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Efficacy of a Loading Dose of Oral Chloroquine in a 36-Hour Treatment Schedule for Uncomplicated *Plasmodium falciparum* Malaria

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The efficacy of a loading dose of 20 mg of chloroquine per kg of body weight per os given at intervals during the first day was evaluated in 27 patients in Madagascar with *Plasmodium falciparum* malaria. The conventional regimen of 25 mg/kg over 3 days (schedule 1) was thus compared with a regimen of 30 mg/kg over 2 days (schedule 2; one dose of 10 mg/kg followed by two doses of 5 mg/kg at 6-h intervals on the first day and two doses of 5 mg/kg at 12-h intervals on the second day) in terms of their clinical and parasitological efficacies, tolerance, and drug concentration-time curves. At 24 h schedule 2 gave higher chloroquine levels in blood, which induced a more rapid decrease in parasitemia. The time required for a 50% decrease in the initial parasitemia was shorter in patients on schedule 2 (14.3 ± 1.6 h) than it was in patients on schedule 1 (35.5 ± 5.4 h; $P < 0.01$). Moreover, negative blood smears were obtained more rapidly with schedule 2 (50.8 ± 3.7 h) than with schedule 1 (72 ± 8.7 h). As predicted by the drug concentration-time curve, no high, potentially toxic peak drug concentration appeared and no adverse effects were observed with the loading dose regimen (schedule 2). These findings support the idea that a loading dose of 20 mg/kg given at intervals during the first 12 h is well tolerated and can be used to obtain a more rapid decrease in parasitemia and to shorten the treatment time of uncomplicated chloroquine-susceptible falciparum malaria in the field.

Despite the increasing widespread resistance of *Plasmodium falciparum*, chloroquine remains the drug of first choice for the treatment of chloroquine-susceptible and low-level-resistant malaria in the field. This is an inexpensive drug, and when administered orally, it is usually well tolerated and effective. Among the several therapeutic schedules, the most commonly used is a total dose of 25 mg of chloroquine per kg of body weight administered either as an initial 10-mg/kg dose followed by subsequent 5-mg/kg doses given 6, 24, and 48 h later (16) or as the World Health Organization regimen, which is 10 mg/kg given at 0 and 24 h and 5 mg/kg given at 48 h (3). With this schedule, nonimmune patients become aparasitemic 60 to 80 h after the beginning of treatment (1, 6, 10, 12). However, in the field, since patients with malaria often stop treatment too early, leading to frequent relapses, a shorter treatment period might be more reliable and effective.

Given the considerable total apparent volume of distribution (100 to 1,000 liters/kg) and the extremely long terminal half-life (30 to 60 days), distribution rather than elimination processes determine the blood concentration curve of chloroquine during treatment (5, 14). These kinetic characteristics suggest that a loading dose followed by subsequent doses on the first day followed by several partial doses on subsequent days could be given in order to enhance the distribution phase of the drug. To test this hypothesis, the conventional 25-mg/kg chloroquine regimen given over 48 h was compared with a total dose of 30 mg of chloroquine per kg given over 36 h as an initial dose of 10 mg/kg followed by successive 5-mg/kg doses. These doses were tested in terms of their clinical and parasitological efficacies, tolerance, and drug levels in whole blood.

MATERIALS AND METHODS

Patients. The study was conducted in the village of Manarintsoa situated in the central highland plateau of Madagascar, a region in which falciparum malaria has recently reappeared (7) and where the transmission level is low (4). The study took place between March and June 1989, which corresponds to the latter part of the transmission period. Twenty-seven partially immune *P. falciparum*-infected patients of both sexes (ages, between 4 and 45 years) were recruited for one of the two regimens, as determined by their order of entry into the study (alternatively, one patient for regimen one and two patients for regimen two). Inclusion criteria were the detection of more than 1,000 asexual pure *P. falciparum* parasites per μl of blood and that full informed consent be given by the patients or, for children, by the parent or guardian. Exclusion criteria were serious illness, impaired consciousness, prostration or convulsions, hyperpyrexia (axillary temperature, ≥38°5), a history of diarrhea or vomiting, and the use of antimalarial agents in the previous 3 weeks. Previous antimalarial agent use was assessed by obtaining a careful drug history from patients and by using a urine test for detection of 4-aminoquinolines; the urine test had a detection limit of 10 μmol/liter (2).

