

## DESCRIPTIVE STUDY ON THE EFFICACY AND SAFETY OF ARTESUNATE SUPPOSITORY IN COMBINATION WITH OTHER ANTIMALARIALS IN THE TREATMENT OF SEVERE MALARIA IN SUDAN

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**Abstract.** Documentation on the efficacy of artesunate in Africa is limited, and no experience of artesunate use in Sudan is documented. Severe malaria in rural areas of Sudan, where facilities for the safe and effective use of parenteral quinine are lacking, is a frequent problem. Early treatment with artesunate suppositories would provide a simple method for use by unskilled staff and would be an alternative approach to treat malaria in settings with poor resources. We describe a hospital-based study of rectal artesunate in 100 adult patients with severe falciparum malaria with a dose derived from pharmacokinetic data (200 mg every 8 hours) over 3 days, which halted progression of severe disease and had a low fatality rate. The dosage schedule led to a rapid clinical response and reduced parasite clearance and fever subsidence times of ( $31.5 \pm 10.1$  hours) and ( $31.4 \pm 11.1$  hours). The sequential treatment of rectal artesunate with either doxycycline or pyrimethamine/sulfadoxine or mefloquine resulted in similar clinical cure rates of around 100%, and the combination of artesunate with either doxycycline or pyrimethamine/sulfadoxine was equally effective as mefloquine in preventing recrudescence. There were no significant adverse effects or signs of toxicity related to the treatment observed during the 28-day follow-up. The combination regimens could be used in areas where there is limited access to parenteral therapy for malaria.

### INTRODUCTION

The increase in malaria disease burden in Africa is of great concern nationally and internationally. An estimated 300–500 million new cases of malaria and an estimated 1.5–2.7 million deaths occur each year. The highest mortality (>90%) occurs in children <5 years old in Africa.<sup>1</sup> *Plasmodium falciparum* malaria is associated with severe morbidity and mortality, and in the absence of early diagnosis and effective treatment, it may be fatal.<sup>2</sup>

Resistance to most antimalarial therapies is well documented worldwide. Multidrug resistance is an increasing problem in Africa and poses a threat to the current management of malaria with inexpensive drugs such as chloroquine and pyrimethamine/sulfadoxine.<sup>3</sup> Drugs derived from artemisinin have been shown to be extremely effective against multidrug-resistant *P. falciparum* malaria and severe malaria.<sup>4</sup> Because their quantitative determination in biologic fluid is a challenging problem, different dosage regimens have been proposed that are largely empirical.<sup>5</sup> The selection of optimal dosage regimens requires precise information on the drug's pharmacokinetics.<sup>6</sup>

Artesunate is a semisynthetic derivative of artemisinin whose water solubility facilitates absorption<sup>7</sup> and provides an advantage over artemisinin because it can be formulated as oral, rectal, intramuscular, and intravenous preparations. Artesunate is rapidly hydrolyzed to dihydroartemisinin, which is the most active schizonticidal metabolite. Extravascular administration of artesunate results in a more rapid systemic availability of artesunate compared with intramuscular artemether. This pharmacokinetic advantage may provide a clinical advantage in the treatment of severe malaria.<sup>8</sup> Rectal artesunate has been shown to be absorbed rapidly, with a considerable interindividual variability.<sup>9,10</sup> Artesunate is highly effective against multidrug-resistant falciparum malaria and severe malaria in Vietnam, Thailand, China, and Myanmar<sup>7</sup>; however, limited studies have been carried out in Africa.

Suppositories of artesunate have been developed for rectal administration as an alternative to oral or parenteral therapy. Clinical studies of rectal administration of artesunate in the treatment of malaria have been undertaken in Thailand, Myanmar, Ecuador, Kenya, and Gabon.<sup>11–16</sup> Table 1 summarizes the doses used and the efficacy obtained in these studies. Suppositories are a major advance in the treatment of severe malaria, especially in rural settings, where resources are meager and the referral of cases is not possible. It is recommended that further studies be carried out for the quantification of the efficacy of artesunate suppositories in the treatment of severe malaria.<sup>17,18</sup>

In Sudan, there has been a rapid spread of chloroquine-resistant *P. falciparum* infections. Parenteral quinine is the main drug widely used in the management of severe malaria. It is available only in urban settings, where expertise and equipment are available. The use of artesunate rectocaps (Mepha Pharmaceutical Research, Aesch-Basel, Switzerland) in treatment of severe malaria may provide advantages.

