SIX-YEARS MONITORING THE EFFICACY OF THE COMBINATION OF ARTESUNATE AND MEFLOQUINE FOR THE TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA

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Abstract. *Plasmodium falciparum* in Thailand is multi-drug resistant. In a previous study it was shown that artesunate and mefloquine were effective, as follow up, we monitored the efficacy of this regimen for six years. During 1997-2002, 516 adult male volunteer patients in Chanthaburi Province were enrolled (50 patients in the first year, 400 patients in 1998-2001 and 66 patients in 2002). The symptom complex and parasite count (thick blood film) were monitored on days 0, 1,2,7,14,21,28,35 and 42. The dosages used were artesunate (ATS) 150 mg and mefloquine (M) 750 mg at hour 0 and ATS 100 mg and M 500 mg at hour 24. Their ages ranged from 30-35 years and their mean body weights were 54-56 kg. The presenting symptoms were fever 100%, headache 97-100%, anorexia 78-90%, and nausea 28-40%. The geometric mean of parasitemia ranged from 7,357-12,750/mm^3. Defervescence in one day was found in 42-76% of patients and 85-100% in 2 days. The sensitivity (S) ranged from 87-94% and RI resistance (recrudescence) ranged from 6-13%. Forty patients demonstrated RI type of response, 37 were cured after being retreated with the same dosage and another 3 patients were cured after the third course of treatment. The aggravated adverse effects included vomiting (8-20%), anorexia (1-41%) and diarrhea (0-16%). These side effects were mild and transient. The efficacy of the artesunate and mefloquine combination for the treatment of uncomplicated falciparum malaria was high. The RI type of response was possibly due to re-infection or multiple broods and not to drug resistance. The adverse effects of anorexia, nausea, vomiting and diarrhea were mild and transient for mefloquine. The combination can be used as stand by treatment in areas of multi-drug resistant falciparum malaria.

INTRODUCTION

Along the Thai-Cambodian border, *Plasmodium falciparum* is highly resistant to most available drugs. These include chloroquine, sulfadoxine-pyrimethamine, quinine , halofantrine, and mefloquine (Bunnag and Harinasuta, 1987; Karbwang and Harinasuta 1992; Ketrangsee *et al*, 1992; Bunnag *et al*, 1993; Thimasarn *et al*, 1995). Artesunate is one of the two artemisinin derivatives which are potent schizontocides. The parasite clearance time in 24 hours was over 95% but with high recrudescent rate when used alone (Bunnag *et al*, l991). Thus combination with a long half-life mefloquine was effective and only two doses are required, with good patients compliance (Bunnag *et al*, 1995). From our recent study (Bunnag *et al*, l997a) the course of treatment was shorter, 6 or 24 hours, with an efficacy of 98-100%. As artemether is not available in Thailand, a study was conducted to compare the efficacy of artemether/mefloquine versus artesunate/mefloquine. The result showed a very effective cure rate of 100% (Bunnag *et al*, 1997a,b). Therefore, we planned to test the efficacy of the combination in the same area of the Chanthaburi Province, along the Thai-Cambodian border, for six years.

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MATERIALS AND METHODS

Geographical area

Chanthaburi Province lies in eastern Thailand along the south-western border of Cambodia. There are nine malaria clinics (Malaria Division, Ministry of Public Health) and four were

invited to participate in the study. They were Makham, Pong Nam Ron, Soi Dao, and Tub Chang, about 90 km from Chanthaburi city center.

Patients

Male patients with uncomplicated falciparum malaria were invited to enroll in the study by staff of the malaria clinics when *P.falciparum* ring forms were diagnosed. They or their guardian signed written informed consent. In the first year, 50 patients were enrolled due to limited funding and 100 patients each year from 1998-2002 when more funds were available.

