ACTIVITY OF ARTEMETHER-AZITHROMYCIN *VERSUS* ARTEMETHER-DOXYCYCLINE IN THE TREATMENT OF MULTIPLE DRUG RESISTANT FALCIPARUM MALARIA

Kesara Na-Bangchang[1], Tozo Kanda[2], Pongsri Tipawangso[1], Aurathai Thanavibul[1], Krit Suprakob[3], Msengi Ibrahim[1], Yupaporn Wattanagoon[1] and Juntra Karbwang[1]

[1]Clinical Pharmacology Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand; [2]Japan Association of Tropical Medicine, Tokyo, Japan; [3]Malaria Sector 4, Region 1, Mae Sot, Tak,Thailand

Abstract. The efficacy of the combination of artemether with doxycycline or azithromycin was evaluated in 60 patients with acute uncomplicated falciparum malaria who attended malaria clinic in Mae Sot, Tak Province (Thai-Myanmar border). Patients (30 each) were randomized to receive (a) 300 mg artemether together with 100 mg doxycycline as initial doses, followed by 100 mg artemether plus 100 mg doxycycline at 12 hours later, then 100 mg doxycycline every 12 hours for another 4 days, or (b) 300 mg artemether together with 500 mg azithromycin, followed by 250 mg azithromycin at 24 and 48 hours. The follow-up period was 28 days. Patients in either group had a rapid initial response to treatment with comparable PCT and FCT. The cure rate of artemether-azithromycin regimen was significantly lower than that of artemether-doxycycline regimen (14.8 *vs* 53.3%). Low cure rate from artemether-azithromycin combination in this study was likely to be due to inadequate azithromycin dosage. However, with the low incidence of gastrointestinal adverse effects, the once daily dose of azithromycin could still be increased in order to enhance its clinical efficacy. The simplicity of drug administration and lesser incidence of adverse effects make azithromycin a more proper partner of artemether than doxycycline. Further dose-finding and pharmacokinetic study with the artemether-azithromycin combination is encouraging.

INTRODUCTION

In Thailand, *Plasmodium falciparum* has been shown to be resistant to all currently available antimalarials. Chloroquine, sulfadoxine-pyrimethamine, quinine and mefloquine resistance are well documented both *in vitro* and *in vivo* (Bunnag and Harinasuta, 1986; Harinasuta *et al*, 1965; Karbwang and Harinasuta, 1992; 1994a; Ketrangsee *et al*, 1992; Pinichpongse *et al*, 1982). The combination of quinine and tetracycline given for 7 days is the treatment of choice for multidrug resistant falciparum malaria, with the cure rate being 95-100% in hospital setting (Karbwang *et al*, 1994b). However, the treatment course for this regimen is too long and therefore patient compliance is poor with home treatment (Thimasarn, unpublished data, 1994). The use of artemisinin compounds with mefloquine is very effective against multidrug resistant falciparum but the degree of mefloquine resistance is increasing rapidly (Karbwang *et al*, 1995). Alternative combination of artemisinin compounds with other antimalarials is needed.

Azithromycin is a macrolide-like antibiotic which is active against *P. falciparum* (Andersen *et al*, 1995a,b). It has longer half-life and more potent antimalarial activity than doxycycline (Foulds *et al*, 1990), which would permit once daily dose regimen of the drug. Furthermore, azithromycin has been shown to augment the potency of artemisinin compounds (Andersen *et al*, 1995b). Accordingly, it is interesting to examine the clinical efficacy of artemether-azithromycin combination for the treatment of multidrug resistant falciparum malaria. We have therefore carried out a comparative trial for the assessment of clinical efficacy of the combination of artemether with azithromycin or doxycycline in patients with acute uncomplicated multidrug resistant falciparum malaria.

MATERIALS AND METHODS

Patients and methods

The study was undertaken in 1995 during the rainy season (June to August). Patients presenting

to the out-patient malaria clinic in Mae Sot, Tak Province (Thai-Myanmar border, a well documented multidrug resistant area) were screened for *P. falciparum* infections. Sixty patients with acute uncomplicated falciparum malaria aged between 15 and 59 years were recruited to the study provided that inform consent for participation was obtained. The study was approved by the Ethics Committee of Ministry of Public Health of Thailand.

On admission, all patients underwent physical examination, monitoring of baseline general symptoms and body temperature. The criteria for inclusion included the presence of asexual form parasitemia of lower than 100,000/µl of blood, and the absence of history of mefloquine or quinine treatment over the last 4 weeks confirmed by drug levels determined in blood using high performance liquid chromatography (Karbwang *et al*, 1991a,b). The patients (30 each) were randomized to receive two oral drug regimens as follow:

Regimen I: Artemether (Artenam®, Arenco nv, Belgium) 300 mg plus doxycycline (Vibramycin®, Pfizer) 100 mg as initial doses, followed by artemether 100 mg plus doxycycline 100 mg at 12 hours later, and then doxycycline 100 mg every 12 hours for another 4 days.

Regimen II: Artemether 300 mg plus azithromycin (Zithromax®, Pfizer) 500 mg, followed by azithromycin 250 mg at 24 and 48 hours.

The patients were admitted as in-patients at the malaria clinic for 28 days. Parasite count was performed every 6 hours until negative then daily until day 28. Monitoring of adverse effects was performed daily until day 7, then once weekly until day 28. Parasite count (per 1,000 red blood cells or per 200 white blood cells) were done using thin and thick blood films stained with Giemsa's stain.