Although artemisinin compounds are effective against multidrug resistance, when administered alone, these agents have led to recrudescence rates of 10–100%, depending on the dose and duration of treatment and severity of the disease.<sup>19</sup> Current recommendations are that artemisinin derivatives should be used only in combination with other antimalarials to reduce the development of resistant parasite strains. Mefloquine has been used widely in combination with artemisinin derivatives and has produced radical cure rates of >90%.<sup>11,12</sup> White and Olliaro<sup>20</sup> and White et al.<sup>3</sup> recommended that clinical studies are needed to assess the efficacy and safety of artemisinin compounds in combination with other antimalarial drugs.

The objectives of this study were to investigate the efficacy and safety of rectal artesunate in combination with 3 other antimalarials in the treatment of severe malaria and to determine recrudescence rates after treatment of adult Sudanese patients. The regimens evaluated were (1) artesunate suppositories for 3 days followed by doxycycline capsules for 4

TABLE 1  
Published results of clinical trials in the treatment of *P. falciparum* malaria by rectal artesunate

Country	No. of patients	Drug regimen	Type of <i>P. falciparum</i> malaria	Radical cure rate (%)	Recrudescence rate (%)	Mortality (%)	Reference
Thailand	30 adults	200 mg at 0,4,8,12,24,36, 48,60 h (1,600 mg) + MF 750 mg at 72 h, 500 mg at 84 h	Severe	92	8	0	Looareesuwan et al., 1995 <sup>11</sup>
Thailand	32 adults	200 mg at 0,4,8,12,36,48, 60 h (1,400 mg) + MF 750 mg at 72 h, 500 mg at 84 h	Severe	96	4	0	Looareesuwan et al., 1996 <sup>12</sup>
Thailand	31 adults	200 mg at 0,12,24,36, 48, 60 h (1,200 mg) + MF 750 mg at 72 h, 500 mg at 84 h	Severe	89	11	0	
Myanmar	13 adults	200 mg/12 h for 3 days, MF 750 mg on day 4 and 500 mg 12 h apart	Severe	92.3	7.7	0	Thwe Ye et al., 1996 <sup>13</sup>
Myanmar	18 adults	AS PR 200 mg/12 h on day 1, 200 mg on days 2 and 3, MF 750 mg on day 4 and 500 mg 12 h apart	Severe	77.8	22.2	0	
Ecuador	40 adults	200 mg/8 h on day 1, 200 mg/12 h on days 2 and 3, then MF 250 mg/8 h started on day 4	Severe	97.5	2.5	2.5	Eduardo and Gomez, 1996 <sup>14</sup>
Kenya	22 adults	200 mg at 0,4,8,12,18,24, 48,60 h, then MF TD 1,000 mg in 2 doses 8 h apart	Severe	86.4	0	13.6	Bhatt et al., 1996 <sup>15</sup>
Gabon	12 children	50 mg at 0 and 4 h followed by P/S SD at 20 h	Uncomplicated	No 28 days follow-up, no radical cure rate	–	–	Halpaap et al., 1998 <sup>16</sup>

Note. Radical cure rate (%): Clinical cure without recrudescence by day 28. MF, mefloquine; P/S, Pyrimethamine/sulfadoxine; SD, single dose; TD, total dose.

days, (2) artesunate suppositories for 3 days followed by single-dose pyrimethamine/sulfadoxine tablets, and (3) artesunate suppositories for 3 days followed by mefloquine tablets divided into 2 equal doses 24 hours apart.

## MATERIALS AND METHODS

**Patients.** The study was conducted at Omdurman Teaching Hospital and the Tropical Disease Hospital in Khartoum State. A total of 2,400 febrile patients were evaluated between January 2000 and January 2001. Patients with microscopically diagnosed *P. falciparum* malaria were considered for entry if they had clinical, biochemical, and parasitologic evidence of severe malaria based on the World Health Organization (WHO) criteria of severe diseases.<sup>2,21</sup>

The inclusion criteria for a patient to enter the study were evidence of severe malaria with  $\geq 1$  of the WHO criteria of severe disease, age 18–60 years, and parasitemia of  $>10,000$  parasites/ $\mu$ l with *P. falciparum* alone. The exclusion criteria included pregnancy, breast-feeding, hemorrhoids, previous rectal surgery, diarrhea for  $\geq 12$  hours, and recent treatment with an antimalarial over the previous 2 weeks. Patients who fulfilled the inclusion criteria were selected randomly during their presentation at the Accident and Emergency Department and sequentially entered into 1 of 3 groups. The Sudanese Ethical Committee (Federal Ministry of Health, National Health Laboratory) gave ethical approval for the study. A written consent was obtained from patients or relatives, as was appropriate.

