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# Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in the treatment of cerebral malaria

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## Abstract

Seventy-nine comatose cerebral malaria patients given standard supportive treatment were randomized to receive specific antimalarial chemotherapy of intravenous quinine, intravenous artesunate, or artemisinin suppositories. Artesunate and artemisinin reduced peripheral asexual parasitaemia significantly more rapidly than quinine (90% clearance time 16 h, 18·9 h and 34·5 h respectively), but did not significantly reduce the duration of coma or mortality. The rapid lowering of peripheral parasitaemia may not ameliorate complications already present. These results demonstrate that artemisinin suppositories are as effective as artesunate and quinine given intravenously, and have economic and practical advantages for the treatment of severe malaria in areas remote from major medical centres. However, large numbers of patients will need to be studied if differences in mortality between the 3 treatment groups are to be demonstrated.

## Introduction

Artemisinin and its derivative artemether, previously extensively studied in China, have now been examined in Burma (PE THAN MYINT & TIN SHWE, 1987; PE THAN MYINT *et al.*, 1989) and Vietnam (ARNOLD *et al.*, 1990; HIEN *et al.*, 1991). Intravenous (i.v.) artesunate and artemisinin suppositories have been shown to be very effective in China in uncomplicated and severe falciparum malaria (LI *et al.*, 1985). Quinine i.v. is the standard recommended treatment for complicated or severe malaria in other countries but, since resistance of *Plasmodium falciparum* to quinine has been reported (WHO, 1987) and is appearing in Vietnam (ARNOLD *et al.*, 1990; HIEN *et al.*, 1991), there is a need for alternative drugs. Parenteral artesunate or artemether are such alternatives but in countries where severe malaria is a major problem these drugs are not available and must be imported at high cost. Also the necessary sterile facilities and basic parenteral administration equipment are not readily available. Artemisinin is more easily and economically obtained and, if effective and safe when given as suppositories, could be a useful alternative to i.v. quinine.

## Patients and Methods

The study was carried out in the intensive care unit of the Centre for Tropical Diseases, Cho Quan Hospital, Ho Chi Minh City, Vietnam, in 1989–1990. Informed oral consent was obtained from the patients' families and ethical clearance was given by the hospital scientific committee. The criteria for inclusion into the study were the presence of asexual forms of *P. falciparum* in the peripheral blood and clinical signs of malaria with unrousable coma (Glasgow coma scale <10). All patients had a spinal tap with examination of the cerebrospinal fluid to exclude other causes of coma. On admission a history was obtained and a physical examination performed. Blood was taken for a full blood count, glucose and creatinine determination. Liver function tests were carried out if indicated. Thick and thin films for a peripheral blood asexual parasite count (Giemsa stain, thick film, number of parasites per 400 white blood cells) were performed every 4 h for 12 h, then 6-hourly until 3 consecutive examinations were negative. The patients were randomized to receive either artesunate intravenously (60 mg at 0 and 4 h followed by 60 mg at 24 and 48 h), artemisinin suppositories (600 mg at 0 and 4 h followed by 400 mg at 24, 32, 48, and 56 h), or quinine dihydrochloride intravenously (500 mg diluted in 250 ml 5% dextrose given over 4 h, repeated 8-hourly) until the patients could swallow. After this the i.v. artesunate and artemisinin suppository group received a single dose of mefloquine 500 mg, and the i.v. quinine group continued with oral quinine sulphate 500 mg every 8 h to complete 14 d treatment. All patients were managed according to World Health Organization recommendations (WHO, 1986). Blood pressure, axillary temperature, pulse rate and Glasgow coma score were measured at 3 h intervals until fever clearance and full recovery of consciousness, and at 6 h intervals thereafter. The 3 treatments were compared with respect to fever clearance time, time to regain full consciousness (Glasgow coma scale=15), parasite clearance time (50%, 90% and 100%), and mortality rate.

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## Results

Seventy-nine patients were studied, 31 receiving i.v. artesunate, 30 i.v. quinine, and 18 artemisinin suppositories. The admission variables, including coma duration before admission, admission Glasgow coma score and admission parasitaemia were comparable with no significant differences ($P>0·05$), as shown in Table 1. Artesunate i.v. was significantly faster than i.v. quinine for fever clearance time, 50% parasite clearance time, 90% parasite clearance time, and 100% parasite clearance time (Table 2 and Figure). However, duration of coma (the time from admission to full recovery of consciousness) was not significantly different in the 2 groups, nor was the overall mortality (Table 2). 50% and 90% parasite clearance times were significantly faster in patients receiving artemisinin suppositories than in patients receiving i.v. quinine (Table 2 and Figure). However, there was no