Clinical data

On enrollment day, general patient characteristics were recorded, including age, body weight and symptom complex of falciparum malaria including body temperature, headache, anorexia, nausea, vomiting and diarrhea. On follow-up days 1, 2, 7, 14, 21, 28, 35 and 42, an interview of aggravated side effects was recorded, body temperature measured, a thick blood film examined, and the parasitemia quantitated. If and when the staff recognized any severe symptoms or drowsiness in the patient he was advised to attend the regional Chanthaburi (Prapokklao) Hospital situated 20-90 km on an inter-city highway.

Drug administration

On the first day artesunate (ATS) 150 mg were given and mefloquine (M) 750 mg and on the following day ATS 100 mg and M 500 mg were given.

RESULTS

The efficacy and adverse effects of the combination of artesunate and mefloquine were evaluated for six years from 1997 to 2002. The results are shown in Table 1. In the first year only 50 volunteer patients were enrolled. From 1998 to 2001, enrollments yearly were 100, 100, 99 and 101 patients, respectively. For the last year 2002 only 66 patients were recruited, since the number of patients visiting the four malaria clinics was considerably reduced. Their ages ranged between 15-60 years with arithmetic means of 30±11 in 1999 and 35±12 in 2001. The body weights ranged between 40 to 89 kg with arithmetic means of 54±5 in 1999 to 56±7.3 kg in 2002. The mean body temperature on enrollment ranged from 38.4±1.09°C to 39±1°C. The parasitemia ranged between 180 ring forms to 450,000 ring forms/mm^3 with geometric means between 7,357 to 12,750 ring forms/mm^3.

Fever clearance time

The fever subsided in one day between 42 to 76% and in two days between 85 to 100%. All patients had no fever on day 7.

Parasite clearance time

The parasitemia was cleared in one day between 50 to 84% and in two days between 86 to 100%. Only one patient had parasitemia on day 7.

Exclusion from evaluation

Ten cases were lost for follow-up on days 21-35 (28.90±4.86 days) ranging between 0 to 4 cases per year for social reasons, they moved to work in other areas.

Sensitivity

Throughout the 6-year period, the parasites were found sensitive in 477 out of 516 patients, the range varying from 87 to 94%. RI type of response occurred in 39 patients, and a questionable RII type of response, a range from 6 to 13%. The reappearance of parasites occurred between 7-42 days.

The sensitivity ranges were from 87 to 94%, thus the RI type of response in 47 cases ranged from 6 to 13% of cases on days 7 to 42 with a median of 28 and a mean of 27.48±7.09.

Retreatment

Thirty-nine cases were retreated (second treatment) with the same dosage as the first, three cases had an RI type of response on days 39, in 1999, 28 in 2001 and 54 in 2000 and all three were cured by the third treatment.

Presenting symptoms

Five hundred and sixteen cases presented with fever (100%), headache (97-100%), anorexia (78-92%) nausea (24-40%), and vomiting (0%).

Adverse effects

Adverse effects (or aggravated symptoms) were recorded in 19 (2000) to 49 (1998) patients. They were anorexia (1-41), vomiting on day 0 and day 1 (8-20), diarrhea on day 0 and day 1 (0-16).

DISCUSSION

Almost all the volunteer patients lived in Chanthaburi Province. They worked in fruit orchards of durian, rambutan, longan, lychees, sweet tamarind and a few others. Their age was approximately 30 years and their body weight 55 kg. The geometric mean of parasitemias was about 10,000 ring forms/mm^3. An investigation on dosing time was carried out prior to these studies using artemether and mefloquine. It showed that the interval of the two doses of 6 hours and 24 hours produced similar efficacy, but higher adverse effects were observed in the 6-hours interval group (Bunnag *et al,* 1997a,b). Thus the 24 hour interval dosage was chosen. The fever subsided in about 90% of the volunteers in two days and the parasitemias were cleared in 95% in two days. There was about 10% of RI type of response. On retreating 40 patients with the same dosage, three again had RI type of response, which occurred on days 28, 39, and 54; the first two patients had previously recrudesced on days 28 and 15 respectively. The third patient had first recrudesced on

Table 1
Six -year monitoring 1997-2002 (Hour 0 : ATS 150 + M 750; hour 24 : ATS 100 + M500).

