EFFECT OF ARTEMETHER ON ELECTROCARDIOGRAM IN SEVERE FALCIPARUM MALARIA

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Abstract. The effect of intramuscular artemether (intramuscular loading dose of 160 mg, followed by 80 mg daily for another 6 doses), in comparison with that of quinine (intravenous infusion of loading dose of 20 mg/kg, followed by 10 mg/kg *q* 8 hourly for 7 days), on the electrocardiograph of severe falciparum malaria patients were investigated in 102 Thai patients (92 males, 10 females) admitted to Pra Pokklao Hospital, Chantaburi, southeast of Thailand. Fifty patients (19 with quinine and 31 with artemether) were eligible for ECG analysis. Hypotension was found significantly more common in the quinine group (13 *vs* 2 cases). Thirteen, 5 and 1 patients with quinine treatment, respectively, had tachycardia, non-specific T-wave change and QTc prolongation. No significant dysrhythmia was found despite high plasma quinine concentrations. Five patients died; their ECGs were not significantly different from those who survived. In the group with intramuscular artemether, 17 cases had tachycardia prior to artemether treatment. QTc prolongation and non-specific T-wave change were found in 2 and 6 cases. One patient had RBBB and second degree AV-block on Day 1, but returned to normal on Day 2. No other dysrhythmia or other significant changes in ECG tracing which would suggest any effect of artemether on cardiovascular system were observed.

INTRODUCTION

Quinine has been the drug of choice in severe falciparum malaria, but RIII type response has recently been reported (Karbwang *et al,* 1994). Widespread multidrug resistant falciparum is increasing (Wernsdorfer, 1994). Alternative drugs for the treatment of severe falciparum malaria are urgently needed. Artemether has been demonstrated to be effective in chloroquine-resistant falciparum malaria in China, Myanmar and Thailand (Bunnag *et al,* 1991, 1992); China Cooperative Research Group on Qinghasu and Its Derivatives as Antimalarials, 1982; Karbwang *et al,* 1992; Myint and Shwe, 1987; Myint *et al,* 1989). Its action in rapid; more than 90% of parasitemia is cleared wihin 24 hours. However, information on its side-effects are very limited. Being a potent antimalarial, clarification on its cardiovascular toxicity is required. We have investigated the effect of intramuscular artemether on the electrocardiogram (ECG) of severe falciparum malaria patients in comparison with the ECGs of patients receiving quinine.

MATERIALS AND METHODS

Patients and methods

The study was carried out at the Pra Pokklao Hospital, Chantaburi Province, southeastern part of Thailand, the area where multidrug resistant falciparum malaria exists. The study was performed during 1992-1994. Male and female (non-pregnant) severe falciparum malaria patients (World Health Organization, 1990) with no history of antimalarial treatment within 24 hours prior to admission, aged between 15-65 years and weighing 45-75 kg, were recruited into the study. Patients with concurrent diseases were not included. Written informed consent for participation to the study was obtained from all patients. The study was approved by the Ethics Committee of the Ministry of Public Health, Bangkok, Thailand.

Patients were randomized to receive either quinine or artemether as follows:

Quinine group: a loading dose of quinine dihydrochloride at 20 mg/kg (intravenous infusion), fol-

lowed by 10 mg/kg *q* 8 hourly for 7 days.

Quinine sulfate was given instead of quinine dihydrochloride as soon as the oral medication was possible. The loading dose was not given to those patients with history of previous oral antimalarial treatment.

Artemether group: a loading dose of intramuscular artemether at 160 mg, followed by 80 mg, daily for another 6 doses.

Dialysis was performed in patients with acute renal failure; the decision was made by the attending physicians.

Electrocardiographic monitoring

Electrocardiogram (ECG) was performed on admission in all patients, and once daily in the quinine group (at 2 hours following infusion of the first dose of the day, until parenteral quinine was discontinued). Patients in the artemether group had ECG recorded at 6 hours after injection (expected to be at peak concentration of artemether) daily until 6 hours after the last dose.

A simultaneous 12-lead computerized ECG recorder and analyzer was used to perform all ECGs. PR, QRS, QTc and RR intervals were measured simultaneously by computer (Seimen®, Sweden). All the electrocardiographic tracings were reviewed by a cardiologist.

Blood pressure monitoring

Blood pressure was monitored every 4 hours throughout the study period.

Baseline quinine levels

Pre-treatment plasma quinine levels in all patients were measured by high performance liquid chromotography according to the method of Karbwang *et al* (1989).

Data analysis

Abnormal ECG tracings were evaluated for the possible cardiotoxic effects of artemether or quinine. The patients with previous treatment based on detection of pre-treatment drug concentrations were excluded from the ECG analysis. Comparison was made between the 2 treatment using Fisher's exact (for proportions) and Mann-Whitney U test (for the prolongation of the QTc intervals) at a statistical significance level of $p = 0.05$. Correlation between the drug concentrations and QTc prolongation was performed using Spearman's Rank Correlation test at the same statistical significance level.

