COMPARATIVE CLINICAL TRIAL OF ARTESUNATE SUPPOSITORIES AND ORAL ARTESUNATE IN COMBINATION WITH MEFLOQUINE IN THE TREATMENT OF CHILDREN WITH ACUTE FALCIPARUM MALARIA

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Abstract. A randomized pilot study to compare the safety and efficacy of artesunate suppositories (15 mg/kg/day for three days) versus oral artesunate (6 mg/kg/day for three days), both in combination with mefloquine (25 mg/kg), was conducted in 52 Thai children with uncomplicated multidrug-resistant falciparum malaria. Forty-five patients (87%) had a full 28-day follow-up in the hospital to assess efficacy and exclude reinfection. Mean [range] times to fever clearance of the two groups were similar (42 hr [15–104] versus 42 hr [6–119]). Artesunate suppositories resulted in significantly longer times to achieve 50% and 90% reductions of the initial parasite counts (17 and 26 hr versus 9 and 15 hr; P < 0.05 and P < 0.001). Time [range] to parasite clearance was longer in the artesunate suppositories group (42 hr [14–93] versus 35 hr [16–69]), but the difference was not significant. The cure rates by days 28 were not significantly different, 92% for artesunate suppository-treated patients and 100% for oral artesunate-treated patients. Both drug regimens are safe and effective. Further studies are needed to characterize the pharmacokinetic properties and the optimum regimen of artesunate suppositories for the treatment of severe malaria.

Increasing antimalarial drug resistance of Plasmodium falciparum poses a major threat in Thailand.1 Use of a regimen of quinine for seven days in 1982 yielded cure rates of only 75%.2 In 1982–1985, an eight-day course of modified, high-dose quinine in the well-supervised treatment of acute uncomplicated falciparum malaria in children improved the cure rate to 85%.3 The cure rate decreased again to 75% in 1996 (Sabchareon A and others, unpublished data). Long-supervised regimens of antimalarials are impractical in the rural tropics and compliance is poor for drug regimens lasting for more than three days.4 A high-dose (25 mg of base/kg) mefloquine regimen yielded cure rates of 98% in 1985–1986,5 but cure rates decreased to 73% in 19906 and to 51% in 1995.7 Thus, mefloquine alone is currently not reliable for the treatment of multidrug-resistant falciparum malaria on the Thai-Myanmar border.7

Artemisinin and its derivatives are the most rapidly acting of all antimalarial drugs. The compounds are active by parenteral, oral, or rectal routes of administration. The artemisinins have proved to be particularly effective treatments for severe malaria, and also for multidrug-resistant falciparum malaria and there has been no major clinical toxicity reported in humans.8 However, when the artemisinins are given alone, recrudescence rates vary from 10% to 100%, depending upon the dose and duration of treatment.9 Recent studies in Thailand showed that oral artesunate, 10–12 mg/kg over three days, plus mefloquine, 25 mg/kg, yielded 28-day cure rates of 96–98%.7,10 and the use of oral artesunate, 4 mg/kg every 12 hr for four doses, followed by mefloquine, 25 mg/kg, yielded cure rates of 100%.11 These studies, however, have been conducted with dose regimens that in the absence of pharmacokinetic information, have been largely empirical.