	1997	1998	1999	2000	2001	2002
Number	50	100	100	99	101	66
Age range	15-60	14-60	15-60	15-60	15-59	15-60
Mean±SD	31±12	32±13	30±11	32±13	35±12	31.1±11.6
Body weight range	46-85	40-89	40-65	45-65	42-72	45-85
Mean±SD	55±7	55±7	54±5	55±4	56±6	56±7.3
Temp (°C) range	38-40	37-40	37-40	36-41	36-41	36.3-40
Mean±SD	39±0.74	39±0.8	39±	39±1	39±1	38.4±1.09
Parasitemia range	240-149,100	180-150,600	300-450,000	240-347,400	540-216,000	330-208,000
G mean (mm^3)	7,357	8,920	10,829	10,033	12,750	10,787.57
FCT in 1 day (%)	76	42	50	53	42	36
2 day (%)	100	85	89	96	87	20
PCT in 1 day (%)	84	53	64	52	60	32
2 day (%)	100	97	100	96	96	33
Excluded for evaluation	0	4	2	2	1	1
on day…		23,28,35,35	28,35	28,28	28	21
Sensitive (S) (%)	94	91	92	91	87	91
Resistance (RI) (%)	6	9	8	8	13	6
	28, 28, 35	21, 28, 28, 35,39	15,18,19,21, 21,28,28,28	7,21,21,28, 28,28,28,28	14,21,28,28, 28,28,28,28, 28,35,35,35,35	28,28,28 34,42,42
Retreatment once n	3	5	8	6	12	6
twice n	0	0	1	1	1	0
(on day…)			(39)	(54)	(28)	
Symptoms : %						
Fever	100	100	100	100	100	100
Headache	100	99	98	97	98	97
Anorexia	78	90	84	80	83	92
Nausea	28	40	36	35	39	24
Vomiting	0	0	0	0	0	
Adverse effect	38	49	41	19	20	23
Anorexia	38	41	35	19	1	8
Vomiting D 0, D1	8	13	8	17	20	13
Diarrhea D 0, D1	16	2	1	0	7	7
Others	0	0	0	0	0	0

day 7, probably due to vomiting on day 0 at less than 2 hours after dosing and when given the second dose recrudesced on day 54. All three cases were cured when given a third treatment.

Twenty-one patients had high parasitemias of 149,100 in 1997, 150,600 in 1998 ; 104,400, 114,000, 147,000, 150,000, 240,000, and 450,000 in 1999; 102,900, 126,000, and 347,400 in 2000; 101,100, 115,200, 139,980, 144,690, 165,000, and 216,000 in 2001; 104,400, 108,000, 121,800 and 208,800 in 2002. (None of the above patients required hospitalization.)

All volunteers presented with mild symptoms. The aggravated adverse effects were due to the high dose of mefloquine 1,250 mg.

To confirm the parasite population, polymerase chain reaction (PCR) should be used in a future study to compare whether they were multiple sensitive broods or a mixture of sensitive and resistant strains which did not respond to the same dosage. It is interesting to note that this area, throughout the six years of observation (1997-2002), the sensitivity of the combination of artesunate 150 mg and mefloquine 750 mg given at hour 0 and artesunate 100 mg and mefloquine 500 mg given on day1 and at hour 24 remained at a very high level (91% in 2002). Interestingly, in the same area over a period of 9 years (1981-1989) the efficicacy of mefloquine alone at 1,000 mg was 100% (Harinasuta *et al*, 1983) but in 1989 the efficacy was reduced to 69% at 1,250 mg (internal report to WHO TDR Program). This same combination can also be used as standby treatment in areas of multidrug resistant falciparum malaria.

Conclusion

The efficacy of the combination of artesunate and mefloquine in 516 cases of uncomplicated falciparum malaria with multidrug resistance was 87% and on retreatment once or twice the cure rate was 100%. This dosage could be used as a standby treatment, The high side effects were for mefloquine, vomiting 20% and diarrhea 16%.

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