Patients with treatment failure were retreated with the combination regimen of artemether-mefloquine (artemether 300 mg plus mefloquine 750 and 500 mg given at 24 and 30 hours after artemether). Those who developed *P. vivax* infection during the follow-up period were given 150 mg (base) of chloroquine to suppress the symptoms; a full course was given on discharge.

Only patients who completed the 28 day follow-up period were included for efficacy assessment. The parameters used in the evaluation of therapeutic outcome included parasite clearance time (PCT: the time taken for the parasite count to fall below the level of microscopic detection), fever clearance time (FCT: the time taken for the temperature to return to normal *ie* below 37.3°C and remain at that value for at least 24 hours), and the rate of treatment failure (RI, RII or RIII) (WHO, 1973). Comparison of the qualitative data was done using chi-square test at a statistical significance level of $p = 0.05$; comparison of the quantitative data was done by Mann-Whitney U test at the same statistical significance level.

Table 1

Clinical data on admission and response to treatment with the combination artemether-doxycycline and artemether-azithromycin (data were presented as median (range) values or number).

	Artemether-doxycycline (N = 30)	Artemether-azithromycin (N = 30)
Age (years)	23 (15-59)	25 (17-45)
Admission parasitemia (per µl)	18,380 (735-83,680)	12,460 (2,190-92,000)
Red blood cells ($\times 10^{12}$/µl)	3.84 (2.91-5.49)	3.65 (2.34-4.75)
Number of patients included	30	27
S Response (n)	16	4
RI Response (n)	14	23
Cure rate (%)	53.3	14.8
PCT (h)	31 (8-54)	28 (18-48)
FCT (h)	26.5 (3-63)	20 (8-35)
P. vivax (n)	0	0

RESULTS

Sixty male patients with acute uncomplicated falciparum malaria were recruited into the study. None had detectable baseline level of mefloquine or quinine. The levels of parasitemia were similar between the two treatment groups (Table 1).

Three patients in the artemether-azithromycin group did not complete the follow-up, the reasons not being related to adverse effects. They were however, discharged from the clinic with no parasitemia or symptoms of malaria.

Patients in either group had a rapid initial response. There were no significant differences in PCT and FCT between the two groups. Fourteen and 23 patients with artemether-doxycycline and artemether-azithromycin treatment, respec-tively had reappearance of parasitemia between days 10 and 22 (RI). The cure rate of artemether-azithromycin was significantly lower than that of artemether-doxycycline regimen (14.8 *vs* 53.3%; p = 0.006, RR = 3.6, 95% CI = 1.3-9.44%).

No serious adverse effect was found in all patients. Transient mild nausea, abdominal discomfort and loss of appetite were common adverse effects; the incidence was significantly higher in the group treated with artemether-doxycycline (12 *vs* 3 cases: p = 0.03, RR = 3.6, 95% CI = 1.14-11.4).

None of the patients developed *P. vivax* malaria during the follow-up period.

DISCUSSION

The combination of artesunate daily for 5 days with doxycycline once daily for 7 days showed the cure to be 80% (Looareesuwan *et al*, 1994). This is considered too low for the regimen to be accepted as first-line drug treatment. Inadequacy of plasma concentrations of doxycycline after the daily dose regimen could have accounted for the low therapeutic efficacy of this combination. Kinetic profiles of doxycycline suggests that the drug should be given as a twice daily, instead of once daily dose regimen (Cunha *et al*, 1990). In the present study however, increasing of dosing frequency to twice daily for 5 days did not show an impressive improvement of cure rate. With only a single day regimen of artemether, recrudescence would be expected in all patients (Bunnag *et al*, 1992). The addition of doxycycline to artemether had thus, at least, improved the cure rate of artemether to 53%. Considering the half-life of the drug, the course of doxycycline treatment might need to be as long as 7 days to cover up the activity against surviving parasites after the artemether doses.

Another combination drug partner, azithromycin, was not also shown to be as potent as had been expected when shortened the duration of treatment to 3 days following a single dose of 300 mg artemether. The drug has been shown to be 100% protective when the duration of drug dosage was 28 days after parasite injection, but only 40% when it was given at 7 day duration after the challenge (Andersen *et al*, 1995a). It has also been demonstrated in an earlier study that failure to protect against the infection was due to undetectable azithromycin level (Kuschner *et al*, 1994). Longer duration of treatment may be required for azithromycin as its action is slow (Yeo and Rieckmann, 1995). Extending the period of artemether dosing to 2-3 days to cover up the activity during the early period when azithromycin has not yet taken the full action may also be an alternative.

Lesser incidence of gastrointestinal adverse effects, together with its being a more potent antimalarial (Andersen *et al*, 1995b) and simplicity of administration (once daily dosage regimen) make azithromycin a more proper partner of artemether than that of doxycycline. The dose of azithromycin used in this study is considered very low (500 mg loading dose with 2 doses of 250 mg maintenance dose). There is still a place for higher dose azithromycin since it is well tolerated even with long-term administration (Andersen *et al*, 1995a). This higher daily dose of azithromycin could be another solution to ensure sufficient plasma drug concentrations of the drug. High dose of azithromycin was shown to completely clear the parasite in a monkey infected with *P. falciparum*, while lower dose (one-third of the high dose) initially cleared the parasites but all recrudesced afterward (Andersen *et al*, 1995b).

Further dose-finding and pharmacokinetic drug interaction study with artemether-azithromycin combination is encouraged. In addition, pharmacokinetic drug interaction study between these two drug components is suggested prior to the dose-finding study since there has been some evidence for such interaction (which in turn influenced the

therapeutic outcome) when artemisinin compounds were given with mefloquine (Karbwang *et al*, 1994c; Na-Bangchang *et al*, 1995).

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