**Clinical procedures.** A full clinical examination was undertaken by a general practitioner on admission. Comatose pa-

tients were graded using the Glasgow Coma Scale every 6 hours until the patient recovered full consciousness with a Glasgow Coma Scale of 15. Rectal temperature, blood pressure, pulse, and respiratory rate were measured every 6 hours during the first 24 hours, then every 12 hours until day 4 and once daily to day 7, then on the follow-up days 7, 14, 21, and 28. The patients were evaluated for the evolution of the signs and symptoms, and any new events elicited during treatment daily for 7 days and weekly till day 28 were recorded.

**Laboratory procedures.** The species differentiation was obtained from thin smears. A parasite count was obtained using thick blood films, counted as the number of parasites per 200 white blood cells. Parasite clearance was monitored using thick blood films every 6 hours during the first 24 hours, then every 12 hours to day 4 and daily to day 7. Follow-up films were taken on days 14, 21, and 28. The thick blood films were considered negative if no parasites were seen in 200 oil immersion fields on thick smears.

Biochemical and hematologic tests included hemoglobin, hematocrit, reticulocyte count, white blood cell total and differential counts, plasma glucose, plasma total bilirubin, serum urea, creatinine, and liver function tests. These tests were done on admission and repeated on days 7, 14, 21, and 28. More tests were performed as necessary for the management of critically ill patients.

**Management of patients.** Patients with severe malaria received nonspecific treatment according to the guidelines published by Gilles<sup>2</sup> and WHO.<sup>21</sup> The specific treatment included the use of the following antimalarial drugs: artesunate suppositories, 200 mg (Plasmotrim-200 Rectocaps-Mepha), mefloquine tablets, 250 mg (Mephaquin-Mepha), doxycycline capsules, 100 mg (Zadorin-Mepha), and pyrimethamine/sulfadoxine, 25 mg/500 mg (Fansidar Roche).

**Therapeutic regimens used.** All patients were treated with rectal artesunate, 200 mg every 8 hours for 3 days (total dose, 1,800 mg), then entered into an open-label design to receive the combined drug as follows:

1. Group A (35 patients): Doxycycline capsules, 100 mg every 12 hours for 4 days, started 12 hours after the last dose of artesunate
2. Group B (35 patients): A single dose (3 tablets) of pyrimethamine/sulfadoxine, 12 hours after the last dose of artesunate
3. Group C (30 patients): Mefloquine tablets (total dose, 15 mg/kg body weight), split in 2 equal doses 24 hours apart, started 12 hours after the last dose of artesunate

A pharmacokinetic study of oral and rectally administered artesunate in Sudanese healthy volunteers was used to devise the suggested dosage regimen of rectal artesunate, 200-mg rectocaps every 8 hours.<sup>10</sup> Patients were laid in a left lateral position, and an artesunate rectocap was inserted into the rectum beyond the anal verge by a trained nurse. The patients were confined to bed for at least 1 hour after the insertion; if the rectocap was expelled within 1 hour of administration, another dose was inserted.

**Evaluation criteria for the treatment efficacy and safety** *Efficacy assessment.* The following laboratory and clinical end points were used to measure response to treatment objectively: fever clearance time (time from the initiation of therapy until body temperature decreased to 37°C and re-

mained so for at least 48 hours), time to consciousness (time from the initiation of therapy until the Glasgow Coma Score = 15), clinical cure rate (the percentage of patients who had initial recovery with complete initial disappearance of parasitemia within 7 days), and fatality rate (the percentage of patients who died after the initiation of therapy). Laboratory measures included parasite clearance time (time from the initiation of therapy until the first negative blood film that remained negative for 48 hours), radical cure rate (the percentage of patients who had clinical cure without recrudescence by day 28), and recrudescence rate (defined according to WHO classification during 28-day follow-up). Improvement of impaired biochemical and hematologic parameters (time from the initiation of therapy until the improvement of the impaired biochemical and hematologic parameters to normal values) also was used.

