Comparison of oral artesunate and quinine plus tetracycline in acute uncomplicated falciparum malaria

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In Thailand Plasmodium falciparum *malaria is highly resistant to available antimalarials. Investigations on the efficacy of existing antimalarials and of alternative drugs are urgently needed. Artesunate has been shown to be effective against falciparum malaria, but is associated with a high recrudescence rate. We have carried out a comparative clinical trial of the standard regimen of quinine + tetracycline versus oral artesunate at a 700-mg total dose given over 5 days to patients with acute uncomplicated falciparum malaria. The 64 male patients who took part in the study were randomized to receive either quinine–tetracycline (33 patients) or oral artesunate (31 patients). All the patients were admitted to the Bangkok Hospital for Tropical Diseases for 28 days.*

Oral artesunate had faster parasite and fever clearance times than the combination quinine–tetracycline, but the cure rate was not significantly different for the two regimens. However, the occurrence of adverse effects, such as tinnitus, was significantly higher in the quinine–tetracycline group. Surprisingly nausea and dizziness were rather common with artesunate. The possibility of neurological adverse effects for artesunate should also be borne in mind.

Oral artesunate (700 mg given over 5 days) is effective and better tolerated than the combination quinine–tetracycline. The cure rate we obtained is higher than that reported in previous studies with 600 mg of oral artesunate given over 5 days. Oral artesunate can be considered as an alternative drug for multiple-drug-resistant falciparum malaria; however, adverse effects, particularly neurotoxicity, should be closely monitored before its widespread use can be recommended. In areas where artesunate is not available, the use of quinine–tetracycline for 7 days is still very effective if its administration can be supervised.

Introduction

In Thailand, multiple-drug-resistant strains of falciparum malaria are increasing and spreading (*1*, *2*). Mefloquine is used as the first-line drug for uncomplicated falciparum malaria in Thailand; however, the efficacy of this drug has dropped dramatically in the country to less than 60% (*3*). The combination quinine + tetracycline improves the cure rate from 75% to 95–100% compared with the use of quinine alone (*2*). This combination is therefore being used as a second-line drug treatment for uncomplicated malaria. However, the compliance of patients limits its use for home treatment. Cinchonism would be expected in practically all patients on this combined regimen. Alternative drugs that are better or equally as effective and which have fewer adverse effects therefore need to be studied.

Artesunate is a derivative of artemisinin and clears parasitaemia as rapidly as artemether (another derivative of artemisinin) (*3–6*). The parasite clearance rate of artesunate is faster than that of any other antimalarial (*3*, *7*, *8*). The potency of artesunate has been shown in several clinical trials in China and Thailand, and the adverse effects reported are very mild and transient (*9–13*). In China, the recommended total dose of artesunate has been 600 mg given

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over 5 days (*14*). However, recent studies in Thailand have shown that at this dosage the cure rate with uncomplicated falciparum malaria was only 72–90% when administered orally (*10–13*). The proper dosage regimen of artesunate for the treatment of multiple-drug-resistant falciparum malaria remains to be decided. Based on the efficacy of oral artesunate reported in recent studies (*9–13*), the duration of the treatment should be at least 5 days and the dose needs to be >600 mg to achieve a cure rate that approaches 100%. It is therefore interesting to assess the efficacy of a higher dose of artesunate in patients with multiple-drug-resistant falciparum malaria compared with that of the second-line drug treatment, quinine–tetracycline.

Patients and methods

A total of 64 adult Thai, male patients with acute uncomplicated falciparum malaria (asexual-form parasitaemia, <5%), aged 15–35 years, and of weight range 43–65 kg were recruited into the study. We excluded patients who had a history of liver or kidney disease, and patients who had received antimalarial treatment for their current episode of illness. Patients with severe manifestations of malaria were also excluded (*15*). The written, informed consent for participation in the study was obtained from all the patients. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Prior to receiving the treatment, blood smears were collected from each patient for malaria parasite identification and 3 ml of venous blood was drawn to determine the baseline drug concentrations of mefloquine and quinine. Patients who had previously received these two drugs were excluded from the study. All patients were admitted to the Bangkok Hospital for Tropical Diseases for 28 days.

