardian of the patient. No age range was specified. The major exclusion criteria were (1) receipt of antimalarial drugs or of medications with antimalarial or hemolytic effects within the previous 7 days; (2) underlying severe diseases or concomitant infections causing fever; (3) hypersensitivity to atovaquone, proguanil, or amodiaquine; and (4) clinically relevant abnormal laboratory values at screening. Patients with symptoms and signs of severe malaria were also excluded.

The study had 3 phases: (1) screening, including investigation of thick blood smear, laboratory parameter evaluation, and clinical examination; (2) treatment for 3 days; and (3) clinical and parasitologic follow-up for 26 days. Scheduled follow-up visits after treatment were made on days 3, 7, and 28. The time of day of sample collection was recorded and used for calculation of parasite and clearance fever times. Parents and guardians of the patients were encouraged to present their child immediately to the study center if the child's clinical condition changed between scheduled visits.

Sample-size calculation was based on results from another study in the same area and assumed a cure rate of 95% in the group that received atovaquone/proguanil and of 80% in the amodiaquine group [3]. Eighty-eight individuals in each group were needed to detect a 15% difference between the treatment arms at a 2-tailed significance level of <5% with 80% power. To allow for losses during follow-up, 100 children per group were enrolled.

End points. The primary end point was the cure rate on day 28. The safety end point was the incidence of adverse events occurring up to 7 days after the start of treatment. "Cure" was defined as a thick blood smear negative for *P. falciparum* on day 28 and no criteria for early treatment failure (ETF) or late treatment failure (LTF). "Early treatment failure" was defined as the development of danger signs or severe malaria up to day 3 after treatment in the presence of parasitemia; an increase from the baseline parasite density on day 2; or a parasite density on day 3 that was >25% of the count at admission. "Late treatment failure" was defined as the development of danger signs or severe malaria after day 3 in the presence of parasitemia or as parasitemia between day 7 and day 28.

Adverse changes in clinical condition were recorded as side effects and classified by severity and relation to the study medications. Secondary efficacy measures were parasite and fever clearance times. Hematologic responses and changes in clinical chemistry findings were also evaluated.

Study drugs and randomization. Treatment in the atovaquone/proguanil group was with fixed-dose, pediatric-strength tablets containing 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride (Malarone; GlaxoSmithKline), crushed and mixed with condensed milk. Children weighing $\geq$5 and <9 kg received 2 tablets and children weighing $\geq$9 and <11 kg received 3 tablets once daily for 3 consecutive days (corresponding to target doses of 20 mg/kg per day and 8 mg/kg per day for atavaquone and proguanil, respectively). Amodiaquine was formulated as a 1% suspension of amodiaquine chlorohydrate (Flavoquine; Hoechst Marion Roussel) and was administered in doses of 10 mg/kg amodiaquine base once daily for 3 consecutive days. Full doses of drug were readministered if patients vomited or spit out a dose within 1 h after administration. Patients who vomited the study drug more than once were withdrawn from the study and treated appropriately.

Randomization was done in blocks of 10 patients. Eligible patients were assigned sequentially to a treatment group according to the treatment allocation provided in sealed envelopes.

Laboratory analysis. A Giemsa-stained thick blood film was prepared at each visit, and asexual parasite density per microliter was assessed using the Lambaréné method [11, 12]. At baseline and on day 28 after treatment, or if the patient discontinued the study prematurely, a venous blood sample (1.7 mL) was obtained in a heparinized tube (Sarstedt) for laboratory analysis, and plasma was separated within 15 min (only for clinical chemistry). Hemoglobin concentration, hematocrit (packed-cell volume), WBC count, and platelet count were determined with the quantitative buffy coat technique (Becton Dickinson). The serum levels of glucose, alanine aminotransferase, creatinine, urea, total bilirubin, alkaline phosphatase, albumin, sodium, and potassium were measured by a semiautomatic dry-slide method (Vitros; Ortho-Clinical Diagnostics). PCR-based genotyping analysis to distinguish recrudescent from new infection, as well as analysis of codon changes in the cytochrome bc_1 gene of *P. falciparum,* will be published elsewhere as part of a separate investigation.

