# A randomized comparative study of artemisinine (qinghaosu) suppositories and oral quinine in acute falciparum malaria

**Keith Arnold[1], Tran Tinh Hien[2], Nguyen Tran Chinh[3], Nguyen Hoan Phu[3] and Pham Phuong Mai[2]** *[1]Roche Asian Research Foundation, Hong Kong; [2]Cho Quan Hospital, Centre for Tropical Diseases, Ho Chi Minh City, Vietnam; [3]Department of Infectious Diseases, Medical School of Ho Chi Minh City, Cho Quan Hospital, Vietnam*

**Abstract**

In adult patients with acute falciparum malaria in Ho Chi Minh City, Vietnam, a more rapid reduction in parasite count (50% clearance in 11·3 h) and complete clearance (41·8 h) was obtained in 32 adult patients randomly assigned to received artemisinine suppositories than was obtained with 30 patients receiving oral quinine (20·8 h and 68·1 h). There were higher degrees of resistance (RII, 3 cases; RI early, 1 case) with quinine than with artemisinine but in a subgroup of patients quinine reduced parasitaemia as rapidly as artemisinine (50% clearance 13·6 h and 10·1 h respectively). Recrudescence (RI, delayed), occurred in 16 patients receiving artemisinine compared with 6 receiving quinine. Artemisinine suppositories, because of ease of administration, efficacy, and lack of side effects or risk of overdose, have advantages for the early treatment of falciparum malaria by possibly reducing the morbidity and mortality associated with a high or sustained parasitaemia.

## Introduction

Falciparum malaria world-wide is becoming increasingly resistant to available drugs such as chloroquine, sulfadoxine-pyrimethamine and even quinine and mefloquine (WHO, 1987).

Artemisinine (formerly qinghaosu), and its derivatives artemether and artesunate, have been extensively studied in China (DING, 1988) and artemether to a limited extent in Burma (PE THAN MYINT & TIN SHWE, 1987; PE THAN MYINT *et al.*, 1989). Most attention has been given to the oral, intramuscular and intravenous preparations. However, a suppository formulation has been studied by LI *et al.* (1985) and LI (1989) in uncomplicated and severe (cerebral) malaria with good results.

Malaria in Vietnam is a major health problem resulting in serious morbidity and mortality. As in other developing countries probable contributing factors to this high morbidity and mortality are delayed diagnosis and treatment due to lack of trained health care personnel and appropriate drugs in health care facilities, at the hamlet and village level. In addition there may be resistance to available drugs, they may be expensive, have side-effects or be slow-acting.

Although the actual cause of cerebral malaria and other complications is controversial, an increase or continuing high level of parasitaemia in untreated or even treated patients is generally considered something to be prevented since it is associated with morbidity and mortality. A rapid decrease in parasitaemia is desirable during the early hours or days of the disease.

The advantage of a suppository, that would make it useful for initial or presumptive treatment in communities highly endemic for malaria, is that it can be readily administered by a health worker or a household member or the patient him- or herself. If it is rapidly effective in lowering parasitaemia and is safe, it may reduce morbidity and mortality.

Before testing this hypothesis in the field a highly intensive monitoring trial was performed in a hospital setting to examine the efficacy and safety of a suppository formulation of artemisinine.

## Patients and Methods

The study was carried out between February and June 1989 in Cho Quan Infectious Diseases Hospital, Ho Chi Minh City, Vietnam. This hospital receives patients from surrounding provinces and suburban areas of the city where malaria is endemic and patients from within the city who have visited such areas. In 1988 there were 7330 patients admitted with malaria of whom 132 died. Most (64·1%) of the patients admitted had *Plasmodium falciparum* infections.

All patients attending the hospital were first seen in an out-patient department. Febrile patients and anyone with a possible differential diagnosis of malaria had an immediate malaria smear performed. For this study, if the smear was positive for *P. falciparum* and the patient was aged 15–60 years, a urine test for chloroquine or amodiaquine (Dill-Glazko) and sulphonamides (lignin) was carried out. If these were negative the patient was admitted to a study ward.