The patients were randomly allocated (open randomization) to receive one of the two drug regimens, i.e., artesunate or the combination quinine–tetracycline as follows:

— 200 mg of artesunate as an initial dose, followed by 100 mg 12 hours later, and 100 mg daily for another 4 days (total dose: 700 mg);

— 600 mg of quinine sulfate at 8-hour intervals plus 250 mg of tetracycline at 6-hour intervals for 7 days.

Both regimens were administered orally with a glass of water under supervision. Based on previous data, the sample sizes chosen for the study were designed to detect a 35% faster parasite clearance rate from artesunate than from quinine–tetracycline (at a 95% confidence level).

Patients who failed to respond to either regimen were treated with 600 mg of quinine sulfate at 8-hour intervals plus 250 mg of tetracycline at 6-hour intervals, for 7 days. Patients who had *Plasmodium vivax* malaria during the follow-up period were given 150 mg of chloroquine base to suppress the symptoms and received a full course of treatment on discharge.

Parasite identification was performed using thick and thin peripheral smears that had been stained with Field's stain; the parasite counts were reported as counts per 1000 red blood cells or per 200 white blood cells. Blood smears were collected at 6-hour intervals until parasitaemia fell below the level of microscopic detection in thick smears, then twice daily until day 28 of the study.

Complete blood counts, blood biochemistry (liver and kidney function tests) and urine analyses were carried out on admission and on days 2, 4 and 7, then weekly until day 28. Electrocardiograms (ECGs) were recorded daily for 7 days in the artesunate group, then weekly for the rest of the follow-up period.

All adverse reactions during the study period were recorded three times daily during the first week then daily until discharge, and the date and time when they occurred and disappeared were noted. Drug-related adverse effects were defined as signs or symptoms which either increased or first occurred after drug administration. All the abnormalities possibly attributable to artesunate or quinine–tetracycline were recorded.

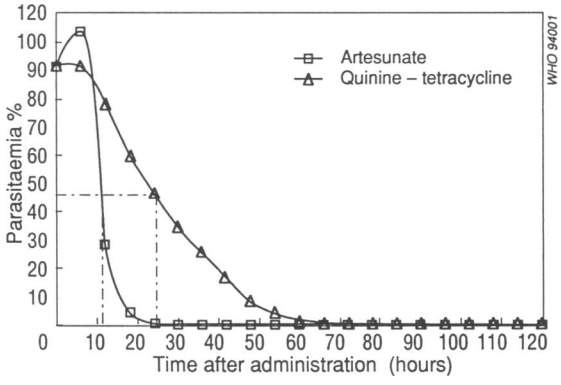
Patients were included for efficacy assessment if they had completed the 28-day follow-up period. The efficacy and adverse effects from the two regimens were compared. The following parameters were used to determine the outcome: parasite clearance time (PCT: the time taken for the parasite count to fall below the level of microscopic detection); fever clearance time (FCT: the time taken for the temperature to return to normal, i.e., <37.3 °C and remain so for at least 24 hours); the rate of treatment failure (RI, RII or RIII) (*15*); and the occurrence of adverse effects. Data from both groups were compared using the Mann–Whitney *U* test. Pretreatment parasitaemia was stratified into three levels (<10 000, 10 000–100 000 and >100 000 parasites/μl). The Mantel–Haenszel test was used to test for differences in the proportions of patients in each treatment group, and the differences in parasite clearance times were tested using analysis of variance. The levels of statistical significance between the groups were calculated using Fisher's exact test (two-tailed) for proportion and the Mann–Whitney *U* test for other outcome variables.

Results

All 64 study patients presented with acute symptoms of malaria. None of the patients had mefloquine or quinine in their blood prior to treatment, based on drug analysis by high-performance liquid chromatography (HPLC). A total of 31 patients received artesunate and 33 received quinine–tetracycline. The admission clinical and laboratory data were similar for both groups (Table 1). No patients had anaemia on admission, and the admission parasitaemia levels were not statistically different ($P = 0.213$) in the two groups according to Mantel–Haenszel tests after stratification of admission parasitaemia into three levels.