Treatment. Chloroquine sulfate was administered as tablets (Nivaquine; Specia, Paris, France) containing the equivalent of 100 mg of drug base by the two following schedules: schedule 1, 25 mg of chloroquine base per kg given over 48 h administered as a 10-mg/kg dose at 0 and 24 h and a 5-mg/kg dose at 48 h (8 patients; group 1); schedule 2, 30 mg

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TABLE 1. Characteristics of the study groups on admission to the study[a]

Patient group (dose [mg/kg])	No. of patients	Age (yr)	Wt (kg)	No. of asexual parasites/μl of blood	Axillary temp (°C)	Level (nmol/liter) of the following in blood:	
						Chloroquine	Monodeethylchloroquine
1 (25)	8	24.4 ± 6.0	40.3 ± 8.1	8.875 ± 2.2661	37.4 ± 0.3	92 ± 22	74 ± 29
2 (30)	19	14.8 ± 2.5	31.4 ± 3.6	24.489 ± 6.005	37.5 ± 0.3	158 ± 52	143 ± 30

[a] Values are means ± standard errors of the mean. The characteristics of the two groups on admission to the study were not significantly different.

of chloroquine base per kg given over 36 h administered as a 20-mg/kg dose on the first day (a 10-mg/kg dose followed by two doses of 5 mg/kg at 6-h intervals) and then 5-mg/kg doses given at 24 and 36 h (19 patients; group 2).

Clinical and laboratory investigations. The clinical examination was carried out; and blood pressure, heart rate, and axillary temperature were determined before and at 24, 48, 96, and 168 h after the initiation of treatment. Patients were asked about the occurrence of side effects (in particular, of pruritus, which is known to be related to chloroquine use). Quantitative parasite counts were carried out on Giemsa-stained thick smears before and at 2, 6, 12, 24, 36, 48, 96, and 168 h after the beginning of treatment. Films were considered negative if no parasites were seen on smears after 1,000 leukocytes were counted. Before and at 2, 12, 24, 48, 96, and 168 h after drug administration, venous blood samples were collected in sterile tubes containing EDTA and were then stored at −30°C until drug analysis. Levels of chloroquine and its main metabolite, monodeethylchloroquine, in whole blood were measured by high-performance liquid chromatography by using UV detection as described previously (9).

Data analysis. Data were expressed as the means ± standard errors of the mean. Student's t test was used to compare the means of normally distributed data. Data not normally distributed were compared by the Wilcoxon test. A bicompartmental model with an absorption phase (5) was used to fit the chloroquine concentration data of each subject. The whole blood concentration-time curves of this drug were obtained by using a multiple-dose nonlinear program (Siphar; SIMED) on an IBM PS computer.

RESULTS

The clinical features and parasitological counts of both groups of patients were comparable on admission to the study (Table 1). Despite a negative history of drug consumption and a negative 4-aminoquinoline urine detection test (2), chloroquine and monodeethylchloroquine were detected only at low levels in the pretreatment blood samples of all subjects in group 1 and 10 subjects in group 2. The mean levels of chloroquine and monodeethylchloroquine in blood on admission were 92 ± 22 and 74 ± 29 nmol/liter, respectively, in group 1 and 159 ± 52 and 143 ± 30 nmol/liter, respectively, in group 2. There was no significant difference in any of the clinical or parasitological parameters or drug levels between the two groups (age, t = 1.767; weight, t = 1.173; parasitemia, t = 1.642; levels of chloroquine in blood, t = 0.803; levels of monodeethylchloroquine in blood, t = 1.374; axillary temperature, t = 0.236).

Both regimens were totally clinically and parasitologically efficacious in all patients by day 7 (168 h). Asexual parasitemia remained constant or even increased during the first 24 h in group 1 patients but decreased rapidly in group 2 patients (Fig. 1). Parasite clearance time (i.e., the time to the first negative thick film) was shorter in group 2 patients (50.8 ± 3.7 h) than it was in group 1 patients (72.0 ± 8.7 h; P < 0.05). In addition, the time required to obtain 50% of the initial parasitemia was shorter in group 2 patients (14.3 ± 1.6 h) than it was in group 1 patients (35.5 ± 5.4 h; P = 0.01). The parasite clearance times were not correlated with initial parasitemia or pretreatment levels of chloroquine in blood.

The decrease in mean axillary temperature was similar in both groups. The temperatures of all patients reached normal values (36.5°C) by 24 h after the beginning of treatment and remained unchanged up to 168 h.

Both schedules were well tolerated. The subjects did not report any major side effects. No significant changes in blood pressure or heart rate were observed during the study. Only one patient in group 1 complained of pruritus after administration of the first 10-mg/kg dose of chloroquine.