*Safety assessment.* Side effects were defined as signs and symptoms that first occurred or became more severe after treatment was started. Any new events elicited during the treatment also were considered as side effects. Biochemical and hematologic parameters were evaluated before and after initiation of therapy to detect any drug-associated effects.

**Data analysis.** The demographic, clinical, and laboratory data for each patient were entered in a form, then entered in SPSS V9 for the performance of the descriptive and comparative statistical analysis. The comparison of data within the groups was carried out by paired Student *t*-test for normally distributed data and by Wilcoxon signed rank test for data that were not normally distributed. One-way analysis of variance was used for the comparison between the groups.

## RESULTS

A total of 2,400 adult patients who presented with fever or a history of fever to the trial site were screened with blood films during January 2000 to January 2001. Of patients, 420 (17.5%) were found to have positive blood films, 404 (96.2%) had *P. falciparum*, and the rest had *P. vivax*. Of the 404 cases, 73.3% were considered to have uncomplicated *P. falciparum* malaria, and 26.7% (n = 108) had criteria ascribed by WHO to severe malaria.

A total of 100 patients (79 men and 21 women) agreed to participate in the study and received an initial treatment with artesunate rectocaps for 3 days. For the second drug, the patients were divided into 1 of the 3 treatment groups (35 in group A, 35 in group B, and 30 in group C). Age range was 18–65 years with a mean (SD) of 30.5 (11.7) years, and weight range was 42–97 kg with a mean (SD) of 64.9 (9.1) kg. The 3 groups were comparable in demographic data, clinical characteristics, and laboratory findings (Table 2).

After the treatment regimens, surviving patients were followed for 28 days. Home visits were conducted for patients who failed to show for the follow-up. One patient died 7 hours after the first dose of artesunate. Fourteen patients had cerebral malaria with a mean (SD) Glasgow Coma Scale of 6 (1); 49 patients were jaundiced with a plasma total bilirubin greater than twice-normal laboratory range. All patients had a parasitemia of >10,000 parasites/μl, 19 patients had hyperpyrexia (>40.1°C), and 37 patients were hypoglycemic. Seven patients had algid malaria with systolic blood pressure <80 mm Hg, and 12 patients had elevated serum creatinine and

TABLE 2  
Mean  $\pm$  SD of the clinical, hematologic, and biochemical parameters at admission of the 3 second-drug treatment groups

Parameter	Group A (n = 35)	Group B (n = 35)	Group C (n = 30)
Age (y)	28.2 $\pm$ 9.9	30.8 $\pm$ 11.9	33.0 $\pm$ 13.3
Weight (kg)	64.4 $\pm$ 7	66.7 $\pm$ 8.2	63.6 $\pm$ 11.9
Ratio of males/females	27/8	28/7	24/6
Glasgow Coma Scale	6 $\pm$ 2	7 $\pm$ 1	6 $\pm$ 1
Rectal temperature ( $^{\circ}$ C)	38.8 $\pm$ 1.1	39.1 $\pm$ 1.2	39.1 $\pm$ 1.1
Blood pressure, systolic/diastolic	97 $\pm$ 12/53 $\pm$ 5	98 $\pm$ 15/56 $\pm$ 10	98 $\pm$ 12/54 $\pm$ 7
Parasitemia (parasites/ $\mu$ l)	38,299 $\pm$ 31,300	39,753 $\pm$ 30,615	61,214 $\pm$ 58,620
Hemoglobin (g/dl) (men, 13–17 g/dl; women, 12–15 g/dl)	12.4 $\pm$ 2.2	13.8 $\pm$ 1.6	12.5 $\pm$ 2.1
Plasma total bilirubin (mg/dl) (1 mg/dl)	2.2 $\pm$ 1.6	2.6 $\pm$ 1.7	3.3 $\pm$ 3.1
Serum creatinine (mg/dl) (0.5–1.5 mg/dl)	1.5 $\pm$ 0.8	1.6 $\pm$ 0.7	1.6 $\pm$ 0.8
Plasma glucose (mg/dl) (55–110 mg/dl)	52.7 $\pm$ 7.5	53.3 $\pm$ 8.9	53.5 $\pm$ 8.5