Artemisinin suppositories represent an advance in the prevention and treatment of severe falciparum malaria, especially in areas where injections can not be given. They are particularly valuable in children.12–14 However, this formulation is available only in China and Viet Nam. In general, artemisinin, the parent compound, is five times less active than its derivatives.8 Artesunate suppositories (Mepha Pharmaceuticals Research, Aesch-Basel, Switzerland) have been recently developed that can be kept in the tropics long term without refrigeration. Stability testing by the manufacturer showed no degradation at 45°C at a relative humidity of 80% for 12 months (Mepha Stability Test Report, 1995, Mepha Pharmaceuticals Research). Suppositories are white, torpedo-shaped capsules with a volume of 0.616 ml, a length of 2.3 cm, and a maximum width of 0.8 cm. A firm, thermostable, outer shell covers the soft gelatin contents. A recent study showed that artesunate suppositories (total dose = 32 mg/kg) over a 60-hr period plus mefloquine, 25 mg/kg in adult patients with severe falciparum malaria yielded cure rates of 92%, and none of the patients had major adverse effects.15 However, there has been no detailed prospective evaluation of artesunate suppositories in children with malaria. Before testing artesunate suppositories in children with severe malaria, we conducted a randomized comparative trial of artesunate suppositories versus oral artesunate, both in combination with mefloquine in uncomplicated malaria in hospitalized children, to obtain safety, efficacy, and pharmacokinetic data that would allow development of rational therapeutic regimens.

Artesunate is hydrolyzed rapidly in vivo to its biologically active metabolite, dihydroartemisinin, which is eliminated more slowly than the parent compound.16 To find the safe and potentially effective dose of artesunate suppositories to be used in this study, we first measured plasma artesunate bioactivity equivalents of dihydroartemisinin in five children with uncomplicated falciparum malaria using a bioassay.17 Two patients received a single dose of artesunate suppositories, 20 mg/kg, and three others received a single dose of oral artesunate, 4–5 mg/kg. The artesunate suppository dose was derived from the parallel observation that at equal weight dosing, artemether suppositories produced approxi-
ultimately three- to four-fold lower plasma dihydroartemisinin and artemether concentrations than oral artemether. The oral dose was the once a day dose of artesunate reported to be safe and the most effective treatment for falciparum malaria in areas of multidrug resistance. Thus, our preliminary results showed that the time to peak level of bioactivity equivalents of dihydroartemisinin for the two artesunate suppository patients was 4 hr while that for the three oral artesunate patients was 0.5 hr (two patients) and 2 hr (one patient). The bioactivity levels for the artesunate suppository patients were slightly lower than for the oral artesunate patients. These data suggested that artesunate suppositories, 20 mg/day, were safe, and could be very effective for the treatment of multidrug-resistant falciparum malaria. Therefore, 20 mg/kg/day was the maximum suppository dose used in this study.

**Patients and Methods**

**Study sites and patients.** A randomized, open, comparative trial involving 52 children with acute uncomplicated falciparum malaria was conducted from May 1995 to August 1996. The subjects were recruited for the study from patients who were admitted to two hospitals in Thailand: the Thongphaphum Hospital, Kanchanaburi Province (34 subjects) and the Bangkok Hospital for Tropical Diseases, Bangkok (18 subjects). The patients were mainly from the western region near the Thai-Myanmar border. They remained in the corresponding hospital for at least 28 days to exclude reinfec tion. Their asexual parasite counts were between 1,000 and 200,000/µl. Subjects were between five and 12 years of age and weighed more than 10 kg. Urine samples from all the patients were negative for 4-aminoquinolines and sulfonamides. Reasons for exclusion were severe malaria, diarrhea, and other concomitant diseases. Parents of all the children gave written informed consent for participation in the study. The study was approved by the Ethical Committee of the Ministry of Public Health, Thailand.

All the patients were monitored closely during the acute stage of their illness. Vital signs were recorded every 4 hr throughout the study for those admitted to the Bangkok Hospital for Tropical Diseases. Vital signs were measured every 6 hr for the first week and then daily throughout the study for those admitted to the Thongphaphum Hospital. Clinical signs and symptoms of all the patients in both hospitals were evaluated daily for the first week and weekly thereafter.

