

INTRAMUSCULAR ARTEMETHER IN FEMALE PATIENTS WITH UNCOMPLICATED FALCIPARUM MALARIA

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Abstract. Thirty-three female patients suffering from acute uncomplicated falciparum malaria were treated with intramuscular artemether for 5 days during May-October 1990. Fourteen patients received 160 mg as an initial dose, followed by 80 mg daily for 4 days. Nineteen patients with low body weight (mean weight of 36.5 kg) were given artemether at 3.2/kg as a loading dose and followed by 1.6 mg/kg/dose for another 4 days. The geometric mean of parasitemia was 17,378/ μ l (range 640-234,720). The mean fever (FCT) and parasite clearance time (PCT) were 41.8 and 49.4 hours, respectively. Two patients had probable intercurrent infection with FCT of over 7 days. Thirty-one patients had completed the 28-day follow-up. The cure rate was 90.3% (28/31). Three patients had RI type of response.

Mild and transient adverse effects were experienced in eleven patients; these consisted of pain at the injection sites, vomiting, dizziness, abdominal pain, palpitation and diarrhea. These symptoms may in part be due to symptom complex of malaria.

The MIC of chloroquine, quinine, quinidine and mefloquine was performed in all patients but only 25 isolates were successfully cultured and tested. The MIC of all tested drugs were shown to be higher than that of previous studies, suggesting that there is a rapid increase of mefloquine resistant strains of falciparum malaria.

In conclusion, artemether proves to be effective against multiple drug resistant falciparum malaria (including mefloquine resistant strains) and can be considered as an alternative antimalarial to mefloquine. The drug was well tolerated in female patients with mild and transient side-effects. Further studies should be carried out to find the optimum dosage regimen to achieve the cure rate of 100% which is needed in areas with multiple drug resistant strains of falciparum.

INTRODUCTION

Artemether is a derivative of artemisinin, it has been shown to be an effective antimalarial drug (Wang and Xu, 1985; Pe Than Myint and Tin Shwe, 1986; 1987). It rapidly clears asexual parasitemia with virtually no side-effects (Bunnag *et al*, 1991a; China Cooperative Research Group, 1982a). Artemether is a promising drug in the treatment of multiple drug resistant parasites. Its efficacy was mainly shown in male patients, there is very limited information on the use of artemether in female patients.

The cure rate of artemisinin group of compounds has been associated with duration of treatment and dose given. Based on the study with artesunate, the dose should be at least 480 mg and the duration of 5 days (Bunnag *et al*, 1991a). We have carried out a study with intramuscular artemether

at maximum dose of 480 mg given over 5 days in female patients with uncomplicated multiple drug resistant falciparum malaria.

PATIENTS AND METHODS

Patients

Thirty-three patients with acute uncomplicated falciparum malaria (asexual form parasitemia of less than 5%), aged between 15 to 60 years and weight range 45 to 60 kg, with no history of liver or kidney diseases were recruited into the study. All patients underwent pregnancy tests, only those with negative pregnancy test were enrolled into the study. Written informed consent to participate in the study was obtained from all patients. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

Each patient had history taken for previous treatment with other antimalarials. Prior to treatment, blood smear was taken for malaria identification and venous blood of 5 ml was drawn for *in vitro* sensitivity test. All patients were admitted in the Bangkok Hospital for Tropical Diseases for 28 days.

Treatment

Artemether (Arthermin[®]) was given according to weight as follows:

Weight > 45 kg: artemether 160 mg IM initial dose, followed by 80 mg IM daily × 4 days

Weight < 45 kg: artemether 3.2 mg/kg IM as loading dose, followed by 1.6 mg/kg IM daily × 4 days

Patients who failed to respond to treatment were treated with quinine sulphate 600 mg at 8 hourly and tetracycline 250 mg four times a day for 7 days. Patients with *Plasmodium vivax* during the 28 day follow-up were treated with chloroquine 150 mg (base) for temporary relief and followed by a full therapeutic course with primaquine after day 28.

Parasite identification

Parasite identification was performed six hourly until negative then once daily until day 28.

Laboratory

Complete blood count, biochemistry were done on admission and days 2, 4, 7 and then weekly until day 28. ECG was done daily for 7 days then weekly for the rest of the period.

Adverse effects

All adverse reactions during the study were recorded with the date and time when they occurred and disappeared. The severity was grading as 1 for normal, 2 for mild, 3 for moderate and 4 for severe. All the abnormalities that were possibly attributable to artemether were recorded.

In vitro sensitivity test

This was performed in all patients prior to drug administration, using microtechnique (Rieckmann *et al*, 1978).