Note. Values in parentheses are laboratory normal range.

blood urea greater than twice normal. Of patients, 49 had  $>1$  criteria of severe malaria as ascribed by WHO (Table 3).<sup>21</sup>

All patients clinically improved within 3 days of starting treatment with artesunate rectocaps. Parasitemia clearance and fever clearance times are shown in Figures 1 and 2. The (mean  $\pm$  SD) of initial parasitemia was 45,683  $\pm$  42,068 parasites/ $\mu$ l (range, 13,133–25,000 parasites/ $\mu$ l). In 87 patients, parasitemia ranged from 13,133–100,000 parasites/ $\mu$ l, and 13 patients had parasitaemia  $>100,000$ –250,000 parasites/ $\mu$ l. There was a highly statistically significant reduction in the mean parasitemia at 6 hours and thereafter following artesunate rectocaps administration ( $P < 0.001$ ). The mean (SD) decrease in parasitemia was 36.2% (2.5%) by 12 hours and 64.1% (29.6%) by 18 hours.

After the insertion of artesunate rectocaps, the overall mean (SD) parasitemia clearance time was 31.5 hours (10.1 hours) (range, 18–72 hours). The mean (SD) reduction of

parasitemia by 24 hours was 88.8% (11.2%) and by 36 hours was 99.8% (0.2%). At baseline enrollment, gametocytes were detected in 5 patients. No new gametocytemia was detected during the treatment or follow-up. The mean (SD) clearance time of gametocytes was 4.2 (1.6) days, supporting the evidence that artesunate clears gametocytes, preventing further transmission.<sup>22</sup>

Figure 2 shows the clearance of fever. The overall mean (SD) initial rectal temperature before treatment was 39 $^{\circ}$ C (1.3 $^{\circ}$ C) (range, 34–40.6 $^{\circ}$ C). There was a highly significant reduction from the initial elevated temperatures achieved by 6 hours after starting treatment ( $P < 0.001$ ). The combined mean (SD) fever clearance time was 31.4 (11.1) hours (range, 12–60 hours).

The mean resolution time for the signs and symptoms ranged from 24–58.3 hours. All patients had excellent initial clinical improvement, and 87% of the patients were asymptomatic within 3 days of starting treatment. Full consciousness was gained by 78.6% of comatose patients at 24 hours, and the remaining patients regained normal higher function by 36 hours.

Hematologic parameters recovered with no evidence of marrow suppression during artesunate treatment or after the second drug in all treatment groups. Liver function, renal function, and blood glucose were comparable at presentation within the 3 treatment groups. All patients recovered except for 1 death at 7 hours after the first artesunate dose. There were no recrudescences in any patient by day 28 (radical cure rates 100%).

TABLE 3  
Patients with more than one criteria of severe malaria

Criteria	No. patients
Cerebral malaria (GCS $\leq$ 6) + hyperpyrexia ( $>40.1^{\circ}$ C) + generalized convulsions	7
Cerebral malaria (GCS $> 6 \leq 8$ ) + plasma total bilirubin $>3$ mg/dl	5
Cerebral malaria (GCS $\leq 6$ ) + hyperpyrexia ( $>40.1^{\circ}$ C) + plasma total bilirubin $>3$ mg/dl + serum creatinine $>3$ mg/dl	2
Hyperparasitemia ( $>100,000$ P/ $\mu$ l) + plasma total bilirubin $>6$ mg/dl + hyperpyrexia ( $>40.1^{\circ}$ C) + generalized convulsions + hemoglobin $<8.5$ g/dl	9
Hyperparasitemia ( $>100,000$ P/ $\mu$ l) + plasma total bilirubin $>3$ mg/dl + hypoglycemia $<40$ mg/dl + generalized convulsions + serum creatinine $>3$ mg/dl	4*
Algid malaria (SBP $< 80$ mmHg) + plasma total bilirubin $>3$ mg/dl	5
Algid malaria (SBP $< 80$ mmHg) + plasma total bilirubin $>3$ mg/dl + serum creatinine $>3$ mg/dl	2
Hyperpyrexia ( $>40.1^{\circ}$ C) + generalized convulsions + plasma total bilirubin $>3$ mg/dl	1
Serum creatinine $>3$ mg/dl + urine output $<400$ ml /24 h + hypoglycemia $<40$ mg/dl + plasma total bilirubin $>3$ mg/dl	4
Hypoglycemia $<40$ mg/dl + generalized convulsions + plasma total bilirubin $>3$ mg/dl	10

\* One fatal outcome.