On admission to the ward, if the patient was not confused or in coma, gave a negative history for antimalaria drug treatment for the present illness, was not pregnant, and did not have heart, liver or renal disease, a repeat blood smear and quantitative asexual *P. falciparum* parasite count was performed (patients with *P. vivax* and mixed infections were excluded). If this was between 1000 and 150 000/µl, the patient, using a table of random numbers, was assigned to receive either artemisinine suppositories* (600 mg at zero and 4 h followed by 400 mg at 24, 32, 48 and 56 h), or quinine sulphate orally (1500 mg in 3 divided doses daily for 14 consecutive days).

Before treatment was started blood was drawn for haematology (haematocrit and red and white blood

Correspondence to Dr K. Arnold, P.O. Box 98595, Tsim Sha Tsui Post Office, Hong Kong.

*Kindly supplied by Dr Li Guo Qiao, Sanya Tropical Disease Institute, Guangzhou College of Traditional Chinese Medicine, Hainan Island, China.

cell, platelet, and reticulocyte counts) and glucose and creatinine levels. These tests were repeated on days 3 and 7 during the period in hospital. The temperature (axillary) was recorded and a quantitative asexual parasite count performed (Giemsa stain, thick film; numbers of parasites per 400 leucocytes) every 6 h until they became normal or negative respectively on 4 consecutive readings. Daily temperature and parasite counts were then carried out until day 7 and then on days 14, 21 and 28.

*Assessment of response to treatment.* Standard measures of response to treatment were used, such as time to clear parasitaemia and to return to normal temperature (the first of 4 consecutive normal readings). However since rapid lowering of initial parasitaemia is desirable, the rate of parasite clearance was calculated by plotting 6 hourly counts as a percentage of the initial count and measuring the time taken to achieve 50% clearance.

The World Health Organization (WHO) standard field and extended tests (WHO, 1973), although devised for chloroquine treatment, were used to evaluate drug response. For this study an RIII (resistant) response was defined as no decrease from the initial count for 6 consecutive counts (36 h), at which time alternative treatment would be given, or given earlier if the patient's clinical condition deteriorated. An RII response was recorded when the count decreased but was still positive by day 7. An RI response was of 2 types, an early recrudescence when the parasites were cleared by day 6 but returned by day 7, or a delayed recrudescence when there was clearance by day 7 but return of parasitaemia before or on day 28. An S (sensitive) response was clearance by day 7 and no return of parasitaemia by day 28. In patients who cleared parasitaemia by day 7 but were lost to follow-up before day 28 it was not possible to distinguish between an S or RI (delayed response), recorded as S/RI.

Patients who failed to respond to treatment or who suffered recrudescence were given sulfadoxine-pyrimethamine-mefloquine.

Patients were observed closely for side effects of the drugs. Each patient gave oral permission to be included in the study and ethical permission to perform the study was obtained from the hospital director and the director of Health Services for Ho Chi Minh City.

## Results

Sixty-two patients were treated, with 32 receiving artemisinine and 30 quinine. Table 1 gives patient characteristics and shows comparability of the 2 treatment groups as regards age, pre-treatment laboratory values and initial parasitaemia, as well as follow-up reticulocyte counts.

There was a significant difference between artemisinine and quinine in the time to clear parasitaemia and the rate of parasite clearance (Table 2), with artemisinine taking 41·8 h and 11·3 h (50% clearance) respectively, compared with 68·1 h and 20·8 h for quinine. Return to normal temperature occurred in 29·8 h for artemisinine and 38·8 h for patients receiving quinine.

There were no RIII response in either group, but 3 (10%) RII responses and 7 (23·3%) RI responses for quinine (6 RI, delayed and 1 RI, early). There were no RII responses with artemisinine but there were 16 (50%) RI (delayed) responses. Although investigators went to the homes of patients on days 14, 21 and 28 to perform follow-up blood smears, 13 patients were not available on day 28. These patients were considered therefore as S/RI (delayed) responses with 8 and 5 patients respectively in the quinine and artemisinine groups. Overall this gives 12 (40%) and 11 (34%) sensitive responses for the patients receiving quinine and artemisinine respectively (Table 2).

