Compliance with a 2 day course of artemether-mefloquine in an area of highly multi-drug resistant *Plasmodium falciparum* malaria

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Aims Multi-drug resistant *Plasmodium falciparum* malaria is a rapidly increasing problem in the world, particularly Thailand. Practical antimalarial regimens which are highly effective against multi-drug resistant parasites with short-term course of administration are needed. In this study, we assessed the patient compliance of a short course regimen using artemether-mefloquine.

Methods Clinical effectiveness (efficacy, tolerability and patient compliance) of a 2-day regimen of artemether-mefloquine was evaluated in 126 patients with acute uncomplicated falciparum malaria who were attending the two malaria clinics in an area of highly multi-drug resistant *P. falciparum* malaria (Thai-Myanmar border). Patients were treated with a single oral dose of 300 mg artemether on the day of attendance. Two additional doses of mefloquine were given for home treatment on the following day (750 and 500 mg after breakfast and lunch, respectively).

Results The combination regimen was effective, with a cure rate of 92.6%. Based upon the concentrations of whole blood mefloquine on day-2, compliance for this 2 day regimen of artemether-mefloquine was 98.1% (full compliance 86.8%, partial compliance 11.3%, non-compliance 1.9%).

Conclusions We conclude that the 2 day regimen of artemether-mefloquine is, at present, a good alternative regimen for the treatment of uncomplicated multi-drug resistant falciparum malaria.

Keywords: *Plasmodium falciparum*, multi-drug resistance, mefloquine, artemether, compliance

Introduction

Multi-drug resistant *Plasmodium falciparum* malaria is a rapidly increasing problem in Thailand, particularly in the border regions [1]. In these areas, the efficacy of mefloquine, which has been used by the Malaria Control Programme as a first-line treatment for uncomplicated falciparum malaria, is lower than 50%, even when given at a higher dose of 1250 mg or 25 mg kg⁻¹ [2–5]. A 7 day course of quinine-tetracycline, which is the standard treatment, gives a high cure rate of over 95% in hospital-based treatment [6–7], but this regimen is associated with high incidence of adverse effects and poor patient compliance when applied for general use outside a hospital environment. Thus, practical antimalarial regimens which are highly effective against multi-drug resistant parasites with short-term course of administration are needed.

A 2 day course of treatment with artemether followed by a longer half-life drug, *i.e.* mefloquine (a single oral dose of 300 mg artemether initially, followed by two doses of 750 and 500 mg mefloquine at 24 and 30 h apart) has been shown to be highly effective against multi-drug resistant falciparum malaria in a hospital setting [8]. However, the effectiveness of this regimen cannot be verified when applied clinically in the rural tropics, as the patients will have to

take the drug (two doses of mefloquine) unsupervised at home and there may be a relatively high incidence of recrudescence due to incomplete treatment.

In the present study, we have assessed the patient compliance of this short- course regimen of artemether-mefloquine in the treatment of multi-drug resistant, uncomplicated falciparum malaria under field conditions.

Methods

The study was undertaken at the two malaria clinics in Mae-Sot District, Tak Province (a well-documented area of multi-drug resistant *P. falciparum*) during November 1994 and May 1995. Malaria is a serious imported medical problem with a peak incidence during May–August and November–January of each year. Most patients are adult males, and approximately 80% of infections are caused by *P. falciparum*. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, and the National Ethics Committee, Ministry of Public Health.

One hundred and twenty-six patients (109 males, 17 females) presenting with symptomatic uncomplicated malaria (asexual form parasitaemia 200–5050 per 200 WBC), who had no history of liver or kidney diseases and no previous history of antimalarial treatment during the previous 4 weeks, were included in the study. Median (range) values

for age and weight of the patients were 29 (15–68) years and 53 (45–64) kg.

Prior to treatment (day 0) a blood sample (2 ml) was taken for the determination of mefloquine concentrations. Patients were treated with a 2 day course of the combination artemether-mefloquine. The initial dose of 300 mg artemether (Artemar[®], Arenco n.v., 50 mg per tablet) was administered under supervision, with the second and third doses of mefloquine (750 and 500 mg: Lariam[®], Roche, 250 mg per tablet) being administered at home the following day after breakfast and lunch, respectively (4–6 h interval). A full dose of artemether was repeated if vomiting occurred within the first hour of intake. When necessary, symptomatic treatment with an antipyretic paracetamol and, an anti-emetic–dimenhydrinate (Dramamine[®]) was administered.

Patients were asked to return for follow-up on the second day of treatment (day 2), and on days 7, 14, 21, 28 and 42, or at any time if fever or symptoms suggestive of malaria developed. At each visit, a parasite count was performed (Giemsa-stain), and a detailed questionnaire for general symptoms was recorded. Blood samples were taken (2 ml) for determination of mefloquine concentrations and compared with reference profiles (with frequent blood sampling at 0, 6, 12 h and on days 14, 21, 28, 35 and 42 after the initial dose of mefloquine) obtained from 20 hospitalised male patients who were receiving the same regimen of artemether-mefloquine under supervision (at the Bangkok Hospital for Tropical Diseases). Whole blood samples were stored at -20°C until analysis by high-performance liquid chromatography. The method has previously been described with intra- and inter-assay coefficients of variation of less than 5%, with limit of quantification of $10\text{ }\mu\text{g l}^{-1}$ [9].

Patients failing to respond were retreated with a 5 day course of artemether (300 mg on the first day, followed by 100 mg for another 4 days). Those who developed *Plasmodium (P.) vivax* malaria in their peripheral blood during the follow-up period were treated with 300 mg (base) of chloroquine to suppress symptoms and a full course of treatment was given at the end of the study period (chloroquine 1500 mg given over 48 h, followed by 15 mg (base) of primaquine daily for 14 days).