The criteria of severe falciparum malaria as ascribed by WHO, 2000.

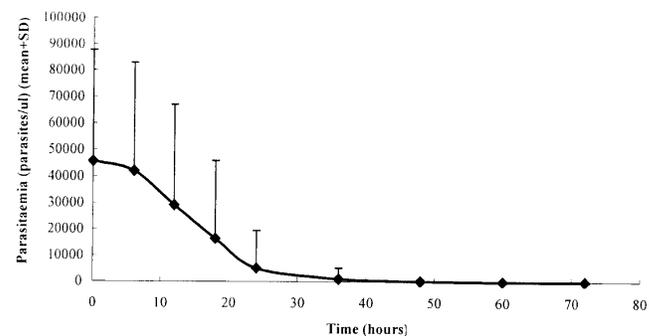


FIGURE 1. Clearance of parasitemia.

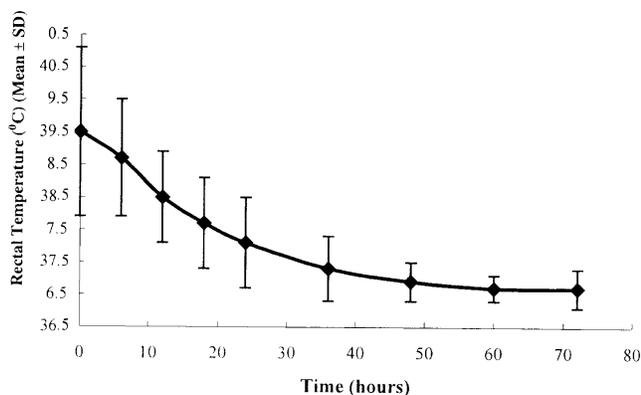


FIGURE 2. Clearance of fever.

## DISCUSSION

The present study investigated a larger number of patients than reported in other studies. Using pharmacokinetic data from healthy volunteers, an appropriate dose of artesunate was selected for administration per rectum that would be expected to provide blood levels of dihydroartemesinin above the minimum inhibitory concentration that eliminates 90% of the parasites ( $MIC_{90}$ ) for  $5.3 \pm 2.1$  hours.<sup>10</sup> The rapid parasite clearance and defervescence of fever in all 99 patients confirms the dosing schedule in this group of patients was entirely appropriate. The parasitemia and fever clearance times in this study were significantly shorter than that reported by Looareesuwan et al.<sup>11,12</sup> and Thwe et al.<sup>13</sup> but not significantly different from that reported by Eduardo and Gomez<sup>14</sup> and Bhatt et al.<sup>15</sup>

The choice of second agent was made based on available data of mefloquine from Southeast Asia and cost because pyrimethamine/sulfadoxine and doxycycline are inexpensive and widely available. All 3 drugs proved equally effective, producing radical cure rates of 100%. The only death in the study was a 50-year-old man, who despite a reduction in parasitemia at 6 hours from 160,000 to 142,000 parasites/ $\mu$ l died suddenly 7 hours after starting treatment. Previous studies reported fatality rates of 40% in severely ill malaria patients.<sup>23</sup> The mortality rates reported in 2 other studies using artesunate rectocaps for the treatment of severe malaria were 2.5% and 13.6%.<sup>14,15</sup> In these 2 studies, the number of patients and the total dose of rectal artesunate were less than in our study (Table 1). We accept that not all subjects meet similar criteria to those published studies, but this study was not intended to show a reduction in mortality as an outcome measure, but this was noted, and we comment on it as a positive finding.

The selection criteria used the WHO<sup>21</sup> definition of severe malaria to include hyperparasitemia, jaundice, hyperpyrexia, cerebral involvement, renal impairment, and prostration, and these were used for selecting patients for the study. Because many of these criteria are clinical and subjective, comparison of disease severity with other studies is difficult. About one quarter of all 404 cases diagnosed as *P. falciparum* (26.7%) were considered severe, however, and recruited into the study. It is of note that only 1 death occurred, and recovery occurred in more than three quarters with 3 days of artesunate treatment. Because the formulation was a rectal supposi-

tory, cultural objection to the use of suppositories needed to be considered. Cultural acceptance is variable and responds to education. There was little resistance to the use of the suppositories by patients or their relatives.