In the artesunate group, all patients had a rapid initial response with mean PCT and FCT of 37 hours and 31 hours, respectively. There was no statistically significant difference in PCT among patients who presented with low or high pretreatment parasitaemia. The parasites in all patients cleared rapidly from peripheral blood (Fig. 1). One patient left the hospital without parasitaemia on day 10. Of the 30 patients included in the efficacy assessment, one experienced reappearance of parasitaemia on day 22 (RI response); the cure rate was 96.7%.

Fig. 1. **Mean parasite clearance times for the artesunate and quinine–tetracycline study groups.**



In the quinine–tetracycline group all patients were cured, with mean PCT and FCT of 73 hours and 55 hours, respectively. There was no difference in the PCT for patients who had a low or high pretreatment parasitaemia. Three patients did not complete the 28-day follow-up period but left the hospital without parasitaemia on days 7, 8 and 12. Based

Table 1: **Admission clinical and laboratory data for the 64 study patients, according to treatment group**

	Treatment group	
	Artesunate ($n = 31$)	Quinine–tetracycline ($n = 33$)
Mean values		
Age (years)	25 (15–35)[a]	23 (17–35)
Weight (kg)	51 (43–65)	51 (45–63)
Temperature (°C)	38.3 (37.5–40)	38.4 (37.5–39.7)
Haematocrit (%)	36 (20–58)	35 (25–45)
WBC (per μl)[b]	5 794 (2 800–8 800)	7 094 (4 200–12 200)
Direct bilirubin (mg/100 ml)	0.47 (0.03–1.78)	0.41 (0.12–2.11)
Total bilirubin (mg/100 ml)	1.92 (0.45–5.40)	1.83 (0.60–4.90)
Alkaline phosphatase (IU)	31 (15–76)	30 (16–60)
SGOT (IU)[c]	45 (19–110)	48 (18–146)
SGPT (IU)[d]	47 (10–201)	46 (10–140)
Creatinine (mg/100 ml)	1.2 (0.8–1.9)	1.2 (0.8–3.5)
BUN (mg/100 ml)[e]	18 (7.8–41.5)	17 (5.5–48)
Albumin (g/100 ml)	3.8 (3.0–4.4)	4.0 (3.1–4.6)
Globulin (g/100 ml)	2.9 (2.2–4.7)	2.9 (2.3–4.4)
Geometric mean		
Parasitaemia (per μl)	50 206 (504–292 560)	35 188 (351–175 010)

[a] Figures in parentheses are the range.
[b] WBC = white blood cell count.
[c] SGOT = serum aspartate aminotransferase.
[d] SGPT = serum alanine aminotransferase.
[e] BUN = blood urea nitrogen.

on the data for 30 patients who completed the follow-up, the cure rate was 100%.

Comparison of the artesunate and quinine–tetracycline groups indicates that PCT and FCT were significantly faster in the artesunate group ($P = 0.000001$ and 0.000041, respectively) (Table 2). Also comparison of the PCT between two treatment groups according to the three levels of pretreatment parasitaemia confirmed the rapidity of parasite clearance with artesunate for all three levels ($P = 0.0085$, 0.000003, and 0.00001 for pretreatment parasitaemia levels <10 000, 10 000–100 000 and >100 000 parasites/μl, respectively). The estimated mean 50%-parasite clearance time from the curves was 11 hours and 24 hours for artesunate and quinine–tetracycline, respectively (Fig. 1). The cure rate was, however, not significantly different for the two groups.

Five patients who were treated with artesunate exhibited *P. vivax* in their peripheral blood between days 13 and 24, while nine patients did so in the combined regimen (between days 21 and 28).

In both treatment groups the adverse effects were mild and self-limiting. Tinnitus was a common finding in the quinine–tetracycline group but not in the artesunate group. The incidences of nausea, dizziness, and vomiting were not significantly different in the two groups (Table 3). Bradycardia occurred in seven patients (23%) in the artesunate group (Table 3), mostly on day 2 to day 7. No other arrhythmias were detected in the ECGs. One patient had convulsions 21 hours after receiving the initial dose of artesunate but at this stage still exhibited parasitaemia (PCT = 36 hours). This patient did not receive any drugs prior to admission; no further convulsions occurred after he received 5 mg of intravenous diazepam.

