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Atovaquone and Proguanil for the Treatment of Malaria in Brazil

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The purpose of this study was to compare an experimental regimen of atovaquone plus proguanil with the standard regimen of quinine plus tetracycline for the treatment of uncomplicated falciparum malaria. The study was designed as an open, randomized study of men presenting with symptoms of uncomplicated malaria and thick-smear slide confirmation of parasitemia (1000–100,000 ring forms/µL). Subjects were hospitalized for 28 days to insure medication compliance and to rule out the possibility of reinfections. With 77 patients in each group, the cure rates were 98.7% and 100% for atovaquone plus proguanil and quinine plus tetracycline, respectively. The parasite clearance times (mean, 56 h) and fever clearance times (mean, 19 h) were significantly shorter in the atovaquone plus proguanil group, and there were significantly fewer side effects in the atovaquone plus proguanil group. Atovaquone plus proguanil is an efficacious, easily administered, safe regimen for the treatment of uncomplicated, multidrug-resistant falciparum malaria in Brazil.

Multidrug-resistant falciparum malaria continues to be a major public health problem in developing countries, requiring new treatment regimens nearly every decade. The problem is especially severe in Brazil, which has experienced a 3-fold rise in malaria during the past decade, to nearly 600,000 infections annually, approximately half of which are falciparum [1]. Nearly all of the malaria is confined to the Amazon region, in which migrant populations, great distances, and poor access to diagnosis and treatment are major obstacles to malaria control. Presumptive treatment without diagnosis has led to overuse of antimalarials and is probably a significant factor in the generation of parasite resistance. Migrant populations can rapidly disseminate resistant strains throughout the region. During the past decades, parasite drug resistance to chloroquine, pyrimethamine-sulfadoxine, and to some extent, quinine [2] has developed at an alarming rate. Currently, the recommended regimens for uncomplicated falciparum malaria in order of priority are quinine plus tetracycline for 7 days, quinine alone for 10 days, and a single dose of mefloquine [3]. The first two regimens have problems with poor compliance and many side effects. Half the patients do not comply for >3 days (de Alencar FEC, unpublished data). Mefloquine is expensive, and because of its long half-life, resistance may develop rapidly through reinfections in malaria-endemic areas.

As in other areas of the world faced with multidrug resistance, the options for alternatives are few and problematic. Increasing the dose of existing regimens may lead to toxicity and only delay the development of resistance. Combining different regimens raises the cost and the chance of side effects and leads to poor compliance. The development of new drugs is costly and slow (relative to the development of parasite resistance), and there is always the possibility of cross-resistance to existing drugs with similar chemical structures. New drugs, widely used in Southeast Asia, are the artemisinin compounds. These are also available in Brazil, where they are...
indicated only for the treatment of severe malaria because of their rapid clinical and parasitologic effects [3]. When used alone for the treatment of uncomplicated malaria, these compounds produce high recrudescence rates [4]. Another promising new drug, atovaquone, has shown few side effects, high efficacy, easy compliance, and little cross-resistance in preliminary studies [5].

Atovaquone is a hydroxynaphthoquinone with a structure different from that of other antimalarials, and it has shown good activity in vitro and in animals [6] against a wide variety of pathogens (Toxoplasma gondii, Pneumocystis carinii, and Plasmodium species) [7–9]. The drug’s rapid absorption and relatively long half-life (70 h) are ideal for rapid clinical response and a reasonable schedule of administration for falciparum malaria [6]. Clinical studies against toxoplasmosis and P. carinii pneumonia have shown little toxicity with relatively high, prolonged doses [7, 10]. Despite these advantages, early clinical trials against falciparum malaria showed high recrudescence rates [11]. On the basis of a synergistic effect against Plasmodium falciparum in vitro [12] and a long history of safe use, proguanil was added to the atovaquone regimen. Since this combination showed high cure rates in Southeast Asia [5] and because in vitro data suggest that 90% of Brazilian isolates are sensitive to proguanil (S. Di Santi, personal communication), we felt that this combined regimen had promise. The purpose of our study was to see whether atovaquone plus proguanil would be effective against the multidrug-resistant strain of P. falciparum in Brazil.

Materials and Methods

Study population. The study was conducted in Peixoto de Azevedo (population ~40,000), a town in the southern Brazilian Amazon. Peixoto has one of the highest malaria transmission rates in Brazil, ~300 cases/week (half vivax and half falciparum). The principal occupations in Peixoto are gold mining, logging, and farming. Adult men (ages 18–65 years) in general good health presenting with smear-confirmed falciparum malaria at the Fundação Nacional de Saúde (National Health Foundation) posts were asked to participate in the study.