The mean chloroquine blood concentration-time curves for both groups are given in Fig. 2. Despite the large interindividual variability, the mean chloroquine concentrations in whole blood of group 2 patients were higher at 12 h

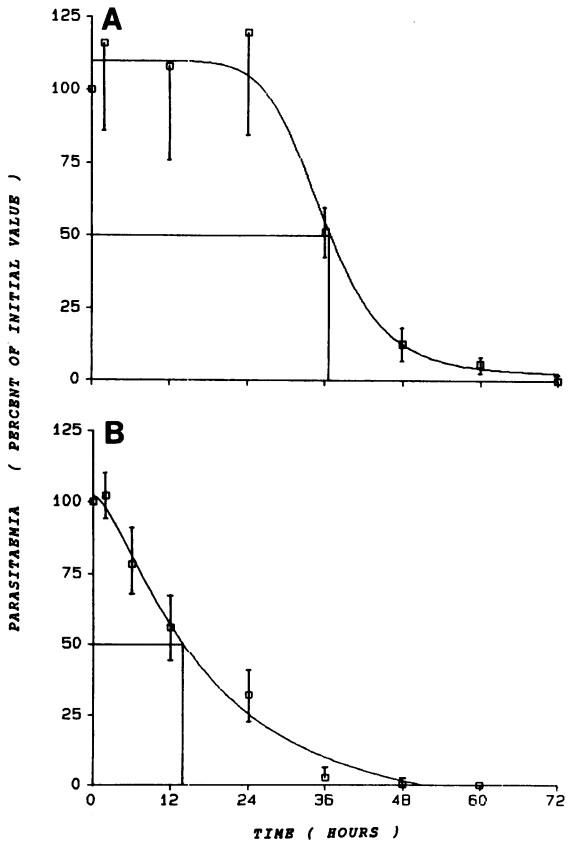

FIG. 1. Decline in parasitemia expressed as percent initial values in schedule 1 (10 mg/kg at 0 and 24 h and 5 mg/kg at 48 h) (A) and schedule 2 (an initial 10-mg/kg dose followed by subsequent 5-mg/kg doses given 6, 12, 24, and 36 h later) (B).

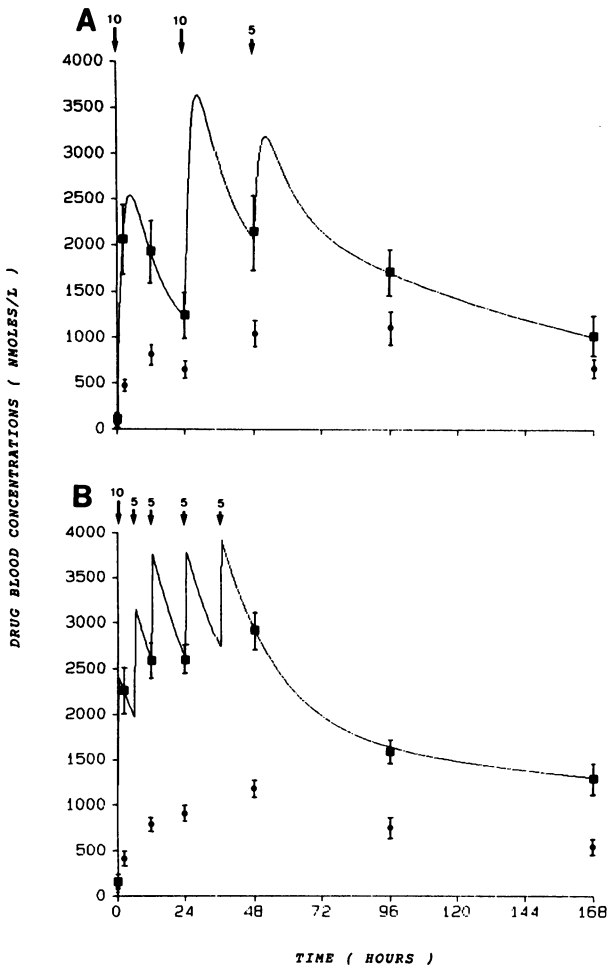

FIG. 2. Mean (± standard error of the mean) chloroquine blood concentration-time curves (■) and corresponding monodeethylchloroquine concentrations in blood (●) obtained with schedule 1 (10 mg/kg at 0 and 24 h and 5 mg/kg at 48 h) (A) and schedule 2 (an initial 10-mg/kg dose followed by subsequent 5-mg/kg doses given 6, 12, 24, and 36 h later) (B). Numbers above the arrows indicate doses, in milligrams per kilogram of body weight.

(2,590 ± 203 nmol/liter), 24 h (2,604 ± 147 nmol/liter), and 48 h (2,929 ± 193 nmol/liter) than they were in group 1 patients (1,934 ± 358, 1241 ± 247, and 2151 ± 442 nmol/liter, respectively) ($P < 0.01$). Mean chloroquine levels in blood at 96 and 168 h were similar in both groups. Areas under the concentration-time curves from 0 to 24 h and from 0 to 168 h were not correlated to parasite clearance times. The monodeethylchloroquine concentrations in blood increased slowly during the treatment (Fig. 2), but mean concentrations in blood for patients on both therapeutic regimens at each time were not significantly different.