Data management and statistical evaluation. Data were entered into individual source documents that also served as patients' medical records. All data were transferred from these documents to a computer database at GlaxoSmithKline, and further quality-assurance checks were made to produce a final

database for analysis. The data were subsequently analyzed using the SAS System for Solaris, version 6.12 (SAS Institute). As an exception, parasite clearance time and fever clearance time data were captured in another database (FileMaker Pro, version 5) and analyzed using a different software package (JMP, version 5, SAS Institute) by the investigator.

For the per protocol (PP) analysis, cure rates were calculated as the proportion of evaluable patients who were cured by day 28. The PP population excluded those patients who were noncompliant with the treatment, had violated the inclusion/exclusion criteria, were lost to follow-up, or withdrew for reasons other than treatment-related adverse events or treatment failure. The intent-to-treat (ITT) population included all patients who were randomized and received at least 1 dose of study drug. For the ITT efficacy analysis, outcomes for patients who were lost to follow-up and therefore were unevaluable were recorded as treatment failures (worst-case scenario).

Fever clearance times were calculated as the time from initiation of treatment until the patient's temperature decreased to ≤37.5°C and remained at ≤37.5°C for at least 24 h (calculation incorporated the recorded daytimes). Correspondingly, parasite clearance times were calculated as the time from initiation of treatment until the first negative blood smear. For comparisons of adverse events, the denominator included all patients at risk (i.e., those who received at least 1 dose of study drug). Adverse event rates (percentages of patients experiencing an adverse event) were calculated for each adverse event. The primary comparison, between the day 28 cure rate (percentage) in the atovaquone/proguanil group and that in the amodiaquine group, was made using Fisher's exact test. The 95% CI of the difference was calculated. Differences in mean changes in laboratory values between admission and last study day were compared across both treatment groups using the paired Student's *t* test. No adjustments for multiple comparisons were made, and no other statistical comparisons were made.

RESULTS

Efficacy. Both groups had similar baseline characteristics, which are summarized in table 1. The mean total doses of atovaquone and proguanil were 48.3 and 19.3 mg/kg, respectively, for patients who received 2 tablets (weight range, ≥5 and <9 kg) and 53.7 and 21.5 mg/kg, respectively, for patients who received 3 tablets (weight range, ≥9 and <11 kg). The

Table 1. Demographic, clinical, and laboratory characteristics at baseline of patients receiving treatment for *Plasmodium falciparum* malaria.

Variable	Atovaquone/proguanil group (n = 100)	Amodiaquine group (n = 100)
Patient characteristic		
Sex, no. of male patients/ no. of female patients	55/45	55/45
Age, years	1.4 ± 0.7	1.5 ± 0.8
Weight, kg	9.4 ± 1.4	9.5 ± 1.3
Temperature, °C	38.6 ± 1.1	38.5 ± 1.3
Parasite density, geometric mean parasites/μL (range)	21,200 (1600–200,000)	22,100 (1100–190,200)
Hematologic findings		
Hemoglobin concentration, g/dL	8.9 ± 1.6	8.8 ± 1.7
Hematocrit, %	29.6 ± 4.9	29.3 ± 5.1
WBC count, cells × 10^3/μL	8.9 ± 3.6	9.4 ± 3.2
Platelet count, platelets × 10^3/μL	195 ± 92	202 ± 99
Biochemical findings		
Alanine aminotransferase level, IU/L	33 ± 34.6	41 ± 58
Glucose level, mmol/L	5.2 ± 1.4	5.3 ± 1.0
Sodium level, mmol/L	136 ± 5.8	137 ± 7.6
Potassium level, mmol/L	3.9 ± 0.7	4.0 ± 0.7
Urea level, mmol/L	2.8 ± 1.2	3.0 ± 1.3
Creatinine level, μmol/L	56 ± 14	56 ± 22
Total bilirubin level, μmol/L	19.2 ± 22	18 ± 15
Alkaline phosphatase level, IU/L	231 ± 84	246 ± 102
Albumin level, g/L	34 ± 3.8	34 ± 4.3

NOTE. Data are mean ± SD, unless otherwise indicated.

mean total dose of amodiaquine was 29.0 mg/kg for the ⩾5 and <9-kg cohort and 29.3 mg/kg for the ⩾9 and <11-kg cohort.