Study design. Patients were admitted to the research ward (a malaria-free area) of the local hospital for 28 days. Upon admission, slides were repeated to confirm the entry criteria of 1000–100,000 ring forms/μL, patient histories were obtained, and physical examinations were done. Specimens were obtained for baseline laboratory examination (complete blood cell counts and differentials, determination of values for serum creatinine, urea, liver enzymes, bilirubin, albumin, and glucose, and evaluation of urinary sediment) and culture of parasites. Patients were removed from study for grossly abnormal admission laboratory results, refusal to stay hospitalized for 28 days, or intolerance to or missing doses of study medication.

Patients were consecutively assigned to one of two study regimens: atovaquone plus proguanil or quinine plus tetracycline. The sequences of individual doses were prepared and randomized by Wellcome Diagnostics (Research Triangle Park, NC). All drugs were administered under supervision of the study staff. Blood for determining serum drug levels was drawn at 8 and 96 h after the first dose. Patients’ temperatures and pulses were checked at 4-h intervals during the first week of admission.

The patients were examined daily for the first week and weekly thereafter. At each examination, signs and symptoms were checked by a standard questionnaire. If any complaint was present, it was checked daily until it disappeared or the patient was discharged. Blood for slides was obtained at 6-h intervals for thick-smear parasite counts, until three consecutive slides were negative; counts were then repeated on days 7, 14, 21, and 28. Blood for cell counts and serum chemistries were drawn on days 3, 7, 14, and 28 after admission. If a patient developed vivax malaria during hospitalization, a suppressive dose of chloroquine (450 mg) was given, followed by a complete treatment at discharge. Resistant cases were treated with mefloquine (1000 mg, single dose).

Parasitemia was determined by examining Giemsa-stained thick smears to count parasites per 200 leukocytes, then adjusting the level of parasitemia according to the patient’s leucocyte count. The level of resistance (levels RII–RIII) was defined according to the WHO criteria for 4-aminoquinolines: RIII, parasite count >25% of the initial parasite count 48 h after initiation of therapy; RII, parasite count <25% of the initial count at 48 h and parasitemia on day 7; RI, clearance of parasitemia by day 7 but recurrence before or on day 28.

Drugs and regimens. Atovaquone (1 g) and proguanil (400 mg) were given together for 3 days as single daily doses 15–30 min after a small amount of fatty food. Quinine (600 mg three times a day) and tetracycline (250 mg four times a day) were given concurrently for 7 days.

Adverse effects. We considered as possible side effects any sign or symptom not present or worse after admission that was not related to malaria and that had onset close to the time of drug administration (~1 week after the last dose).

Statistical analysis. Baseline data were examined to assess the comparability of the 2 study groups. Outcome parameters (fever clearance times, parasite clearance times, cure rates) and side effects were compared between groups. Statistical tests (χ², analysis of variance, nonparametric tests of means, and confidence intervals) were done with Epi Info (version 6.0, USD, Stone Mountain, GA).

Results

From April 1995 to January 1996, 175 patients were entered into the study. Of them, 21 were withdrawn because of the following reasons: 6 left the ward before day 28, 1 failed to take the study drug for 24 h, 9 were treated with a complete regimen of chloroquine and primaquine before we decided to use suppressive chloroquine doses, 2 were mistakenly diagnosed with falciparum rather than vivax malaria, 1 had mixed falciparum and vivax infection, 1 had concomitant cutaneous leishmaniasis, and 1 had a hemolytic syndrome. Thus, there was a total of 154 patients for analysis (77 using atovaquone plus proguanil; 77 using quinine plus tetracycline). Both groups were comparable regarding baseline parameters (mean ± SE) for age (30.2 ± 1.1 vs. 28.2 ± 1.2 years), episodes of falcipa-
rum malaria in the previous 2 years (11.9 ± 1.7 vs. 16.1 ± 3.9), time living in malarious area (10.7 ± 0.9 vs. 9.5 ± 0.8 years), percentage with fever on admission (81.8% vs. 72.7%), proportion with splenomegaly (77/77 vs. 74/77), degree of splenomegaly (4.1 ± 0.2 vs. 3.9 ± 0.2 cm), days ill prior to admission (4.7 ± 0.5 vs. 4.1 ± 0.4), and initial parasite count (12,059 ± 1696 vs. 9589 ± 1357 parasites/mm³) for atovaquone plus proguanil and quinine plus tetracycline groups, respectively (P > .05 for all).

Similarly, both study groups were comparable for admission laboratory values (mean ± SE) except for higher mean alanine aminotransferase levels in the quinine plus tetracycline group (P = .03), with 3 atovaquone plus proguanil and 6 quinine plus tetracycline subjects having levels above the upper normal limits. Blood laboratory values for the atovaquone plus proguanil and quinine plus tetracycline groups, respectively, were as follows: hematocrit, 38.6% ± 0.5% versus 39.8% ± 0.6%; leukocyte count, 3745 ± 170/mm³ versus 4068 ± 158/mm³; total bilirubin, 0.9 ± 0.1 versus 1.0 ± 0.1; creatinine, 1.1 ± 0.06 versus 1.2 ± 0.06; urea, 34.4 ± 1.3 versus 33.6 ± 1.4; glucose, 99.8 ± 2.3 versus 99.3 ± 2.4; aspartate aminotransferase, 20.2 ± 1.1 versus 24.2 ± 2.9; alanine aminotransferase, 17.4 ± 1.1 versus 24.4 ± 3.5.

