MEFLOQUINE LEVEL MONITORING IN PATIENTS WITH MULTIDRUG RESISTANT *PLASMODIUM FALCIPARUM* ON THE THAI MYANMAR BORDER

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Abstract. A total of 42 patients with uncomplicated falciparum malaria who attended the malaria clinic in Mae Sot, Tak Province were treated with single oral dose of MSP 3 tablets (Fansimef®, equivalent to 750 mg of mefloquine) concurrently with primaquine (30 mg). They all contracted the infection from Cambodia. The aim of the study was to monitor the efficacy of MSP 3 tablets for the treatment of this highly multiple drug resistant strains of *Plasmodium falciparum* in this area. Of the 39 patients included for efficacy assessment, 13 (33.3%) patients had sensitive responses, whereas 15 (38.5%) and 8 (20.5%) had RI and RII types of response, respectively. Melfoquine concentrations on Day-3 after treatment in patients with sensitive and treatment failure groups were comparable; the respective mean (SD) values were 665 (279) and 772 (264) ng/ml.

INTRODUCTION

In Thailand, *Plasmodium falciparum* has developed resistance to almost all of the available drugs (Karbwang and Harinasuta, 1992a). Increasing treatment failure rate with the previously effective antimalarials such as chloroquine, sulfadoxine/pyrimethamine has led to the more widespread use of melfloquine, a quinoline methanol antimalarial. Over the period 1985 to 1990, mefloquine was used in combination with sulfadoxine and pyrimethamine (MSP: Fansimef®) as the first line treatment for multidrug resistant *P.falciparum* in Thailand. The initial cure rate all over the country was high, approaching 100% after a single oral dose of 3 tablets which is equivalent to 750 mg of mefloquine (Malaria Division, 1986). Despite its restricted use by government health services, the efficacy of this drug has dropped drastically after 5 years of its introduction to approximately 60 - 70% all over the country (Malaria Division, 1990). Melfloquine-resistance as an operational problem seems however, be confined to some areas such as the eastern part (Thai-Cambodian border) of the country. It is at the moment the hard core area of mefloquine resistance and due to population transmigration, the spread of these highly resistant strains of *P. falciparum* to other areas occurs rapidly, particularly to the western part of the country (Thai-Myanmar border).

The present study has assessed the efficacy of MSP 3 tablets in relation to drug level during Day-3 after treatment in patients who were residents of the western part area. These patients contracted malaria infection from a gem mining site in Cambodia, where there are highly multiple drug resistant *P.falciparum* strains.

MATERIALS AND METHODS

Study site

The study was carried out during December 1990 - July 1991 at the malaria clinic in Mae Sot District, Tak Province. This is situated close to the Thai-Myanmar border. Gem mining is the main occupation of the population in the area. People usually go forth and back to the eastern part of the country to the gem mining location in Cambodia, where they contract malaria infection.

Approval of the study was obtained from the Ethics Committee of the Ministry of Public Health, Thailand.

Patients

A total of 42 Thai male patients who attended the malaria clinics with blood slides positive for asexual forms of *P. falciparum* between 125 -

12,500 per 1,000 red blood cells or 1,000 - 100,000 per μl of blood were recruited to the study. They were aged between 17 and 48 years. All contracted the infection in Cambodia and had no history of taking antimalarials within 2 weeks.

Patients were given single oral dose of MSP 3 tablets (Fansimef®, equivalent to 750 mg of mefloquine), concurrently with primaquine 30 mg. The drug was administered with a glass of water under supervision. One ml of whole blood was taken for mefloquine levels on Day - 3 after treatment. Mefloquine levels were measured in whole blood by high performance liquid chromatography, according to the method of Karbwang *et al* (1989). Any occurrence of vomiting was recorded with time and frequency. Concurrent drug therapy was kept to an absolute minimum and when it was subscribed, full details were recorded.

Patients had blood slide examination for the presence of asexual form of *P.falciparum* on Days 0, 2, 3, 7, 14, 21 and 28. All were medically examined, interviewed about the adverse drug reactions. Response to the treatment within 28 days of the follow-up period were graded into RI, RII and RIII, according to the criteria of WHO (1976).

All treatment failure cases were retreated with the combination of quinine (600 mg *tid,* over 7 days) and tetracycline (250 mg *qid,* over 7 days).

RESULTS

A total of 42 patients was included in the study, of which 3 cases dropped out due to the regurgitating tablets immediately after ingestion. The geometric mean of the initial parasite densities was 11,897 per μl.

There were 3 patients who did not complete the follow-up period, and were classified as S/RI response. Thirteen patients (33.3%) responded well to the treatment with no reappearance of parasitemia within 28 days of the follow-up period. RI and RII types of response were observed in 15 (38.5%) and 8 (20.5%), respectively.