The clinical outcome from of a 2 day course of artemether-mefloquine was evaluated in the group of patients presenting to malaria clinics in Mae-Sot who completed the 42 day follow-up period. Treatment failure cases were classified (RI, RII or RIII) according to the World Health Organization criteria [10]. Patient compliance was evaluated based upon day 2 concentrations of mefloquine in the reference profiles obtained from the hospitalised patients. Statistical analysis of the data was performed by a Mann-Whitney-U test with a significance level of $P=0.05$.

Results

All patients had a rapid initial response to treatment with parasites cleared from peripheral blood within 3 days of an initial dose of artemether. Fifty-four patients completed the 42 day follow-up period. Four patients recrudesced on days 14, 22 and 25 (2, 1 and 1 cases, respectively). One patient developed *P. vivax* infection on day 28. The cure rate for this combination regimen was therefore 92.6% (50/54). The

most common adverse effects were nausea (6.6%), dizziness (24.6%), vomiting (6.6%), headache (6.6%), and diarrhoea (3.3%). All occurred during the day of mefloquine administration (day 1). None vomited after an initial dose of artemether. Of the 108 patients whose mefloquine concentrations were measured, 55 (50.9%) had undetectable baseline mefloquine level, whereas 23 (21.3%), 18 (16.7%) and 12 (11.1%) cases, respectively, had concentrations of less than 100, between 100 and 500, and more than $500\text{ }\mu\text{g l}^{-1}$ [median (range): 46.5 (13–85) *vs* 332 (108–496) *vs* 649 (511–1542) $\mu\text{g l}^{-1}$].

Figure 1 describes median whole blood mefloquine concentrations in 20 hospitalised patients who were taking the drug under supervision. Median (range) concentrations on day 2 were $2262\text{ (}1198\text{--}3254\text{) }\mu\text{g l}^{-1}$, with a 95% C.I. of $1587\text{--}2572\text{ }\mu\text{g l}^{-1}$ (reference interval). Two, four and two cases, respectively had baseline concentrations of <100 , $100\text{--}500$ and $>500\text{ }\mu\text{g l}^{-1}$.

Since mefloquine has a very long half-life drug (14–21 days in patients), the decrease in the concentrations within 2 days is insignificant and therefore day 2 concentrations in patients who had measurable baseline concentrations were estimated by subtraction of baseline concentrations from the measured day 2 concentrations. Ninety-two patients with home treatment had day 2 mefloquine concentrations within or above the reference interval (full compliance). Fourteen cases exhibited concentrations below the reference interval, but two had severe vomiting within the first 1 h of mefloquine intake. Twelve cases were therefore considered to show partial compliance. In two cases, mefloquine concentration was undetectable (non-compliance); both had complete parasite clearance on day 2 (3 days after the initial dose of artemether) but were lost to follow-up afterwards. Compliance with this 2 day combination was therefore 98.1% [full compliance 86.8% (92/106), partial compliance 11.3% (12/106), non-compliance 1.9% (2/106)]. Recrudescence occurred in three patients with full compliance and one case of partial compliance (Figure 1). At the time of recrudescence, only two patients had measurable concentrations of mefloquine on days 22 and 25 (655 and $541\text{ }\mu\text{g l}^{-1}$; Figure 1).

Discussion

A good initial response was observed in all patients where parasitaemia was cleared within 3 days after the initial dose of artemether. Parasite clearance was observed in the two patients who did not take mefloquine (non-compliance). This suggests that with a single dose of artemether, parasites can be cleared transiently from the circulation although early recrudescence might be expected [11]. The present combination of artemether-mefloquine improved the cure rate from approximately 50% with mefloquine alone [5] to 92.6%, but, more importantly, reduced the risk of high grade resistance (RII, RIII) to zero. The lower cure rate of this short course of artemether-mefloquine compared with that previously reported by our group [8, 12] highlights the rapidly increasing incidence of highly mefloquine resistant *P. falciparum* in this area. Using mefloquine alone against falciparum malaria in this area is no longer effective as evidenced by the high failure rate from this drug in the

Figure 1 Median mefloquine concentration profile and 95% C.I. of day 2 concentrations in 20 hospitalised patients who administered mefloquine doses under supervision; ■ represents concentrations on day 2 in each individual patients with sensitive response; ● represents day 2 concentrations in the four patients with treatment failure, ○ represents the concentrations at the time of recrudescence in two patients.

treatment of previous malaria episodes despite measurable concentrations of mefloquine on admission ($> 500 \mu\text{g l}^{-1}$). Furthermore, parasites may have survived despite exposure to concentrations of mefloquine previously associated with successful treatment [3, 13–14]. Treatment failure from the combination in one specific case could be ascribed to inadequate mefloquine concentrations resulting from poor compliance with the second dose of mefloquine (partial compliance).

Non-compliance with mefloquine could be confirmed only in two patients who did not take either dose of the drug. Full compliance of 87% with this short course regimen (2 day) of artemether-mefloquine can be considered excellent by comparison with compliance to long treatment courses of other antimalarials *e.g.* a 7 day course of quinine/tetracycline, where prolonged drug administration or a relatively high incidence of cinchonism contributes to less than 70% compliance in field trials (Fungladda –personal communication). The relatively low concentrations of mefloquine observed in 12 cases are likely to be due to a failure to take the missing of the second dose of the drug as none vomited within the first hour [15].

We conclude that the effectiveness (patient compliance, efficacy, tolerability) of the 2 day regimen of artemether-mefloquine is, at present, a good alternative regimen for the treatment of uncomplicated multi-drug resistant falciparum malaria.

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