All patients in the quinine plus tetracycline group were cured, and 1 patient had recrudescence in the atovaquone plus proguanil group (RI, positive on day 21), giving a cure rate of 100% (confidence interval [CI] = 95%–100%) for the quinine plus tetracycline group and 98.7% (CI = 92%–99%) for the atovaquone plus proguanil group. When we exclude all subjects who developed and were treated (complete or incomplete regimen) for vivax malaria prior to day 28, 72 of the 73 subjects (98.6%, CI = 92.6%–100%) in the atovaquone plus proguanil group and 69 subjects (100%, CI = 94.8%–100%) in the quinine plus tetracycline group were cured. The mean parasite clearance times (mean ± SD) were shorter in the atovaquone plus proguanil group (56.1 ± 14.1 h) than in the quinine plus tetracycline group (64.5 ± 23.1 h; P = .008), as were the fever clearance times for the 63 atovaquone plus proguanil subjects (18.8 ± 17.7 h) and the 56 quinine plus tetracycline subjects (28.5 ± 19.8 h) who were admitted with fever (P = .05).

Forty-eight patients (62.3%) had side effects in the atovaquone plus proguanil group, compared with 69 (89.6%) in the quinine plus tetracycline group. The most common side effects observed were tinnitus, dizziness, abdominal pain, nausea, weakness, headache, diarrhea, anorexia, pruritus, and vomiting. There were more patients complaining about tinnitus (55 vs. 3; P < 0.01), dizziness (39 vs. 10; P < 0.01), nausea (22 vs. 12; P = 0.05), and anorexia (13 vs. 5, P = .04) in the quinine plus tetracycline group than in the atovaquone plus proguanil group (table 1). No subjects with normal admission values developed abnormal laboratory values during treatment, except for elevated eosinophilia, which we attributed to intestinal parasites.

Table 1. Number of patients receiving atovaquone plus proguanil (n = 77) or quinine plus tetracycline (n = 77) who had adverse side effects.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Atovaquone + proguanil</th>
<th>Quinine + tetracycline</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus</td>
<td>3</td>
<td>55</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>39</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>20</td>
<td>18</td>
<td>.71</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>22</td>
<td>.05</td>
</tr>
<tr>
<td>Weakness</td>
<td>9</td>
<td>15</td>
<td>.08</td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
<td>9</td>
<td>.08</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>9</td>
<td>.26</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5</td>
<td>13</td>
<td>.04</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6</td>
<td>4</td>
<td>.51</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>5</td>
<td>.73</td>
</tr>
<tr>
<td>Without any side effect</td>
<td>29 (37.6)</td>
<td>8 (10.4)</td>
<td></td>
</tr>
</tbody>
</table>

* By χ² analysis.

Discussion

Early diagnosis and effective treatment are the cornerstones of malaria control in the Amazon, where vector control is extremely difficult. The rapid development of parasite drug resistance has been and will continue to be a serious obstacle to control in this region. The task is even more difficult because not only must new efficacious therapies be discovered, but the regimens must also be easy to use and have few side effects since poor compliance will lead to the rapid development of resistance to the drugs. We have shown that our atovaquone plus proguanil study regimen fulfills all these criteria of high efficacy, easy administration, and few side effects. Furthermore, the relatively short half-life minimizes the possibility of developing resistance via reinfections occurring when posttherapeutic drug levels are low.

Regarding new treatments for falciparum malaria, the alternatives are few. Mefloquine, once considered an ideal alternative because of the ease of administration and the few side effects, has achieved indices of 50% resistance in some areas of Thailand [13]. Perhaps this is due to its cross-resistance with quinine, which was used for long periods prior to the introduction of mefloquine, or its long half-life in areas with high reinfection rates. Brazilian patients are poorly compliant with quinine and tetracycline regimens because of long, frequent dosing schedules and frequent side effects. This leads to poor effectiveness, which further exacerbates poor compliance. One of the newer options is the combination of artemisinin derivatives and slow-acting schizonticides [14], but this is not yet a well-established alternative.

Regarding the high efficacy rates of atovaquone plus proguanil, our results agree with what has been shown in other areas of the world [15]. Although the semi-immune status of our subjects may have contributed to their good clinical and parasitologic response to both drugs, the high cure rate, shorter fever
and parasite clearance times, and lower rates of side effects would make atovaquone plus proguanil the preferred regimen in this region of the world, should the cost be reasonable.

References