Mefloquine concentrations on Day-3 after treatment in patients with sensitive response were comparable to those with treatment failure (RI and RII types fo response). The respective mean (SD) values were 665 (279), and 772 (264) ng/ml. Fig 1 shows the concentrations on Day-3 in both groups.

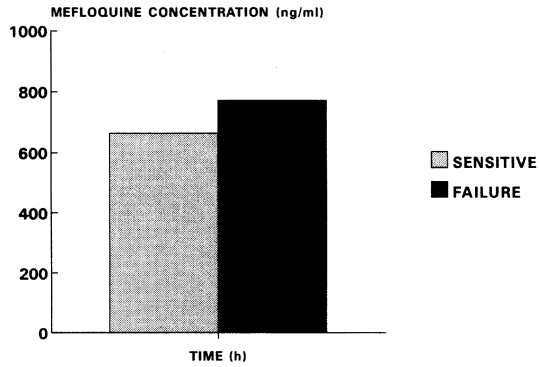

Fig 1—Mean whole blood mefloquine concentrations on Day-3 in patients with sensitive and treatment failure response after a single oral dose of MSP 3 tablets.

DISCUSSION

P.falciparum malaria has been documented to be highly resistant to mefloquine in some areas of Thailand, *ie* the area along the Thai-Cambodian border in the east and that along the Thai-Myanmar border in the west. Apart from treatment failure due to the decrease in susceptibility of parasites to drug (true resistance), previous studies have indicated that host factors (pharmacokinetics) also contribute to the failure (Boudreau *et al,* 1990; Karbwang *et al,* 1991a; 1991b; 1993; Na Bangchang *et al,* 1993). The importance of maintaining whole blood or plasma mefloquine concentrations during the acute phase of malaria infection have been pointed out in these studies.

In the present study, efficacy assessment of MSP 3 tablets (equivalent to 750 mg mefloquine) in relation to drug levels on Day-3 was investigated in patients with uncomplicated malaria living in the western part along the Thai-Myanmar border. All patients included into the study were gem miners who contracted the infection from the gem mining location in the eastern Thai-Cambodian border, the area of highly resistant strains of *P.falciparum.* Malaria transmission in this area is intensive and due to population movement (for gem mining), the spread of these highly resistant parasites to other areas is rapid. These two areas (Thai-Myanmar and Thai-Cambodian borders) are transmigration areas where the problem of multi-drug resistant *P.falciparum* is most marked. However, in the western area, mala-

ria transmission is not as intensive as the eastern part, and this allows reinfection to be excluded. It was found that the efficacy of MSP 3 tablets observed in the present study in this area dropped markedly (33%) when compared with that of the previous 2 years (60%) (Malaria Division, 1990). The failure rate would be expected to be even higher if the follow-up period had been extended to 42 days (Karbwang *et al,* 1992b). Furthermore, RII type of reponse from MSP 3 tablets was increased compared to previous years.

There was no difference in mefloquine level on Day-3 after treatment between patients with sensitive and with treatment failure responses. Therapeutic levels of mefloquine differ from one area to another (Karbwang *et al,* 1993; Na Bangchang *et al,* 1993). The level of above 1,959 ng/ml on Day - 3 after treatment has been reported to produce S types of response in patients with highly mefloquine resistant *P.falciparum* who were residents of this area (bordering Cambodia), whereas a concentration of 1,650 ng/ml was associated with treatment failure. It is noted that mefloquine levels in that group of patients were considerably higher than those found in the present study, in which the respective mean concentrations of 665 vs 772 ng/ml were observed in successful and treat ment failure groups. The unusual high concentrations in patients living in the eastern area may be the result of repetitive treatment with mefloquine for that episode of infection. Patients in the western area on the other hand, are likely to recieve treatment with mefloquine only once for the present episode of infection, since their resident area is not as highly endemic as the eastern area. This indicated that adequate mefloquine concentrations for resistant strains of *P.falciparum* were not attained in this group of patients, since relatively low concentrations below the therapeutic levels were found in all patients in the present study. The result therefore suggests that treatment failure from MSP in the group of patients in the present study was due mainly to inadequate plasma concentrations to cope with resistant strains of *P.falciparum.* Plasma mefloquine concentrations maintained during the acute phase of the infection may not be high enough for killing all the parasites. MSP or mefloquine alone is probably still useful in this group of patients; improvement of the cure rate may be possible by increasing the dose to 5 tablets (or 1,250 mg mefloquine, 2 divided doses at 6 hours apart). However, with the presence of highly resistant strains (as suggested by the high percentage of RII response), a higher dose of mefloquine is likely to be effective for a limited time period in the future.

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