The clinical and laboratory findings during and after the treatment showed no evidence of toxicity or side effects to the 3 combination regimens during treatment and the 28-day follow-up. In group B, there was an increase in the number of patients with hemoglobin and hematocrit below normal at days 7 and 14, which suggested that this combination may have an adverse effect. Previous studies using pyrimethamine/sulfadoxine combined with artesunate in the treatment of uncomplicated falciparum malaria reported that there were no adverse effects on laboratory parameters.<sup>24</sup> The clinical significance of this finding remains to be confirmed in a larger number of patients.

In studies in which artemisinin compounds were administered alone, recrudescence rates varied from 10% to 100% depending on the dose, duration of treatment, and severity of the disease.<sup>19</sup> These drugs often are combined with mefloquine to reduce the rate of recrudescence. Limited studies reported the efficacy of doxycycline or pyrimethamine/sulfadoxine combined with artesunate in treatment of uncomplicated malaria. The present results indicate that sequential treatment of severe malaria with artesunate rectocaps followed by either doxycycline (100 mg every 12 hours for 4 days) or a single dose of pyrimethamine/sulfadoxine was equally effective to that followed by mefloquine in preventing recrudescence. The dosage regimen of mefloquine (total dose 15 mg/kg body weight) divided in 2 equal doses 24 hours apart used in this study improved its tolerability because no serious adverse effects occurred.

Artesunate rectocaps in treatment of severe malaria have many advantages in rural settings in developing countries such as Sudan. Their administration does not require sophisticated facilities and skilled personnel, and they can be used as an alternative to parenteral quinine with all its known side effects. The use of artesunate rectocaps in rural areas where malaria transmission is higher and the disease is more prevalent is more appropriate for the type of health facilities available. The early administration of treatment to patients where referral is not possible, especially for children, could reduce complications and reduce mortality. The use of a single dose of pyrimethamine/sulfadoxine or 2 doses of mefloquine in adults and children would improve compliance to the important second drug necessary to prevent resistance. Doxycycline can be used as an alternative in adults.

The main goal of this study was to evaluate the efficacy and safety of an alternative therapy to parenteral quinine in areas where there is poor access to well-structured health facilities, such as exist in Sudan and many other parts of the Third World and where patient referral is impractical. A novel dosage regimen of artesunate rectocaps (200 mg every 8 hours for 3 days) achieved substantial and rapid decreases in parasitemia and fever in patients presenting with severe falciparum malaria. The drug regimen was well tolerated and produced a clinical cure in most patients by day 3. The addition of 1 of 3 second-line drugs prevented recrudescence of malaria. The regimen was designed for use in settings with poor resources and limited expertise, and its ease of use may have a significant impact and effectiveness that may reduce complications and mortality from falciparum malaria. The sequential com-

binations of artesunate rectocaps followed by doxycycline or pyrimethamine/sulfadoxine were equally effective as mefloquine in preventing recrudescence and in this study had a 100% radical cure rate. The combination regimens seem safe and highly effective and could be lifesaving in patients with severe malaria, particularly in rural areas. The present results can be pooled in the future with results from other areas to determine the actual efficacy of artesunate suppositories compared with current therapeutic options used in different regions of the world.

Received April 23, 2002. Accepted for publication October 14, 2002.

**Acknowledgments:** We deeply thank all the medical staff in Omdurman Teaching Hospital and Tropical Disease Hospital, particularly Dr. Omer Nemiri, Dr. Fatima A., Dr. Angal Almahdi, and Dr. Amel Hajnour, for their assistance and collaboration in carrying out the clinical trial. We thank Mr Tarig Elfaki, Mr Salah G. Elzaki, Mr. Mohamed A/gadir, and Mr. Afiefi, for their technical assistance throughout this work.

**Financial support:** This work was supported by the British Chevening Scholarship, University of Khartoum, Tropical Research Institute, and Malaria National Administration in Sudan. We thank Mepha Pharmaceutical Research, Aesch-Basel, Switzerland, for the donation of artesunate rectocaps.

The clinical trials were conducted in Khartoum-Sudan. Data interpretation and writing were undertaken at Robert Gordon University, United Kingdom, and University of Khartoum, Sudan.

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