All patients received at least 1 dose of study drug and were therefore included in the ITT population (100 patients in the atovaquone/proguanil group and 100 in the amodiaquine group). The outcome on day 28 was evaluable for 92 children treated with atovaquone/proguanil, and these children were included in the PP population. Eight patients were excluded from the PP analysis, including 3 patients who were lost to follow-up, 1 patient who was excluded because of a protocol violation (this patient had all efficacy information recorded and was therefore included in the ITT analysis), 1 who withdrew because of severe concomitant disease, 2 patients who withdrew because of adverse events unrelated to treatment, and 1 who could not be evaluated for efficacy because the result of the blood smear on day 7 was not available. In the amodiaquine group, 78 patients had an evaluable outcome on day 28 and were included in the PP population. Twenty-two patients were excluded from the PP analysis, including 11 who were lost to follow-up, 2 who committed a protocol violation, 3 who withdrew as a result of serious adverse events, 3 who were noncompliant with treatment (repeated vomiting of study medication), 1 whose parents withdrew consent, and 2 for whom no day 7 or day 28 smear was available and who were therefore unevaluable. The rate of losses to follow-up was significantly higher in the amodiaquine group than in the atovaquone/proguanil group (11 of 100 patients vs. 3 of 100 patients; $P = .024$, by Fisher's exact test).

Efficacy results for treatment with atovaquone/proguanil and amodiaquine for all evaluable patients are shown in table 2 (PP analysis). The combination of atovaquone with proguanil led to a cure rate on day 28 of 95% (87 of 92 patients), compared with 53% (41 of 78 patients) in the amodiaquine group. The point estimate for the difference in cure rates between both groups was 42% (95% CI, 30%–54%; $P < .0001$). ETF occurred in 1 patient treated with atovaquone/proguanil (patient had a parasite density on day 2 that was greater than that on day 0), 1 patient withdrew because of a drug-related adverse event (repeated vomiting), and 3 patients had LTF. ETF occurred in 3 patients in the amodiaquine group (2 patients with parasite density on day 2 that was greater than that on day 0 and 1 patient with parasite density on day 3 that was >25% of that on day 0), and 34 patients had LTF (PP analysis). The day 28 cure rate for the ITT population was 87% for the atovaquone/proguanil group, compared with 42% for the amodiaquine group (difference of 45%; 95% CI, 33%–57%; $P < .0001$).

Treatment outcome was not affected by the atovaquone/proguanil dosing regimen used; there was no discernible difference between weight categories in the number of treatment failures (data not shown). The median parasite clearance time was only slightly shorter in the amodiaquine group (70 h; interquartile range, 24 h) than in the atovaquone/proguanil group (72 h; interquartile range, 10 h). In addition, the median times to defervescence did not differ between the treatment regimens (46 vs. 47 h).

In addition, no differences in rates of improvement of malaria-associated symptoms were seen between the treatment regimens (data not shown). The results for hemoglobin concentration and hematocrit suggest that use of atovaquone/proguanil resulted in a superior hematologic response, in terms of changes in hemoglobin concentration from baseline to the last study day, compared with use of amodiaquine (1.3 vs. 0.6 g/dL; table 3). Table 3 also summarizes changes in clinical chemistry findings from baseline to study end.

Despite a potential adverse pharmacologic interaction between atovaquone/proguanil and metoclopramide, these drugs were coadministered in 2 patients; however, this did not appear to affect the efficacy of the atovaquone/proguanil combination (both patients had average parasite clearance times and remained free of parasites up to day 28).