Of the 32 patients treated with artemisinine, 27 had a lower parasite count at 6 h (mean of 67% of original 100% count at zero time) which continued falling, while 5 patients had a rise at 6 h (mean 175%) which fell to 59% at 12 h. Of the 30 patients receiving quinine, only 17 had a lower count at 6 h (mean 65% of original 100% count at zero time) which continued falling, while 7 had a rise at 6 h (mean 191%) with readings of 154% at 12 h and 76% at 18 h and

**Table 1. Characteristics of artemisinine and quinine treatment groups[a]**

| | Artemisinine | Quinine |
|---|---|---|
| Males | 31 | 27 |
| Females | 1 | 3 |
| Mean age (years) | 28·8±9·1[b] | 28·3±8·3[b] |
| Range | 17–56 | 17–50 |
| Temperature on admission (°C) | 38·7±1·2[b] | 38·9±1·3[b] |
| Range | 37–41 | 37–41 |
| Red blood cells ($10^6$/mm$^3$) | 3·6±0·7[b] | 3·6±0·9[b] |
| White blood cells (per mm$^3$) | 5470±2085[b] | 5601±1829 |
| Platelets (per mm$^3$) | 146000±67000[b] | 170000±62500[b] |
| Reticulocyte count (%) | | |
| Day 0 | 1·1 | 1·2 |
| Day 3 | 1·2 | 1·6 |
| Day 7 | 1·7 | 2·1 |
| Serum creatinine (μmol/litre) | 106±35 | 102±33 |
| Blood sugar (mmol/litre) | 5·7±0·99 | 5·6±1·19 |
| Mean parasitaemia (per μl) | 20634±4873[c] | 22056±4736[c] |
| Range | 1080–135 640 | 1040–113 660 |

[a]There was no statistically significant difference ($P>0·05$) in the listed characteristics between treatment groups.
[b]Standard deviation.
[c]Standard error.

**Table 2. Results of treatment**

| | Artemisinine | Quinine | *P* |
|---|---|---|---|
| Fever clearance time (h)[a] | 29·8±21·3 | 38·8±21·6 | >0·05 |
| Parasite clearance time[b] | | | |
| 50% | 11·3± 6·4 | 20·8±14·7 | <0·05 |
| 50%[c] | 10·1± 6·2 | 13·6± 8·3 | >0·05 |
| 100% | 41·8±10·1 | 68·1±34·6 | <0·05 |
| S (sensitive) | 11 (34%) | 12 (40%) | >0·05 |
| S/RI | 5 | 8 | |
| RI | 16 (50%) | 7 (23·3%) | <0·05 |
| RII | 0 | 3 (10%) | |
| RIII | 0 | 0 | |

[a]Mean±standard deviation.
[b]Mean±standard deviation. Initial parasite count was taken as 100% and 6 hourly parasite counts plotted as a percentage of this against time. The 50% clearance rate is the time taken to reach half the initial count; 100% clearance is the time taken for complete clearance (the first of 4 consecutive 6 hourly negative counts).
[c]27 artemisinine vs 17 quinine treated patients (see text and Figure).

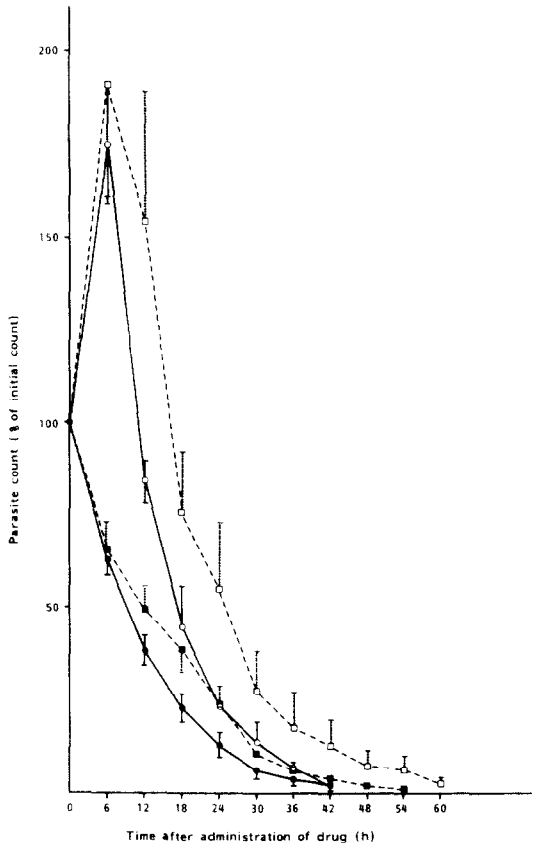


Figure. Rate of parasite clearance with artemisinine and quinine. ●——● Group A artemisinine: 27 patients; 6 h count < zero time count. ○——○ Group B artemisinine: 5 patients; 6 h count > zero count. ■——■ Group A quinine: 17 patients; 6 h count < zero time count. □——□ Group B quinine: 7 patients; 6 h count > zero time count. The immediate pretreatment count was taken as 100% and subsequent 6 h counts plotted as mean±standard error of this initial count.

subsequent decreases (Figure). The remaining 6 patients treated with quinine (3 of whom were RII) had very fluctuating parasite counts.