**Table 1. Admission variables of the three groups of patients**

| | Artesunate intravenous | Artemisinin suppository | Quinine intravenous |
|---|---|---|---|
| No. of patients | 31 | 18 | 30 |
| Male/female | 26/5 | 18/0 | 26/4 |
| Age (years) | | | |
| Mean | 29 | 30 | 28 |
| Range | 16–50 | 15–50 | 19–52 |
| Temperature (°C)[a] | 38·8 (1·0) | 38·1 (0·9) | 38·4 (0·7) |
| Coma duration before admission (h)[a] | 15 (16) | 21 (19) | 13 (11) |
| Glasgow coma scale[a] | 7·48 (2·12) | 7·56 (1·17) | 6·78 (2·3) |
| Haematocrit (%)[a] | 28 (8) | 29 (9) | 30 (7) |
| Leucocytes (no./μl)[a] | 11854 (6890) | 10394 (3565) | 11276 (12363) |
| Blood sugar (μmol/litre)[a] | 7·74 (3·38) | 6·66 (2·22) | 7·23 (1·93) |
| Creatinine (μmol/litre)[a] | 210·00 (173·64) | 278·18 (157·27) | 226·36 (191·8) |
| Parasitaemia on admission | | | |
| Mean[a] | 48034 (62782) | 30553 (44211) | 61204 (136149) |
| Geometric mean | 18323 | 12133 | 17100 |
| Range | 676–248000 | 860–168959 | 1730–657300 |

[a]Mean (standard deviation in parentheses).

**Table 2. Therapeutic response in the three groups of patients**

| | Artesunate intravenous | Artemisinin suppository | Quinine intravenous |
|---|---|---|---|
| Fever clearance time (h)[a] | 39 (30) | 77 (48) | 78 (102) |
| Parasite clearance time (h)[a] | | | |
| 50% | 5·4 (3·2) | 9·7 (7·2) | 16·6 (10·7) |
| 90% | 16·0 (7·7) | 18·9 (8·2) | 34·5 (13·8) |
| 100% | 28·1 (11·2) | 37·9 (17·4) | 51·2 (23·2) |
| Time to regain full consciousness[b] | | | |
| Mean (range) | 68·9 (5–453) | 56·1 (12–120) | 58·1 (7–144) |
| Median | 35 | 49 | 48 |
| Mode | 17 | 24 | 43 |
| Deaths | 5 (16·5%) | 5 (27·8%) | 8 (26·7%) |

[a]Mean (standard deviation in parentheses).
[b]Glasgow coma scale=15.

significant difference in 100% parasite clearance time, fever clearance time, coma duration and mortality (Table 2). Four of the 5 patients who died in the artesunate and artemisinin groups had a fall in peripheral parasitaemia

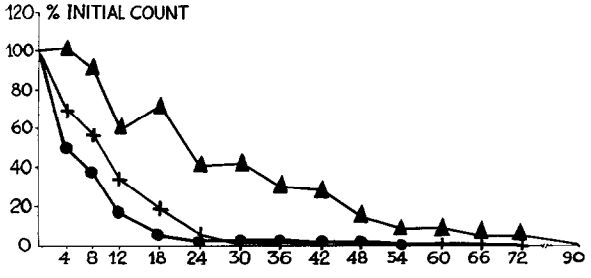


Figure. Parasite clearance expressed as a percentage of initial parasite count for the three treatment groups: ● artesunate group; + artemisinin group; ▲ quinine group.

or achieved parasite clearance before death, while 2 quinine patients were still positive and 5 had increased parasitaemia. Most deaths were due to acute renal failure. As in previous studies no side effect was reported by patients receiving artesunate or artemisinin.

## Discussion

There were fewer patients in the artemisinin group because the sole manufacturer of the suppositories in China ceased production and no further supply was available. The study was therefore terminated prematurely. The results confirm the efficacy of i.v. artesunate and artemisinin suppositories in rapidly reducing parasitaemia in severe malaria, but do not demonstrate a significantly beneficial effect on duration of coma or mortality. Because of the small sample size, a type II error may be present leading to a false 'insignificant' conclusion regarding duration of coma and mortality, since rapid reduction of parasitaemia is thought to be beneficial. However, peripheral parasitaemia counts may not take account of sequestration and cytoadherence (WHITE & KRISHNA, 1989) and, if this is so, rapid lowering of high peripheral parasitaemia may be more important in preventing complications than in ameliorating complications already present. The slow clearance of parasitaemia with quinine, the occurrence of positive blood films at the time of death, and the delayed response to treatment seen by clinicians suggest that quinine resistance or the dosing schedule used may be a problem in Vietnam. Since January 1991 Vietnam has started growing *Artemisia annua* commercially and is producing artemisinin suppositories. The Vietnam government is keen to promote artemisinin suppositories for use throughout Vietnam. A large study is indicated to determine whether i.v. artesunate and artemisinin suppositories reduce mortality better than i.v. quinine. There is a need to confirm the artemisinin results because administration by suppositories is obviously more convenient, economical and potentially more practical when treating such seriously ill patients in community hospitals far away from major medical centres.

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