**Laboratory studies.** Samples of blood were taken from each child and the following laboratory tests were performed: red blood cell count, hemoglobin, hematocrit, white blood cell count and differential count, platelet count, electrolytes, and total and direct bilirubin, albumin, globulin, alkaline phosphatase, aspartate and alanine aminotransferases, cholesterol, blood glucose, urea, and creatinine. Urine was tested for albumin, glucose, and bilirubin levels, as well as the presence of sediments. These tests were done before treatment and repeated on days seven, 14, 21, and 28. Asexual parasites were counted from Field’s stained thick and thin blood films before treatment (hour 0), at 6, 18, and 24 hr, then every 12 hr during parasitemia, and then daily for the remainder of the study. Parasite density was calculated from the red blood cell or white blood cell count and expressed as parasite per microliter. Blood films were considered negative if no parasites were seen in 200 oil-immersion fields in a thick blood film.

Blood samples were also taken from patients who received artesunate suppositories (nine patients) and oral artesunate (10 patients) for determination of plasma dihydroartemisinin and artemesin concentrations. The samples were taken before dosage (hr 0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 30, 36, 48, 54, 60, and 72 hr after starting drug administration. Plasma was separated from heparinized blood within 30 min after the sample was taken. Plasma was stored at −20°C. The plasma samples from Thongphaphum Hospital were transported on dry ice to Bangkok. Plasma dihydroartemisinin and plasma artesunate were quantified using high-performance liquid chromatography with electrochemical detection based on the method described previously at the Department of Immunology and Medicine, Armed Forces Research Institute of Medical Science, Bangkok.

**Treatment.** Patients were allocated at random in blocks of 10 to receive one of two treatments. The first group received whole artesunate suppositories (Plasmotrim® Rectocaps®, lot no. 94162, 200 mg/capsule; Mepha, Ltd., Aesch-Basel, Switzerland) and the second group received oral sodium artesunate (Plasmotrim® Lactab®, 200 mg/tablet; Mepha, Ltd., lot no. 92789, 250 mg/tablet; Mepha, Ltd.), 15 mg of base/kg and 10 mg of base/kg, 6 hr apart, on day 2 (or at 50 ± 30 ± 30 ± 30 mg/kg/day (Table 1) once a day for three days (or at 0, 24, and 48 hr) with two doses of mefloquine (Mephaquine®, lot no. 92789, 250 mg/tablet; Mepha, Ltd.), 15 mg of base/kg and 10 mg of base/kg, 6 hr apart, on day 2 (or at 48 and 54 hr) (MA-S group). The second group received oral sodium artesunate (Plasmotrim® Lactab®, 200 mg/tablet; Mepha, Ltd.) 6 (5–7) mg/kg/day (Table 2) once a day for three days with mefloquine on a schedule similar to that for the first group (MA-O group). The high-dose mefloquine (25 mg/kg) was divided into two doses to reduce the incidence of mefloquine-associated vomiting. The antimarial drugs were administered under direct supervision of a ward nurse. The artesunate suppositories were inserted beyond the anal verge, and each patient was remained in bed for at least 30 min after suppository administration. For patients who required more than one suppository, all (up to three per patient) were given at the same time.
The oral medications were given as intact tablets to older children or as crushed tablets in syrup to younger children. Drug administration was observed in all cases. If artesunate suppository–treated or oral artesunate–treated patients had expulsion or vomiting within 15 min after drug administration, a full dose of corresponding formulation of artesunate was repeated. Similarly, a full dose of mefloquine was repeated if patient vomited within 1 hr of taking this drug.

Outcome measures. The response to treatment was characterized according to the World Health Organization system:22 patients were considered cured if no recrudescence occurred during a 28-day follow-up observation period. Parasite clearance time was taken as the time from the initiation of treatment until the first time a slide was negative. Parasite reduction times to 50% and 10% of the initial count were calculated. Fever clearance time was the time from the initiation of treatment until the oral temperature decreased to less than 37.5°C and remained below this threshold for at least 24 hr. The safety of the drug regimens was assessed by serial clinical observations, blood tests, and urinalysis. Adverse experiences were defined as any clinical finding that first occurred, or increased in severity, during treatment or within seven days after initiation of treatment.