No significant drug-related blood profiles or biochemical changes occurred during the course of follow-up in either group, and no significant change in the haematocrit was observed in any of the patients.

Table 2: **Comparison of the therapeutic responses in the 64 study patients, according to treatment group**

	Treatment group	
	Artesunate ($n = 31$)	Quinine–tetracycline ($n = 33$)
Mean value[a]		
PCT (hours)	36.5 (24–52)[b]	73.2 (36–135)[c]
FCT (hours)	31.3 (4–67)	55.4 (4–104)[d]
Responses[e]		
Total number of patients	30	30
No. with S	29	30
No. with RI	1	–
No. with RII	–	–
No. with RIII	–	–
Cure rate on day 28	96.7%	100%
No. of patients with *P. vivax*	5 (days 13–24)	9 (days 21–28)

[a] PCT = parasite clearance time; FCT = fever clearance time.
[b] Figures in parentheses are the range.
[c] Significantly different from artesunate at $P = 0.000001$ (95% CI = –42 to –24).
[d] Significantly different from artesunate at $P = 0.000041$ (CI = –37 to –16).
[e] S = cure, i.e., no reapparance of parasite within 28 days; RI = disappearance of parasitaemia but reappearance within 28 days; RII = decrease of parasitaemia but parasite never disappears from the peripheral blood; RIII = no marked decrease or even increase in parasitaemia 48 hours after treatment.

Table 3: **Adverse effects among the 64 study patients in the two treatment groups**

	No. of patients	
Adverse effect	Artesunate ($n = 31$)	Quinine–tetracycline ($n = 33$)
Nausea	14 (45)[a]	20 (60)
Dizziness	16 (52)	16 (48)
Vomiting	8 (26)	30 (91)[b]
Tinnitus	0	29 (88)[c]
Convulsions	1 (3)	0
Bradycardia	7 (23)	Not done

[a] Figures in parentheses are percentages.
[b] Significantly different from artesunate ($P = 0.000005$; 95% CI = 0.0083–0.146).
[c] Significantly different from artesunate ($P = 0.000001$).

Discussion

This is the first comparison of the curative efficacy and adverse effects of a 700-mg dose of oral artesunate and quinine–tetracycline for the treatment of multiple-drug-resistant falciparum malaria. Oral artesunate produced a faster reduction in parasitaemia and FCT than the quinine–tetracycline regimen; however, the cure rates of the two treatments were not statistically different. Use of oral artesunate at this dosage regimen is as effective as that reported for oral artemether in the treatment of multiple-drug-resistant falciparum malaria in a recent study (*3*).

In previous studies, artesunate has been associated with high recrudescence rates. The maximum dose of oral artesunate used in these studies was 600 mg and the longest duration was 5 days; nevertheless, the regimen was associated with a recrudescence rate of 10–28% with uncomplicated falciparum malaria (*10–13*). In the present study, the higher dose of 700 mg produced similar PCT and FCT to all the previous studies with intravenous or oral artesunate at different dosage regimens, but the cure rate

was higher. The previous recommended dose for artesunate (600 mg) may not be suitable in areas with high-grade, multiple-drug-resistant malaria because of the high recrudescence rate; however, in other areas this dose may be adequate (*14*).

In Thailand, the second-line therapy for the treatment of falciparum malaria is quinine + tetracycline for 7 days. The cure rate for this combined regimen in the present study was 100%, but because of the long course of treatment and the adverse effects, it is unsuitable for treatment at home due to compliance difficulties. In a recent field study the failure rate was approximately 20% (K. Thimasarn, unpublished observations, 1993). However, under close supervision, the cure rate was found to be satisfactory. The results from the present study confirm the effectiveness of the combination quinine–tetracycline, as previously found for hospitalized patients (*7*).

