EFFICACY AND EFFECTIVENESS OF FIVE DAY TREATMENT OF UNCOMPLICATED FALCIPARUM WITH ARTEMISININ OR ARTESUNATE IN VIETNAM

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Abstract. A study on efficacy and effectiveness of artemisinin (total dose of 60 mg/kg) and artesunate (total dose of 12 mg/kg over five days) in treatment of uncomplicated malaria was conducted in highly malaria transmitted areas in Vietnam. 126 uncomplicated malaria cases finished 14 day follow-up. 100% cure rate achieved at day 14 in patients of the efficacy groups received either artemisinin or artesunate, while it was 83 % and 93 % in patients treated respectively with artemisinin and artesunate of the effectiveness groups. Compliance of the treatment regimens was discussed.

INTRODUCTION

Malaria is a major public health problem in Vietnam. According to the national annual report on malaria control for 1997, 34 million people, nearly half of the total population, live in malaria risk areas. *Plasmodium falciparum*, resistance to chloroquine and other antimalarials such as "Fansidar", quinine is highly prevalent, especially in the southern part of the country (Sy, 1995).

Since 1984, artemisinin and its derivatives have been produced and studied in Vietnam. In 1991, these drugs were introduced as first line antimalarials in areas of multi-drug resistance. Schedules of artemisinin 60 mg/kg over 5 days or artesunate 12 mg/kg over 5 days have been used as standard treatment of suspected or confirmed falciparum malaria in these areas.

The purpose of this study was to establish a methodology for monitoring the therapeutic efficacy of standard artemisinin and artesunate treatments, and to compare efficacy with effectiveness of routine treatment. The study was designed to detect a possible difference in cure rate between patients whose full treatment course was administered by a health worker (efficacy) and patient who would themselves administer prescribed treatment (effectiveness). Any such difference would be due to a compliance problem.

METERIALS AND METHODS

The study was conducted in January and February 1996 in Phuoc Long district, Song Be Province, southern Vietnam, and in May and July 1996 in Chu Se district, Gia Lai Province, central Vietnam.

Uncomplicated falciparum malaria patients with ≥ 500 asexual parasites/μl blood were included. Pregnancy in first trimester, symptoms of severe malaria and chronic diseases were criteria for exclusion. Previous treatment was not a criterion for exclusion, but was carefully recorded. Oral informed consent was obtained from all patients. At each site the patients were radomly divided into two groups. Half of the patients were allocated to supervised treatment, *i,e* administered morning and evening by a health worker (efficacy group); half were allocated to unsupervised treatment administered by themselves, except for the first dose (effectiveness group).

In Song Be, treatment was artemisinin 20 mg/kg on the first day, and 10 mg/kg on each of the following four days. In Gia Lai, treatment was artesunate 4 mg/kg on the first day and 2 mg/kg on each of the four following days. All daily doses were divided in two, to be taken morning and evening. Both artemisinin and artesunate were provided as tablets in blister packs (Mediplantex, Hanoi, Vietnam).

In the efficacy group, parasitemia and clinical signs were checked on day 0, 1, 2, 3, 4, 5, 6, 7 and 14. In the effectiveness group, after parasitemia and clinical signs had been ascertained on day 0, the drugs were given to the patients with a written and verbal explanation on how to use them. For small children, the tablets were divided and wrapped in daily doses and given to the mother. The patients were asked to come back for follow-up on Day 7

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and 14. However all patients were recommended to come back at any time if they became worse. All drug administration and all clinical examinations were carried out by members of the study team.

Patients, who defaulted from follow-up were traced at home on the same day by a member of the study team.

Data was managed and analyzed by EPI-info software. Significance tests used were χ^2, Student's *t*-test and Mann-Whitney tests as appropriate.

RESULTS

Thirteen patients in Song Be and ten patients in Gia Lai did not complete the study for reasons not related to the treatment or the disease, according to information provided by their relatives. They are not included in the data presentation and analysis. The number of patients in each treatment group, who completed follow-up in each site was 30-34. The baseline variables for these patients are presented in Table 1. Some patients were afebrile on presentation, but all reported having had fever within the last few days.

The mean fever subsidence time (FST) was 1.11 days (SD = 0.32) for artemisinin and 1.25 days (SD = 0.44) for artesunate; The mean parasite clearance time (PCT) was 2.15 days (SD = 0.34) and 1.59 days (SD = 0.16) respectively. Outcome variables are presented in Table 2. All cases in efficacy group treated either with artemisinin or artesunate showed adequate response (AR).

In the effectiveness group no early treatment failure (ETF) was observed, but in five patients treated with artemisinin and in one treated with artesunate, parasites reappeared on day 13 or 14. Among them only one patient treated with artemisinin had suffered from fever and sought the health worker for help on day 13 with temperature of 37.8°C. In the five other patients parasites were detected by a routine check on day 14. They were all afebrile and without complaint despite parasitemia, ranging from 32/µl to 35,040/µl.

Table 1
Clinical and laboratory variables before start of treatement.

