A RANDOMIZED CLINICAL TRIAL OF COMBINATIONS OF ARTESUNATE AND AZITHROMYCIN FOR TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN THAILAND

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Abstract. Recently, a combination of artesunate and mefloquine has proved effective, although is contraindicated in early pregnancy and young children. Azithromycin, a widely used antibiotic and has antimalarial effects, replace mefloquine as a new alternative antimalarial regimen. Two hundred and two uncomplicated falciparum malaria patients were randomly assigned to 1 of 3 regimens. Patients in group I (n = 68) received artesunate 200 mg once daily for 3 days, group II (n = 67) received artesunate 200 mg together with mefloquine 10 mg/kg on the first 2 days and artesunate 200 mg together with mefloquine 5 mg/kg on the third day, and group III (n = 67) received artesunate 200 mg together with azithromycin 50 mg once daily for 3 days. The 28 day cure rates were 44, 98 and 56%, respectively. The median time to recrudescence was significantly longer in group III. In conclusion, a combination of artesunate and azithromycin might be useful in treating children in whom bacterial and malarial infections may be concomitant. However, further work is required in order to enhance its clinical efficacy.

INTRODUCTION

Malaria is the major cause of death and of public health problems in Thailand. The morbidity and mortality rates have declined dramatically since 1951. It is still one of the public health problems in this area. In fiscal year 1997, 3.7 million (6.8%) were living in malaria endemic areas. There were 99,679 malarial cases registered (1.78/1,000 population) and 826 deaths (1.38/ population) (Annual Report, 1998).

Among the four human malaria parasite species, *Plasmodium falciparum* is the most dangerous and the major cause of death. Treatment of *P. falciparum* malaria in Thailand is now becoming more difficult because of increasing resistance to all available standard antimalarial regimens (Looareesuwan *et al*, 1992a). The combination of quinine and tetracycline given for seven days is a standard regimen for multidrug-resistant *P. falciparum* strains in Thailand. The cure rate of this combination is 90% when it was given under supervision (Looareesuwan *et al*, 1992b). Moreover, the unfavorable effects of quinine (*eg* cinchonism) and a short half-life of both drugs which necessitates frequent dosing causes a problem of treatment compliance, particularly among outpatients.

Mefloquine, a long half-life antimalarial drug was developed for treatment of multidrug-resistant malaria. It is better tolerated than quinine and can be administered during a day even some cases experienced adverse reactions such as nausea, vomiting (White and Breman, 1998). This drug used to have a satisfactory response with a cure rate of 98% when used alone from 1983-1986 (Harinasuta *et al*, 1987; Nosten *et* al, 1987). By 1990 the efficacy at the dose level of 15 mg/kg had rapidly declined to 71% (Nosten *et al*, 1991). In addition, the artemisinin derivative; artesunate, has now been registered in Thailand. It is also well tolerated but the use as a monotherapy requires at least five days for effectiveness. Recently, artesunate plus mefloquine has proved effective and well tolerated (Looareesuwan *et al*, 1992c; Looareesuwan *et al*, 1994, 1996; Nosten *et al*, 1994; Prince *et al*, 1995, 1997). Adverse effects of mefloquine are reported commonly.

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Azithromycin, a macrolide-like antibiotic, has antimalarial effects and has been used for prophylaxis and treatment of falciparum malaria (Gingras and Jansen 1993; Kuschner *et al*, 1994; Andersen *et al*, 1994a,b; Andersen *et al*, 1995; 1998; Na-Bangchan *et al*, 1996; Taylor *et al*, 1999). It is well tolerated and can be used in children and pregnant women. Because of its long half-life, this drug can be administered only once daily (White and Breman 1998; De Mol *et al*, 1996; Peters *et al*, 1992). It might be possible to replaces mefloquine with azithromycin in combination with fast acting blood schizonticides such as artesunate while azithromycin could prevent recrudescence. We report here the results of a randomized clinical trial of artesunate combined with azithromycin for the treatment of multidrug-resistant falciparum malaria, a potential alternative antimalarial regimen.

PATIENTS AND METHODS

Uncomplicated falciparum malaria patients admitted to Bangkok Hospital for Tropical Diseases between December 1998 to May 1999 were enrolled for the study if they met the following criteria: aged at least 14 years, body-weight at least 40 kg, had positive asexual forms of *P. falciparum* in blood smear, and had given an informed consent. Others were excluded for the following reasons: had signs of severe or complicated malaria according to WHO criteria 1990 (Warrell *et al*, 1990), inability to tolerate oral medications, pregnancy or lactation, allergy or sensitivity to drugs or a history of serious allergy to any medication, consumption of any antimalarial drug therapy within 2 weeks prior to admission. This study was approved by the Ethics Committees of the Faculty of Tropical Medicine and of Mahidol University, Bangkok, Thailand.