Data analysis

The patients were included for efficacy assessment if they had a complete 28 day follow-up. The parameters that were used in determination of the out-come included fever and parasite clearance times, the rate of recrudescence (R I, II, III) and the occurrence of adverse effects.

RESULTS

Thirty-three female patients with acute uncomplicated falciparum malaria were included in the study. Admission clinical and laboratory data are shown in Table 1. All patients were presented with acute symptoms of malaria. Fourteen patients received 480 mg total dose and 19 patients had a weight of lower than 45 kg, thus received 3.2 mg/kg as a loading dose and followed by 1.6 mg/kg/dose for another 4 days.

All patients had a rapid initial response with mean PCT and FCT of 44.5 and 45.6 hours, respectively (Table 2). Two patients had prolonged FCT which was associated with intercurrent infection. Two patients did not complete the 28 day follow-up period for social reasons but all of them left the hospital without parasitemia on days 18 and 21. Three patients showed reappearance of

Table 1

Admission clinical and laboratory data.

Age (years, mean ± SD)	23.0 ± 8.3
Weight (kg, mean ± SD)	55.1 ± 7.9
Parasitemia (Geometric mean)	136,018
(range)	(28,680-359,100)
Hct (%)	36.5 ± 8.7

Table 2

Therapeutic response.

FCT (hours)	41.8 ± 24.1
PCT (hours)	49.4 ± 14.2
S	28 (90.3%)
RI	3 (9.7%)
RII	0
RIII	0
S/RI	2

Table 3
In vitro sensitivity test.

Drug	MIC μ M (mean \pm SD)
Chloroquine	1.1 \pm 0.7
Quinine	4.2 \pm 3.0
Quinidine	1.5 \pm 0.8
Mefloquine	0.3 \pm 0.2

falciparum parasites on days 22, 27 and 28. The cure rate was 90.3%, based on 31 patients. Five patients developed vivax malaria between days 11 and 23.

Side-effects were few, mild and self-limiting. The symptoms composed of pain at the injection sites, vomiting, dizziness, abdominal pain, palpitation and diarrhea. There were no significant drug related blood profile, biochemical and ECG changes during the course follow-up in either group.

Twenty-five isolates were successfully cultured and tested for drug sensitivity. The MIC of chloroquine, quinine, quinidine and mefloquine are shown in Table 3.

DISCUSSION

There is very limited information on the use of artemether in female which may be due to its side-effects in the fetus in animal studies (China Cooperative Research Group, 1982b). The drug is still contraindicated in pregnancy. In areas where multiple drug resistant strains of falciparum exist, there are numbers of female patients suffering from malaria. It is therefore important to have alternative drugs available for female patients as well as male patient.

Artemether (Arthermin[®]) at the total dose of 600 mg given daily over 5 days in female patients were well tolerated. All except two patients were free from symptoms and parasitemia within 48 hours. The cure rate of 90% obtained from the present study was higher than that obtained from oral artesunate at 600 mg given over 5 days in our two previous studies (Bunnag *et al.*, 1991b, c). It is not clear whether artemether is more potent than artesunate or not, from the present data as the route of administration was different. The bio-

availability of the two drugs is not known. The interpretation would be possible if the pharmacokinetics of the two drugs in falciparum malaria patients were available. However, it is obvious that intramuscular artemether would be a better choice than oral artesunate in severe falciparum malaria. The therapeutic efficacy of intramuscular artemether was better than intravenous artesunate in a comparative study performed in 34 cerebral malaria patients in China. The cure rate was 94% with artemether and 86% with artesunate (Li *et al.*, 1982). Although pharmacokinetics of artemether and artesunate in malaria patients are not available, based on pharmacokinetics in animal studies and limited studies in healthy volunteers, the lower cure rate from artesunate may be due to its shorter half-life than artemether, thus more asexual parasites can escape destruction and be able to complete the maturation cycle and proliferate (Trigg 1987; China Cooperative Research Group, 1982c).

The cure rate of 90% obtained from the present study is not satisfactory in areas with multiple drug resistance, as there are numbers of parasites which can escape destruction and further spreading of the resistant strains. Although the cure rate is not 100%, we still consider artemether as alternative antimalarial to mefloquine or quinine because of its rapid action on the small ring which would prevent further development of the parasites to older forms and this could reduce the risk of severe malaria. Further studies are clearly needed to assess the curative efficacy of different dosage regimens of artemether. Parenteral artemether followed by oral administration is another regimen that needs to be explored, as it would be relevant in the practical use of this drug in clinical malaria.

Vivax malaria was found as early as day 11 in the present study. This is in accordance with that found with artesunate (Bunnag *et al.*, 1991a, b, c) which confirm the ineffectiveness of artemether against exoerythrocytic stages of *P. vivax*, thus, primaquine is still required for radical cure of vivax malaria.

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