Tolerability. Both treatment regimens were well tolerated. In the group that received atovaquone/proguanil, 48 patients reported ⩾1 adverse event, compared with 43 patients in the group that received amodiaquine (table 4). Most adverse events were mild to moderate in intensity. There was no difference in adverse event rates between the treatment regimens. Overall, the most frequent adverse events in both treatment arms were

Table 2. Efficacy of atovaquone/proguanil versus amodiaquine for treatment of *Plasmodium falciparum* malaria in infants and children in Gabon.

	Intent-to-treat population				Per protocol population			
Variable	Atovaquone/proguanil group ($n = 100$)	Amodiaquine group ($n = 100$)	Difference (95% CI)	P	Atovaquone/proguanil group ($n = 92$)	Amodiaquine group ($n = 78$)	Difference (95% CI)	P
Cure, no. (%) of patients	87 (87)	42 (42)	45 (33–57)	<.0001	87 (95)	41 (53)	42 (30–54)	<.0001
Treatment failure, no. of patients	13	58	…	…	5	37	…	…
PCT, median h (IQR)	…	…	…	…	72 (10)	70 (24)	…	.0002
FCT, median h (IQR)	…	…	…	…	47 (48)	46 (43)	…	.85

NOTE. FCT, fever clearance time; IQR, interquartile range; PCT, parasite clearance time.

Table 3. Mean changes in laboratory values between admission and last study day (day 28 or day of withdrawal) among infants and children receiving treatment for *Plasmodium falciparum* malaria.

	Atovaquone/proguanil group		Amodiaquine group	
Laboratory value	Mean difference	No. of patients evaluated	Mean difference	No. of patients evaluated
Hematologic				
Hemoglobin concentration, g/dL	1.3	85	0.6	71
Hematocrit, %	3.7	87	1.8	61
WBC count, cells $\times 10^3/\mu$L	0.1	83	0.2	59
Platelet count, platelets $\times 10^3/\mu$L	161	85	113	60
Biochemical				
Alanine aminotransferase level, IU/L	−13.8	81	−15.7	50
Glucose level, mmol/L	−0.5	81	−0.4	58
Sodium level, mmol/L	3.9	83	2.2	59
Potassium level, mmol/L	0.1	76	0.2	54
Urea level, mmol/L	−0.2	84	−0.7	60
Creatinine level, μmol/L	3.3	40	−0.11	28
Total bilirubin level, μmol/L	−16.6	17	−9.5	22
Alkaline phosphatase level, IU/L	21.0	86	13.3	62
Albumin level, g/L	3.5	85	2.2	62

diarrhea (experienced by 12% of patients in the atovaquone/proguanil group and 15% of patients in the amodiaquine group), coughing (14% and 13%, respectively), and vomiting (7% in each group). Four serious adverse events occurred during the study. In the amodiaquine group, 3 serious adverse events requiring hospitalization of the patients were reported (severe anemia on day 2, dystonia after concurrent administration of metoclopramide for repeated vomiting of study drug on day 1, and pneumonia on day 3). In the atovaquone/proguanil group, 1 patient suffered from convulsions on day 0 and was withdrawn from the study. The investigators judged all 4 severe adverse events to be unrelated to the study drugs.

DISCUSSION

The results of the present study demonstrate the high efficacy of an oral regimen of atovaquone and proguanil, with a cure rate of 95% among children weighing ⩾5 and <11 kg (PP analysis). This response rate is consistent with the results of previous studies that involved older patients [1–3, 7]. In addition, the combination of atovaquone and proguanil resulted in a favorable hematologic response. The case of ETF in the atovaquone/proguanil group was exclusively defined by parasitologic criteria, and treatment was considered to have failed because of a parasite count on day 2 that was greater than that on day 0. Because we could not find and treat this child at home soon after this laboratory result became available (on day 2), we did not see this patient until the next scheduled study visit (on day 3), at which point the results of the blood smear were negative even though no additional treatment had been administered.