Before treatment, baseline data such as demographic data, clinical and laboratory data were obtained. Pretreatment investigations included complete blood count, urinalysis, liver function test, blood urea nitrogen, creatinine, and serum electrolytes were also performed and repeated weekly until the 28th day of admission. Malaria parasite counts were examined prior to treatment and every 12 hours until negative then once daily for 28 days in hospital. Parasite counts per μl using Giemsa-stained, were determined by counting the number of asexual parasites against 200 white blood cells in thick blood films or against 1,000 red blood cells in thin blood films. Blood films were considered negative if no parasites were seen in 200 oil immersion fields in a thick blood film.

Oral temperature, pulse and respiratory rate were obtained every 4 hours while blood pressure was measured once daily. To search for adverse effects of study drugs and clinical signs and symptoms of malaria, thorough daily examination for the first 7 days of hospitalization and weekly thereafter were performed.

Each patient was randomly assigned to one of three regimens: group I received artesunate 200 mg once daily for 3 days; group II received artesunate 200 mg together with mefloquine 10 mg/kg on the first 2 days, on the 3rd day artesunate 200 mg together with mefloquine 5 mg/kg; and group III received artesunate 200 mg together with azithromycin 500 mg given once daily for 3 days. Patients who vomited within one hour after drug administration were redosing. All patients were admitted in the hospital for 28 days in order to observe adverse effects and to exclude reinfection. Some patients left the hospital before a 28-day admission in the hospital. However, those patients agreed to stay in non-malaria endemic areas and came for follow-up weekly to complete a 28-day follow-up.

The parameters of the response to treatment were the 28-day cure rate, parasite clearance time, and fever clearance time. According to the WHO classification system: sensitive was defined as no reappearance of asexual forms of *P. falciparum* within 28-day follow-up; resistance at level I was defined as no parasitemia on day 7 after the initial treatment but asexual forms of *P. falciparum* reappeared during the follow-up period of 28 days; resistance at level II was defined as resistant parasitemia at day 7 after the initial treatment: resistance at level III was defined as failure to reduce the parasitemia by ≥ 75% of initial count, or deterioration in clinical condition after 48 hours of the initial treatment. Parasite clearance time (PCT) was defined as the time from the start of treatment until the first negative blood film and remained negative for the next 24 hours. Fever clearance time (FCT) was defined as the time from the start of treatment until the oral temperature fell to 37.5ºC and remained below that level for the next 48 hours.

Patients in whom *P. falciparum* reappeared were treated by a standard antimalarial regimen of the hospital *eg* artesunate 600 mg in 5 days followed by mefloquine 25 mg/kg divided into two

doses 6 hours apart, or quinine plus tetracycline for 7 days. For those who relapsed with asexual forms of *P. vivax*, they were treated with a single dose of 450-mg base of chloroquine (Harinasuta *et al*, 1985). Since *P. falciparum* in Thailand is resistant to chloroquine, they were not withdrawn from the study. Primaquine 15-mg base was given once daily for 14 days after the patient completed the study.

We performed statistical analysis using Epi Info Version 6.04 (USD, Inc, Stone Mountain, GA USA) software packages. Means of various parameters for the 3 groups were compared by analysis of variance while using chi-square test or Fisher's exact test where appropriate for comparing categorical variables. Two-tailed tests were used throughout and a p-value <0.05 was considered statistically significant.

RESULTS

A total of 202 patients were enrolled in the study. Some patients left the hospital before a 28-day admission in the hospital with social reasons not associated with adverse effects of antimalarial drugs. There were 68, 67, and 67 in group I, group II, and group III, respectively. The baseline data including age, sex, height, weight, history of previous infection, duration of fever before admission, parasite density, clinical and biochemical characteristics were comparable (Table 1). Most of the patients were experiencing their first malarial infection (52, 62, 41%, respectively).

The mean of parasite clearance time (PCT) and fever clearance time (FCT) did not show any difference among the three groups. However, the fever clearance time of group III was slightly shorter than the others (Table 2).

With a 28-day follow-up, 61 patients in group I, and 55 patients in group II and group III completed the study. Thirty-one patients (7 in group I and 12 in group II and group III) were lost to follow-up because of social reasons unrelated to drug treatment or side effects. All of them were asymptomatic and negative for asexual forms of *P. falciparum* when they left the hospital. The cure rates were significantly different among the three groups. Group II patients responded significantly better to both group I and group III regimens (cure rate of 44.3% in group I, 98.2% in group II, and 56.4% in group III) (p = 0.001, Table 2). In addition, there was an almost two-fold increased risk of developing RI resistance among group III patients who had an initial parasite density of more than 15,000 per μl (RR = 1.95, 95%CI = 1.06-3.58, p = 0.03). The parasites were all cleared from the peripheral blood smear within 84, 96, and 108 hours, respectively (Fig 1).