It is not surprising that most of the patients who received quinine–tetracycline experienced tinnitus. However, this condition seemed to affect the compliance of the patients, and as a consequence resulted in treatment failure. The occurrence of nausea and dizziness was more frequent than that reported in a recent study for a 600 mg total dose of artesunate (*13*). The most striking finding was the occurrence of convulsions in one patient after two doses of artesunate; this has not been reported in previous clinical trials of the drug (*9–13*). The convulsions may not have been due solely to artesunate because they can be caused by malaria as well, although it is uncommon in uncomplicated cases. However, caution should be exercised, particularly with higher doses of artesunate. Monitoring of this adverse effect should be encouraged since there is some evidence from animal studies that higher doses of artemisinin compounds can have an effect on the central nervous system (CNS) (*17*). In dogs a CNS abnormality was observed after a single high dose (400 or 800 mg/kg) of artemisinin, but the effect was transient and disappeared within 48 hours (*17*). The incidence of nausea, dizziness and vomiting found in the present study appears to be greater than that found in a recent report on artemether at a 700-mg total dose (*3*). The bioavailability, pharmacokinetics, and drug metabolism of oral artesunate and artemether clearly need to be determined.

The occurrence of vivax malaria was found within a month of beginning the treatment with either of the two regimens and this is comparable to oral artemether (*4*). The appearance of *P. vivax* indicates the ineffectiveness of artesunate and quinine–tetracycline against the intrahepatic stage of this parasite. Primaquine is therefore, required for radical cure.

In conclusion, the duration of treatment with artesunate is shorter than quinine–tetracycline and there are fewer adverse effects. Furthermore, artesunate has a more rapid PCT and FCT, which should prevent the occurrence of complications in acute uncomplicated falciparum malaria. We suggest that 700 mg of artesunate given over 5 days is an effective alternative antimalarial in areas with multiple-drug-resistant parasites; however, the adverse effects, particularly neurotoxicity, should be closely monitored. In areas where artesunate is not available, quinine–tetracycline can still be used effectively if administered under supervision.

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Résumé

Comparaison entre l'artésunate par voie orale et l'association quinine–tétracycline dans le paludisme à falciparum aigu non compliqué

En Thaïlande, le paludisme à *Plasmodium falciparum* est très résistant aux antipaludéens habituels. Il est donc urgent d'entreprendre des études sur l'efficacité des antipaludéens existants et des médicaments susceptibles de les remplacer. L'artésunate s'est révélé efficace contre le paludisme à falciparum, mais son emploi s'accompagne d'un taux de recrudescence élevé; toutefois, la posologie idéale pour les formes multirésistantes de la maladie reste à déterminer. Nous avons effectué un essai clinique pour comparer le traitement classique avec l'association quinine-tétracycline et l'artésunate par voie orale (dose totale de 700 mg étalée sur cinq jours) dans le paludisme à falciparum aigu non compliqué.

Soixante-quatre patients ont été répartis de façon aléatoire en deux groupes: 33 ont été traités avec la quinine-tétracycline et 31 avec l'artésunate. Tous ont été admis à l'Hôpital des Maladies tropicales de Bangkok pendant 28 jours.

L'artésunate a provoqué la disparition de la parasitémie et de la fièvre plus rapidement que l'association quinine-tétracycline, mais le taux de guérison n'a pas présenté de différence significative. Toutefois, la survenue d'effets indésirables, comme des bourdonnements d'oreille, a été nettement plus élevée dans le groupe traité avec la

quinine-tétracycline. Les nausées et les étourdissements ont été relativement fréquents avec l'artésunate, ce qui est surprenant car ces effets avaient été rarement constatés dans une étude récente portant sur l'artéméther. Il ne faut pas sous-estimer le risque d'effets neurologiques de l'artésunate, car un patient a présenté des convulsions après deux doses de ce médicament.

L'artésunate par voie orale (700 mg répartis en cinq jours) est efficace et mieux toléré que l'association quinine-tétracycline. Le taux de guérison obtenu dans cette étude a été plus élevé que dans des études précédentes au cours desquelles 600 mg avaient été administrés en cinq jours. L'artésunate par voie orale constitue donc une autre forme de traitement possible du paludisme à falciparum multirésistant; toutefois, ses effets secondaires, et notamment sa neurotoxicité, doivent être soigneusement évalués avant que son utilisation généralisée puisse être recommandée. Dans les régions où l'artésunate n'est pas disponible, l'administration de quinine-tétracycline pendant sept jours reste très efficace à condition qu'elle se fasse sous surveillance.

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