DISCUSSION

Although an in vivo oral dose of chloroquine given as 10 mg/kg at 0 and 24 h and 5 mg/kg at 48 h is the standard regimen established by the World Health Organization (3) for the treatment of uncomplicated *P. falciparum* malaria, an initial 10-mg/kg dose followed by 5-mg/kg doses given 6, 24, and 48 h later (16) is often used. Moreover, even in areas where *P. falciparum* is moderately chloroquine resistant, a 35-mg/kg chloroquine dose over 5 days has been described as an effective treatment (14).

Total clinical and parasitological efficacies were obtained by day 7 without side effects in the patients in the present study. Late recrudescence (reapperance of parasites after day 7) could not be observed because a 28-day follow-up was not possible in these patients, and so potential recrudescence could not completely be excluded. The 20-mg/kg loading dose of chloroquine during the first 12 h induced a more rapid decrease in parasitemia, as shown by the shorter time required to decrease 50% of the initial parasitemia in group 2 patients in comparison with that in group 1 patients (Fig. 2). In addition, negative blood smears were obtained more rapidly in group 2 patients than they were in group 1 patients. The lack of correlation between the times to decrease parasitemia and (i) chloroquine concentrations in blood at 24 h and (ii) the areas under the concentration-time curves between 0 and 24 h could probably be explained by variabilities in the patients' immunity levels or by the heterogeneous chloroquine susceptibility of *P. falciparum* strains in the central highland plateau of Madagascar (8). On the other hand, despite the similar in vitro activities of monodeethylchloroquine and chloroquine against chloroquine-susceptible *P. falciparum* isolates (11), the lack of differences in monodeethylchloroquine levels in blood observed in both groups implies that differences in efficacy might be attributed solely to unchanged chloroquine. The parasite clearance times observed with the 25-mg/kg schedule over 48 h were in good agreement with those described previously in similar studies (1, 6, 10). The time required to decrease 50% of the initial parasitemia was a little longer after the 20-mg/kg oral loading dose than it was after 3.5-mg/kg intramuscular injections given every 6 h (8.9 ± 1.3 h), as described previously in children with severe *P. falciparum* malaria (15). This difference is probably related to the shorter time to peak concentration observed after intramuscular administration (0.5 h) than that observed after oral administration (2 to 4 h) (16). Nevertheless, the oral loading dose gives effective high concentrations more rapidly than the standard 25-mg/kg regimen does and could thus induce a better efficacy earlier, close to that obtained by the intramuscular route.

However, the chloroquine concentrations in whole blood which are effective in treating *P. falciparum* malaria have not been determined precisely. Drug levels of about 1,500 to 2,000 nmol/liter in blood maintained for 3 or 4 days, which corresponds to about two maturation cycles of the parasite, could be considered effective treatment against chloroquine-susceptible infections (14).

The administration of a 20-mg/kg loading dose in the first 12 h (10 mg followed by two doses given at 6-h intervals) might avoid the low and potentially subtherapeutic drug concentrations in blood observed 12 to 24 h after a single 10-mg/kg dose. The concept of a loading dose suggested by the kinetic properties of chloroquine has also already been proposed for prophylaxis to avoid subtherapeutic chloroquine concentrations obtained with a weekly 5-mg/kg regimen during the first weeks of prophylaxis (5, 13). In addition, the successive 5-mg/kg doses enhance the distribution phase of chloroquine and reduce the difference between peak and residual concentrations. Chloroquine concentrations in blood of about 2,000 nmol/liter were maintained for only between 24 and 72 h in patients on schedule 1 but were maintained for between 3 and 72 h in patients on schedule 2. Despite the negativity of the specific and sensitive 4-aminoquinoline detection test (2), chloroquine and monodeethyl-

chloroquine concentrations in blood were observed before treatment. This was due to the frequent chloroquine self-medication which is common in Madagascar. These concentrations in blood (below 210 and 180 nmol/liter for chloroquine and monodeethylchloroquine, respectively) were nevertheless too low to prevent the occurrence of infection and to interfere significantly with the treatment.

Severe adverse effects have been described in cases in which chloroquine concentrations in plasma were higher than 3,000 nmol/liter, which corresponds to at least 6,000 nmol/liter in blood (5, 14). As predicted by the drug concentration-time curve, with the total dose given as 10 mg/kg and then successive 5-mg/kg doses at 6- and then 12-h intervals, the concentrations of chloroquine in blood were lower than 4,000 nmol/liter and accounted for the good tolerance of this regimen. Subjects not known to have taken or not suspected of having taken chloroquine previously (absence or low drug levels in urine) could be given this regimen, with particular attention given to early potential cardiovascular effects.

An oral loading dose of 20 mg of chloroquine per kg given at intervals during the first 12 h followed by two administrations of 5 mg/kg at 12-h intervals was shown to be useful in partially immune patients for the more rapid treatment of uncomplicated chloroquine-susceptible falciparum malaria.

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