All of the patients, whose drug failed to clear parasitemia or were as considered having RI resistance, were given the rescue antimalarial medications according to the hospital's standard regimen. There were no RII or RIII responses in those patients after the rescued treatment. The median interval to *P. falciparum* reappearance was significantly delayed in group III versus group I (21 *vs* 16 days, p = 0.001, Table 2).

No death occurred during the trial. Most adverse events were mild to moderate severity. It was difficult to differentiate whether it was drug-associated side effects or signs and symptoms of malaria itself since most patients had typical malaria symptoms *eg* fever, chills, rigors, anorexia, nausea, vomiting, dizziness and headache at baseline. These events disappeared within a week after the drugs were administered. Furthermore, several patients had abnormal hematology and biochemistry values at the beginning, but all of these also improved few weeks after treatment.

DISCUSSION

Artemisinin derivatives are commonly used as antimalarial drugs especially in areas where multidrug resistant malaria is endemic. Their action on killing parasites is rapid. They reduce more parasite biomass in 48 hours than any other antimalarial drug (White, 1997), whereas recrudescence rates are high, depending on doses, duration of the treatment, and severity of the disease (Looareesuwan S, *et al*, 1992, 1997a,b; Bunnag *et al*, 1991, 1992). Combinations of artesunate and mefloquine have proved highly effective even against multidrug resistant *P. falciparum* (White, 1997), however adverse reactions such as nausea, dysphoria and vomiting are relatively common. Azithromycin has not only antibiotic effects but also antimalarial effects. It was effective against both liver and blood stage parasites (Andersen *et al*, 1994b, 1995).

In this study, a combination of artesunate with azithromycin showed a 28-day cure rate of 56.4%. On the other hand, a previous study, a

Table 1
Clinical and laboratory characteristics of study groups before treatment.

		Group I[a] (n=68)	Group II[b] (n=67)	Group III[c] (n=67)	p-value
Sex (Male: Female)	No. (% male)	45:23 (66)	44:23 (66)	46:21 (69)	0.92
Age (years)	Means ± SD (min-max)	25.7 ± 8.4 (12 - 49)	24.5 ± 8.8 (14 - 61)	24.8 ± 8.7 (13 - 49)	0.70
Height (cm)	Means ± SD (min-max)	159.6 ± 9.3 (132 - 174)	159.4 ± 7.8 (143 - 175)	160.1 ± 10.1 (116 - 175	0.89
Weight (kg)	Means ± SD (min-max)	53.5 ± 12.4 (28 - 95)	50.57 ± 9.5 (35 - 85)	50.1 ± 10.6 (33 - 84)	0.17
Duration of fever before admission (days)	Median (range)	3 (0 - 20)	3 (1 - 10)	3 (1 - 10)	0.67
First malaria attack	No (%)	33/63 (52)	39/63 (62)	27/66 (41)	0.06
Parasite density (per μl)	Geometric mean (range)	3.82 (1.9 - 5.1)	3.65 (1.5 - 5.2)	3.85 (1.5 - 5.4)	0.35
- < 5,000	No (%)	28 (41)	32 (48)	27 (40)	
- 5,000-14,999	No (%)	14 (21)	13 (19)	10 (15)	
- 15,000-49,999	No (%)	16 (23)	16 (24)	15 (22)	
- ≥ 50,000	No (%)	10 (15)	6 (9)	15 (22)	
Temperature (ºC)	Means ± SD (min-max)	38.0 ± 0.8 (36.3 - 40.0)	38.0 ± 1.0 (36.2 - 40.3)	38.0 ± 0.9 (36.0 - 40.0)	0.92
Hepatomegaly	No (%)	11 (16)	9 (13)	15 (22)	0.37
Splenomegaly	No (%)	12 (18)	9 (13)	5 (7)	0.21
Laboratory data	Means ± SD (min-max)				
- Hemoglobin (gm%)		11.8 ± 2.3 (7.2 - 15.8)	11.5 ± 2.5 (5.8 - 16.8)	11.7 ± 2.2 (6.3 - 16.5)	0.81
- WBC count (per μl)		5.8 ± 1.9 (2.0 - 10.5)	5.8 ± 2.0 (2.4 - 13.0)	6.2 ± 2.2 (2.5 - 13.2)	0.58
- Blood urea (mg/dl)		15.3 ± 15.6 (5.5 - 132)	12.8 ± 4.8 (4.5 - 25.7)	13.5 ± 4.2 (5.5 - 24.5)	0.31
- Serum creatinine (mg/dl)		1.0 ± 0.3 (0.6 - 2.7)	1.0 ± 0.2 (0.6 - 1.0)	1.0 ± 0.2 (0.7 - 1.3)	0.60
- Total bilirubin (mg/dl)		1.6 ± 1.2 (0.4 - 7.0)	1.5 ± 1.4 (0.2 - 7.5)	1.6 ± 1.1 (0.4 - 5.4)	0.83
- Serum AST		47.8 ± 36.6 (11 - 170)	44.0 ± 36.4 (14 - 203)	58.7 ± 64.8 (16 - 399)	0.18
- Serum ALT		47.2 ± 38.3 (5 - 183)	48.6 ± 43.3 (10 - 211)	53.0 ± 48.5 (10 - 254)	0.72
- Albumin (g/dl)		4.1 ± 0.5 (2.3 - 4.8)	4.0 ± 0.4 (3.3 - 4.8)	2.9 ± 0.5 (2.1 - 4.8)	0.54