Statistical analysis. Comparison of groups with normally distributed data was performed by analysis of variance or Student’s t-test. Parasite counts were compared after logarithmic transformation. Data that did not have a normal distribution were compared by the Wilcoxon or Mann-Whitney nonparametric tests. Proportions were compared by the chi-square test with Yates’ correction or Fisher’s exact test.

RESULTS

There were 26 patients in both the MA-S group and the MA-O group. The two groups were comparable in terms of clinical features and laboratory indices on entry into the study (Table 3). All patients had clinical improvement within 24 hr following initiation of treatment. However, two in the MA-S group and five in the MA-O group withdrew later from the study (range = 4–14 days, mean = 0 days) for reasons unrelated to their drug treatment or side effects. All of these patients were well and had no detectable malaria parasites in their blood when they left the hospital. Their fever and parasite clearance times were more or less similar to the rest of the patients. A total of 45 patients (87%) remained in hospital for a full 28-day follow-up. Only patients who were followed for 28 days were included in assessment of drug efficacy.22

Clinical and parasitologic responses. The responses are shown in Table 4. Artesunate suppositories gave a considerably slower early parasitologic response than oral artesunate, i.e., the parasite counts decreased more slowly than in the MA-O group (Figure 1). Eleven MA-S patients (42%) and nine MA-O patients (35%) had an early increase in parasite count (per μl) on entry into the study (range = 4–14 days, mean = 0 days) for admission (days)

PCV (%),‡

Parasite count (per μl)

Geometric mean

Range

Disease type

No. (%) with an RI response

No. (%) cured at 28 days†

Fever clearance time (hr)†

Parasite clearance time (hr)†

Mean (SD)

Range

Mean (SD) reduction time to 50% of initial parasitemia (hr)‡

Mean (SD) reduction time to 10% of initial parasitemia (hr)§

** Treatment groups are defined in Table 3.
† P > 0.05, MA-S vs. MA-O.
‡ P < 0.05.
§ P < 0.001.

<table>
<thead>
<tr>
<th>Treatment group*</th>
<th>MA-S (n = 26)</th>
<th>MA-O (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with 28-day follow-up</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>No. (%) cured at 28 days†</td>
<td>22 (92%)</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>No. (%) with an RI response</td>
<td>2 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Recrudescence on days</td>
<td>20,21</td>
<td>0</td>
</tr>
<tr>
<td>Fever clearance time (hr)†</td>
<td>42.5 (24.5)</td>
<td>42.1 (31.2)</td>
</tr>
<tr>
<td>Range</td>
<td>15–104</td>
<td>6–119</td>
</tr>
<tr>
<td>Parasite clearance time (hr)†</td>
<td>42.2 (20.6)</td>
<td>35.2 (19.8)</td>
</tr>
<tr>
<td>Range</td>
<td>14–93</td>
<td>16–69</td>
</tr>
<tr>
<td>Mean (SD) reduction time to 50% of initial parasitemia (hr)‡</td>
<td>16.8 (11.7)</td>
<td>8.9 (4.2)</td>
</tr>
<tr>
<td>Mean (SD) reduction time to 10% of initial parasitemia (hr)§</td>
<td>26.2 (14.7)</td>
<td>14.6 (5.2)</td>
</tr>
</tbody>
</table>

FIGURE 1. Parasite clearance: percentage of initial parasitemia in the treatment groups. MA-S = three days of artesunate suppositories, 15 mg/kg/day, plus mefloquine, 25 mg/kg; MA-O = three days of oral artesunate, 6 mg/kg/day, plus mefloquine, 25 mg/kg.

Table 4

Response to treatments of malaria patients

Table 3

Clinical and laboratory features before treatment*
asitemia in the first 6 hr. Three MA-S patients had parasite counts that remained greater than their initial counts until 36 hr. Five MA-S patients (19%) had fluctuating counts for 36 hr (Figure 2), and two of them failed subsequently, recrudescing on days 20 and 21, respectively. In contrast, none of the MA-O patients had fluctuating parasitemia after treatment. All had sharp decreases in parasitemia, and their counts were lower than initial counts at 18 hr and thereafter. By 18 hr, the mean proportion decreases in parasitemia were 60% (SE = 15.9%) for the MA-S group and 98% (SE = 1.5%) for the MA-O group (P < 0.05). By 48 and 72 hr, 65% and 99% of the 52 patients, respectively, were afebrile.