RESULTS

One-hundred and two Thai patients with severe falciparum malaria (92 males and 10 females) were randomized to receive either the standard regimen of quinine infusion or intramuscular artemether. Only 50 patients were eligible for the ECG analysis (patients with no plasma pre-treatment drug concentration); 19 received quinine and 31 received artemether. The patients in both groups were comparable in age, body weight, admission parasitemia, hematocrit, white cell count, coma score (cerebral malaria).

Hypotension was found to be significantly more common in quinine group (13 *vs* 2, $p = 0.007$). Thirteen patients had tachycardia, 5 had nonspecific T-wave changes and one had prolongation of QTc interval on admission (pre-treatment). QTc prolongation, notch- and T-wave changes were common findings after quinine treatment. However, no significant dysrhythmia was observed during ECG monitoring, despite high concentration of quinine in some patients. Five patients out of 19 patients with quinine died: the ECGs on these patients were not significantly different from those who survived. No significant difference was seen on Days 0, 1, 3, 4, 5, 6 and 7, but the QTcs on Day 2 were significantly longer in patients who survived despite lower quinine concentrations.

Tachycardia was found at pre-artemether administration in 17 patients, QTc prolongation was found in 2 patients and non-specific T-wave change was found in 6 patients. One patient had RBBB and second degree AV block on day 1 but returned to normal on Day 2. No other dysrhythmia or other significant changes in ECG tracing were observed which would suggest any effect of artemether on cardiovascular system.

DISCUSSION

Quinine is the drug of choice for the treatment of severe falciparum malaria for many decades. Its cardiovascular side-effect has been known with prolongation of QTc, as well as hypotension, as a major cardiovascular effect. However, sudden death with ventricular tachycardia or ventricular fibrillation from quinine toxicity in malaria treatment has not been reported. A concentration of over 20 mg/l is often seen in severe malaria patients treated with quinine, but no severe cardiovascular side-effects were observed. This is due to the increase in α_1- acid glycoprotein during acute infection, resulting in an increase in quinine protein binding (Silamut et al, 1985). In this study, no severe arrhythmia was seen with the patients receiving quinine. Common findings such as non-specific T-wave change, notch T-wave and prolongation of QTc interval could be either the effect of malaria infection (as 5 patients already had these changes pre-treatment), or the effect of the drug. Modulation of sympathetic tone, fluid and electrolyte imbalance could also produce these abnormalities. The ECG changes in patients who died and those who had survived were not significantly different, suggesting that quinine toxicity is unlikely to be the cause of death in these patients. No significant dysrhythmia was seen in any patients who died.

Artemether is a very potent antimalarial against multidrug resistant falciparum malaria. It is replacing quinine in the areas with quinine resistant *P. falciparum* such as along the Thai-Cambodian and Thai-Myanmar borders. It was shown that the parasite clearance time is faster and the survival rate is higher than quinine (Karbwang *et al,* 1995). However, in areas with less quinine resistant parasite strains, superiority of artemether over quinine was not significant (Hein *et al* 1996; Hensbroek *et al,* 1996; Taylor *et al,* 1993). Nevertheless, all studies agree on its rapid clearance of parasites compared with quinine. Furthermore, Taylor *et al* (1993) reported faster resolution of coma in children with severe falciparum malaria who were treated with artemether. Artemether is being used extensively in Asian countries, particularly in China. There is no doubt that artemether will come to play an increasing role in the treatment of multidrug resistant falciparum malaria. Although severe side-effects have not yet been reported in man at the doses used at present *ie* maximum of 10 mg/kg total dose, extensive or repeated use may occur in the future. Thus, it is important to carefully assess the possibility of cardiovascular side-effects of this compound. It was shown in a dog study that artesunate (another derivative of artemisinin) can decrease blood pressure at the dose of 320 mg/kg but not at the dose of 160 mg/kg or below (Zhao, 1985). Although two patients receiving artemether showed hypotension, it may not have been associated with artemether since the dose used in this study was only 10mg/kg. The patients in this study were all in severe condition, hypotension might have occurred as a part of the pathological process of severe malaria. However it should be kept in mind the possibility of this side effect even at a dose of 10 mg/kg. Nevertheless, artemether is still considered to be safe in this context when compared with quinine. Non-specific ECG changes found in 6 patients could be due to electrolyte imbalance which is one of the common findings in malaria, due to modulation of sympathetic tone which is the result of fever (tachycardia found in 17/31 pre-treatment). Two patients showed QTc prolongation, suggesting that artemeter might have some membrane stabilizing effect like quinine (effect on myocardial repolarization). These two patients however, belonged to the sinus bradycardia group which in general always show a prolongation of the QTc interval. Other possibilities are electrolyte imbalance *ie* hypokalemia (prominent QU), hypocalcemia, myocardial ischemia and hypothyroidism.

It is unfortunate that plasma levels of artemether have not been measured in the patient who had 2nd degree AV-block. Artemether might suppress the heart, as in dogs, especially the conduction system (Zhao, 1985). Further observations are needed.

In conclusion, there was no hard evidence from ECG assessment that would suggest any effect of artemether on the cardiovascular system. However, two cases of hypotension and a case of suppression of the conduction system (second degree AV-block) did cause a concern and these should not be overlooked in the patients receiving artemether, particularly in patients with pre-existing cardiopathy.

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