[a]Artesunate.
[b]Artesunate + Mefloquine.
[c]Artesunate + Azithromycin.

Table 2
Therapeutic responses.

		Group I[a] (n=68)	Group II[b] (n=67)	Group III[c] (n=67)	p-value
No. of patients with 28-day follow-up	No. (%)	61 (89.7)	55 (82.1)	55 (82.1)	0.36
No. of patients drop out[d]	No. (%)	7 (10.3)	12 (17.9)	12 (17.9)	0.36
RI response	No. (%)	34 (55.7)	1 (1.8)	24 (43.6)	<0.001
Cure rate at 28 days	No. (%)	27 (44.3)	54 (98.2)	31 (56.4)	<0.001
Recrudescence day (days)	Median (range)	16 (11 - 23)	16 (16)	21 (14 -25)	<0.001
Fever clearance time (PCT)	Means ± SD (min-max)	37.9 ± 29.0 (0 - 152)	38.8 ± 32.1 (0 - 152)	33.6 ± 27.2 (0 - 120)	0.62
Parasite clearance time (PCT)	Means ± SD (min-max)	43.7 ± 13.6 (21 - 80)	45.3 ± 14.7 (11 - 97)	43.5 ± 17.3 (5 - 103)	0.80

[a]Artesunate.
[b]Artesunate + Mefloquine.
[c]Artesunate + Azithromycin.
[d]lost to follow-up.

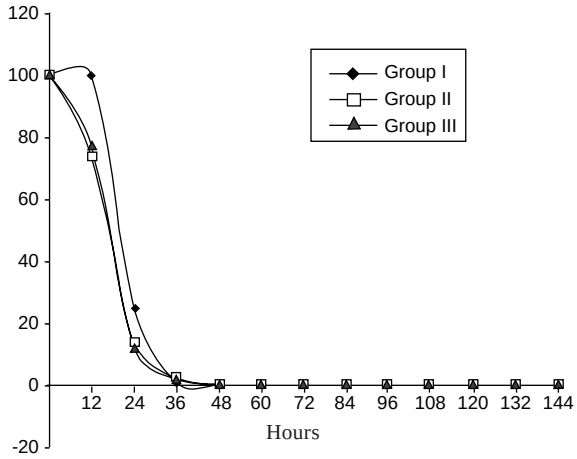

Fig 1–Mean of malaria parasite reduction (%) after treatment.

combination of artemether-azithromycin (300 mg artemether together with 500 mg azithromycin at 24 and 48 hours), showed a cure rate of 14.8% (Andersen *et al*, 1994). The higher cure rate obtained in this study could be related to the longer duration of artemisinin derivative and azithromycin administraion (3 days instead of 2 days). However, this combination was not as effective as the regimen of artesunate followed by mefloquine.

Following the artesunate-azithromycin regimen, recrudescence was significantly delayed compared to artesunate alone. Second, there was almost a two-fold risk of developing RI among the patients with an initial parasite count of more than 15,000 per µl. Furthermore, there were no clinical signs of adverse drug interactions between the combination of artesunate and azithromycin. Unfavorable effects were minimal and difficult to differentiate from signs and symptoms of malaria. These results indicate that the dosage of azithromycin in this trial might have been inadequate.

In conclusion, the results of this study revealed that the combination of artesunate and azithromycin was well tolerated. The simplicity of drug administration and minimal adverse events made azithromycin interesting as an alternative partner of artemisinin derivatives mefloquine. This combination might be useful particularly in treating African children in whom bacterial and malarial infections are commonly concomitant. Further study is required in order to enhance its clinical efficacy.

In general seven-day courses of short acting antimalarials are required for optimum cure rates. Azithromycin has unusual pharmacokinetic properties with a very slow terminal elimination half-life but the residual azithromycin concentrations were clearly insufficient for adequate antimalarial activity. A longer dose regimen may be more effective.

ACKNOWLEDGEMENTS

We are grateful to Professor NJ White for reviewing the manuscript and staff at the Hospital for Tropical Diseases for their help. This study was supported by the World Health Organization Regional Office in Thailand.

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