The cure rates were 92% (22 of 24 patients) and 100% (21 of 21 patients), respectively, for the MA-S group and the MA-O group, but there was no significant difference in the cure rates between the two treatment groups. Both of the MA-S failures had body weights of 25 kg and received two artesunate suppositories per day or 16 mg/kg/day. Unfortunately, blood samples for drug concentrations were not obtained from these two patients. Times to 50% and 90% reduction of the initial parasite count for the MA-S patients (16.8 hr and 26.2 hr) and for the MA-O patients (8.6 hr and 14.6 hr) were significantly different (P < 0.05 and P < 0.001). The mean [range] parasite clearance time was slower (42 hr [14–93]) in the MA-S group than in the MA-O group (35 hr [16–60]). However, the difference was not significant.

There was no difference between the two drug regimens in clinical responses. By 48 hr, 61% of the 52 patients were afebrile. By 72 hr, the percentage of afebrile patients increased to 81%. The mean [range] of fever clearance time of the two groups was similar (42 hr [15–104] and 42 hr [6–119]), respectively. There were no significant correlations between fever and parasite clearance times.

**Adverse effects.** There were no major adverse effects during treatment and the 28-day follow-up period. Symptoms developing after treatment in the MA-S and MA-O groups, respectively, were abdominal pain in 12% and 0%, vomiting in 14% and 15%, diarrhea in 12% and 4%, and pruritus in 4% each. None of the patients in the two groups had mefloquine-associated vomiting. All episodes of vomiting occurred before mefloquine administration. The recorded symptoms in the two treatment groups were not significantly different. These symptoms usually occurred within the first two days of treatment and coincided with high fever. It was difficult to distinguish between symptoms of acute malaria and drug-related effects. None of the MA-S patients had spontaneous expulsion of the suppository. Biochemical and hematologic data of all the patients showed no change in white blood cell, differential, and platelet counts or in renal and liver function test results other than those expected with acute uncomplicated malaria.

**DISCUSSION**

Artemisinin and its derivatives have resolved the potentially dangerous problem of untreatable drug-resistant *P. falciparum* infections in Asian countries. Their rapidity of action against even highly multidrug-resistant strains of *P. falciparum*, and their lack of clinical toxicity have led to a considerable increase in their use in southeast Asia. However, recrudescence within 28 days after monotherapy may be up to 100%, depending upon dosage, duration of treatment, and severity of diseases. Therefore, these drugs are often combined with mefloquine to shorten the treatment course and to improve efficacy and compliance. Although mefloquine pharmacokinetics have been reportedly altered in uncomplicated malaria when the drug was administered after oral artesunate, differences were not large and the clinical significance of this finding remains to be determined.

The results of this study show that oral artesunate, 6 mg/kg/day once a day for three days, plus mefloquine, 25 mg/kg, is well tolerated and highly effective in the treatment of children with uncomplicated multidrug-resistant falciparum malaria, similar to a study reported recently. The combination regimen is currently the most effective treatment for acute uncomplicated falciparum malaria in areas of multidrug resistance in Thailand. However, the same drug regimen produced a cure rate of only 70% in hyperparasitemic patients, and a longer course of artesunate (i.e., 5–7 days) in combination with mefloquine is needed for patients with hyperparasitemia in areas of multidrug resistance.