If the 50% clearance time of the 27 patients receiving artemisinine (referred to above) is compared with the 17 similarly responding quinine patients, there is no significant difference, 10·1 h vs 13·6 h respectively. But due to the small number of patients a type II or β error cannot be excluded.

Side effects in patients receiving quinine included mild nausea, dizziness and occasional tinnitus. No side effects were reported in patients treated with artemisinine. There was no anal irritation or complaints of proctitis.

The laboratory data were unremarkable. Because of reported accounts of artemisinine affecting the reticulocyte count, this was performed on days 0, 3 and 7 and the results (Table 1) did not show any appreciable effect of either drug. The total leucocyte count, blood sugar and creatinine values were not abnormal before treatment or on follow-up. The haematocrit and erythrocyte counts were initially lower than normal in many patients but recovered in some; the problem of differentiating dietary causes from the effects of the disease itself limits further interpretation of these observations.

## Discussion

This study showed that artemisinine suppositories rapidly reduce and quickly clear *P. falciparum* asexual parasites. The suppositories are easily administered, well tolerated systemically and locally, but may have a delayed RI resistance response. These observations have been previously noted by Li (1989), who found return to normal temperature in 15–39 h and parasite clearance in 35–52 h. Li and colleagues (personal communication) have also studied the pharmacokinetics of artemisinine suppositories and found a $C_{max}$ of 129·7 mg/litre and a $t_{max}$ of 6·6 h with a β half life of 4·2 h at a dose of 10 mg/kg.

Oral quinine in this study cleared parasitaemia rapidly in many patients (17 of 30) but there were several patients who developed high parasite counts after starting the drug and who had a fluctuating, prolonged parasitaemia. The clinical impression of the treating physicians is that quinine, both orally and intravenously, is becoming less effective than in previous years.

Quinine if used alone needs to be given for 10–14 d in order to prevent delayed recrudescences but in this study recrudescences still occurred even with this long duration of treatment. Quinine has side effects and compliance is a problem, even if given for only 7–10 d in association with another drug such as tetracycline.

Vietnam and other countries with a serious malaria situation need to diagnose and treat patients early in the disease but it is difficult to establish an efficient community health care system to do this because of limited resources. Presumptive treatment is an alternative approach, but which drugs and at what level of health care delivery should such drugs be made available?

Oral drugs are the only ones that could be made available at the most remote health station or in the home, but there are few of them, there is resistance, they have side effects, and they may be expensive. The most important reason they are not readily available in the home is because there is the problem of misuse, accidental or intentional overdose and self-poisoning by children.

None of these considerations applies to artemisinine suppositories, especially the last, since chidren would have difficulty swallowing them because of their size and to overdose rectally presents practical problems.

The most serious disadvantage of artemisinine is the delayed RI response. Further dose-finding studies with more prolonged treatment need to be performed. In the meantime this can be managed by giving all patients who receive artemisinine a single dose of either mefloquine or a combination preparation.

A further consideration concerning the use of suppositories is that they may be extruded spontaneously, or with a diarrhoeal stool, without being noticed. Therefore a false sense of security regarding sufficient dosage is a potential danger.

If the provision of artemisinine suppositories for presumptive treatment is decided upon, educational efforts would have to be made concerning the

acceptibility of this mode of therapy and the reasons why all patients must attend as soon as possible at the nearest health station for confirmation of the diagnosis and to receive supplementary treatment. Any disadvantages of such an approach are outweighed by managing early and successfully the acute emergency of a high, sustained or rising parasitaemia.

In conclusion, oral quinine clears parasitaemia rapidly in patients that have sensitive *P. falciparum* parasites. Artemisinine suppositories also clear parasitaemia rapidly and with minimal side effects. If these suppositories are used as presumptive or early treatment in the community, the morbidity and mortality from falciparum malaria may be reduced. A field trial is indicated.

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