The combination of atovaquone with proguanil was well tolerated, and there were no differences in the incidence of adverse events in the 2 groups. In contrast to reports published elsewhere [3, 7], vomiting after administration of atovaquone/proguanil occurred at the same low frequency as after administration of amodiaquine in the study population we describe (7% of patients in each cohort).

There was a higher rate of dropouts in the amodiaquine

Table 4. Most commonly reported adverse events (those occurring in ⩾4% of study patients) between initiation of therapy and day 7, among patients receiving treatment for *Plasmodium falciparum* malaria.

	Treatment group, no. (%) of patients	
Adverse event	Atovaquone/proguanil (n = 100)	Amodiaquine (n = 100)
None	48 (48)	43 (43)
Cough	14 (14)	13 (13)
Diarrhea	12 (12)	15 (15)
Vomiting	7 (7)	7 (7)
Common cold	1 (1)	4 (4)
Weakness	1 (1)	4 (4)
Respiratory tract infection	4 (4)	0
Upper respiratory tract infection	2 (2)	2 (2)

group than in the atovaquone/proguanil group; this could have contributed to either an underestimation (both PP and ITT analyses) or an overestimation (only PP analysis) of the day 28 cure rate in the amodiaquine group. The possibility that the parents of the patients sought treatment elsewhere because the children were not responding to the study drug cannot be discounted completely but is nevertheless highly unlikely. The Albert Schweitzer Hospital has an excellent reputation in a study area with only limited alternative treatment options, and patients therefore are likely to return for additional treatment (S.B. and B.L., personal observation). Consequently, the high number of losses to follow-up in the amodiaquine group should not have led to an overestimation of the cure rate, and it is more plausible that an underestimation of the cure rate occurred (especially in the ITT analysis). Taken as a whole, the higher dropout rate in the amodiaquine group might have been a chance finding or the result of factors not related to the allocation to different study medications.

The lack of genotyping might have resulted in an underestimation of the cure rate for amodiaquine because of a failure to classify reemergent parasitemia as a new infection and the lack of comparability with the atovaquone/proguanil group (prolonged inhibition of parasite growth has been demonstrated in vitro [13]). However, we have several reasons to trust our results, most importantly, the fact that the estimated average infection rate in the study area is 1 case per person per year [14], which translates into ~1 infection among 25 patients at risk for 2 weeks or the misclassification of at most 3–4 reappearant cases of parasitemia as treatment failures when, in fact, they were reinfections.

Treatment with amodiaquine led to a cure rate of 53%, which is well below the recommended threshold of 75% for an effective antimalarial drug [15] and is lower than the cure rate reported in studies conducted in the same area that involved pediatric and adult patients [3, 16]. Several factors may account for the low amodiaquine efficacy that we observed: (1) a number of the LTFs associated with amodiaquine could, in fact, be reinfections, as discussed earlier and as was the case in a pediatric treatment study at the same study site, in which 7 of 30 amodiaquine failures were shown by PCR to be reinfections rather than recrudescences [16]; (2) parasite resistance to amodiaquine may be increasing; (3) acquired immunity may not yet be sufficiently developed in our very young study population [17]. The low cure rate associated with amodiaquine calls for a reassessment of the value of amodiaquine in other areas where results from trials in older populations might be misleading. If our finding is substantiated in other trials, this will further limit the choices of effective antimalarial drugs for use in Central African countries.

In summary, our study results indicate that the combination of atovaquone and proguanil could be a promising candidate for the treatment of uncomplicated falciparum malaria in infants. Nevertheless, unease about the long-term efficacy of this combination continues [18], and the extent and scope of a recently introduced preferential pricing policy is uncertain. Both issues need to be resolved before this currently prohibitively expensive antimalarial drug can find a place in national malaria-control programs on the African continent.

Acknowledgments

We are particularly indebted to the participating children and their parents. We thank Erika Deboever for her assistance with the manuscript. We thank Marcel Nkeyi and Anselme Ndzengue for their help with patient recruitment. We also acknowledge the support of the former Swissair for transport of study material.

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