Artesunate suppositories are a potentially effective treatment of severe forms of malaria and associated deaths in remote areas and may represent an important mechanism for reducing mortality in these areas where parenteral administration of antimalarials is either not possible or not safe. The present results show that a regimen of artesunate suppositories, 10–19 mg/kg once a day for three days, plus mefloquine, 25 mg/kg, is well tolerated, clears parasitemia rapidly, and is highly effective in treating children with uncomplicated multidrug-resistant malaria. The delayed RI type responses in two MA-S patients are likely to have been related to the sensitivity of the parasite to mefloquine. Both rectal and oral artesunate, in combination with mefloquine, restore the uncomplicated patient to health very rapidly and prevent early recrudescence of the infection. These findings have obvious practical relevance. Artesunate suppositories should be...
very useful in lowering parasitemia and preventing complications in patients with uncomplicated malaria who cannot tolerate oral medication and in situations where safe administration of parenteral antimalarials is not possible.

Pharmacokinetic parameter estimates for dihydroartesinisin and artesunate obtained from 19 patients in this study showed that the mean [standard deviation] and median [range] of maximum concentration (C_{max}) for dihydroartesinisin in the MA-S patients (2,382 [2,091] and 1,700 [245–5,730] nM) was significantly lower than in the MA-O patients (6,979 [4,981] and 6,755 [1,130–16,030] nM) (P < 0.05). The apparent half-life (t_{1/2}) for dihydroartesinisin in the MA-S patients (0.7 [0.5] and 0.5 [0.4–1.8] hr) was significantly shorter than in the MA-O patients (1.2 [0.81] and 0.9 [0.3–2.7] hr) (P < 0.05). The area under the curve from zero to 12 hr (AUC_{0–12}) for dihydroartesinisin in the MA-S patients (4,073 [3700] and 2,556 [207–8,686] nM.hr/L) was also significantly smaller than in the MA-O patients (13,523 [8,139] and 13,081 [2,413–27,079] nM.hr/L) (P < 0.01). The C_{max}, t_{1/2}, and AUC_{0–12} values for artesunate in the two treatment groups were not significantly different (Teja-Isavadharm P and others, unpublished data). The significantly longer times for parasitemia to decrease to 50% and 10% of the initial counts in the MA-S group reported here are most likely related to the lower dihydroartesinisin concentrations indicated by the lower C_{max}, the smaller AUC_{0–12}, and the shorter t_{1/2} for dihydroartesinisin.

The parasite clearance time was 7 hr longer in the MA-S group, but the difference did not reach statistical significance. This may be due to the small sample size. The lower concentration and faster clearance of dihydroartesinisin, coupled with the long dosing intervals (24 hr), in this study might lead to subtherapeutic drug levels, with significant parasite multiplication between doses and fluctuation of parasitemia in the first 36 hr in the five MA-S patients. The evidence suggests that the 24-hr dosing intervals of artesunate suppositories are adequate for children with uncomplicated falciparum malaria. Based on previous findings,24 and results of this study, a longer course with more frequent dosing intervals of artesunate suppositories may be needed for patients with hyperparasitemia or severe malaria in the areas of multidrug resistance. The successful treatment of severe malaria in adult patients using artesunate suppositories reported recently15 could also be due to the more frequent dosing intervals during the first and second 24 hr. However, further studies are needed to characterize the pharmacokinetic properties and to identify the optimum dosage, dosing intervals, and duration for a regimen of artesunate suppositories for the treatment of severe forms of malaria.

Drug administration to children in the field, where often only untrained personnel are available, requires simple and convenient methods. Since tablets could be divided accurately into portions of halves and quarters, we gave portion(s) of tablet(s) to children according to body weight (Table 2). At the time of study, oral artesunate produced by Mepha Ltd. (Aesch-Basel, Switzerland) was not observed in this study. Division of high-dose mefloquine (25 mg/kg) into two doses to prevent mefloquine-associated vomiting may be not necessary when use after a three-day regimen of artesunate.

When mefloquine was given (by 48 hr), 61% of the patients were already afebrile and the rest had mild symptoms. This probably explains why mefloquine-associated vomiting was not observed in this study. Division of high-dose mefloquine (25 mg/kg) into two doses to prevent mefloquine-associated vomiting may be not necessary when use after a three-day regimen of artesunate.

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