	Number and (%) in each group					
	Artemisinin Phuoc Long, Song Be			Artesunate Chu Se, Gia Lai		
	Eflicacy	Effective-ness	p[a]	Efficacy	Effective-ness	p[a]
No. of patients	32	30		30	34	
Age, years, mean (SD)	15.2 (13.7)	12.0 (12.7)	0.31	14.9 (13.3)	11.8 (13.8)	0.15
Ethnic group:						
S'tieng	15(46.9)	18(60)	0.30			
Giarai				18(60)	25(73.5)	0.37
Kinh	17(53.1)	12(40)		12(40)	9(26.5)	
Males/Females	19/13	17/13	0.83	14/16	17/17	0.80
Fever (T≥37.5°C)%	24(75)	16(53)	0.07	20(65.6)	24(76.6)	0.25
Previous treatment %	2(6.6)	3(9.0)	0.6	2(6.7)	5(14.7)	0.3
Parasitemia/µl, GM (geometric SD)	5,217 (317)	3,382 (274)	0.028	4,426 (270)	3,467 (379)	0.24

p[a]: statistical p - value for comparison between supervised and unsupervised group by χ^2 - test (categorical variables) or Student's *t* - test (continuous variables).

Table 2
Recrudescence rate and clinical response to treatment regimes.

	Artemisinin			Artesunate				
	Efficacy -ness	Effective	p^a	Efficacy -ness	Effective	p^a	p^b	p^c
No. of patients	32	30		30	34			
FST (days) mean ± SD	1.11 ± 0.32	na		1.25 ± 0.44	na		0.18	
PCT(days) mean ± SD	2.15 ± 0.34	na		1.59 ± 0.16	na		<0.0001	
No. of recrudescences Day 13, 14 (%)	0	5 (16.7)	0.02	0	1 (2.9)	0.58		0.07

p^a = Comparison between efficacy and effectiveness.
p^b = Comparison between the two efficacy groups.
p^c = Comparison between the two effectiveness groups.
na = not applicable.

Side effects

Both artemisinin and artesunate were well tolerated. Vomiting in the first 30 minutes after drug administration was not observed. No severe adverse effects were recorded. Headache, nausea or dizziness were recorded during the first days in some patients but were difficult to differentiate from disease symptoms and they all passed as the patients recovered. One patient treated with artemisinin complained for a week of backache, which also disappeared without special treatment.

DISCUSSION

Efficacy

The cure rate by day 14 was 100% for both artemisinin and artesunate, as in previous studies (Hassan, 1995; Bunnag,1991). With longer follow-up, one would expect some recrudescences with both treatments (Sy, 1995; Bunnag *et al,* 1991). There were no differences between fever subsidence time (FST) ($p = 0.18$), but the parasite clearance time (PCT) in the artesunate group were shorter than in the artemisinin group ($p < 0.001$). There has not been a randomized controlled trial comparing the two drugs and it is uncertain whether the difference found here is due to a difference in drug efficacy or different patients or parasite characteristics in the two areas.

Effectiveness

Five recrudescences were observed in the artemisinin group (16.7%) and one in the artesunate group (2.9%). With artemisinin, the rate of recrudescence in the effectiveness group was significantly higher than in the efficacy group ($p = 0.02$), while with artesunate, the difference was not significant ($p = 0.58$). We noted that the education and economic level of patients was much higher in Chu Se, Gia Lai Province, than in Phuoc Long, Song Be Province. We therefore believe that the main reason for the discrepancy is better compliance in the former site.

The main result of our study is thus an increase of the recrudescence rate observed at day 14, by 16.7% in artemisinin treated patients in Song Be Province, and by 2.9% in artesunate treated patients in Gia Lai Province, when treatment was self-administered instead of completely supervised. This increase can only be ascribed to insufficient number of treatment doses due to incomplete patients compliance. The compliance in the effectiveness groups was probably the best that could be obtained in clinical routine, since patients were given oral and written instruction by members of study team.

With a parasitological cure rate at day 14 of more than 80%, the five day regimen, given without supervision, but with careful explanation can be expected to prevent the development of severe disease in the great majority of patients . Five of six of the recrudescences were asymptomatic, so the immediate clinical problem would seem not to be too serious. However, the difference in effective-

ness between supervised and unsupervised patients might have been greater, if the observation period had been extended. Furthermore, the recrudescences which were asymptomatic when observed at day 14 could become symptomatic if left untreated. They could also develop gametocytes and contribute to the maintenance of transmission.

In a malaria control program, which aims at gradually reducing transmission, and where the potential development of drug resistance is of great concern, it is desirable to look for regimen which can yield a very high cure rate in routine patient care. Although we know of no study documenting effectiveness as opposed to efficacy, (Looareesuwan *et al,* 1996; Sabchareon *et al,* 1998) of three days combination of artemisinin with mefloquine, it is likely that compliance would be better than with five days of monotherapy. However, mefloquine is too expensive for general use in the Vietnamese national malaria control program. Because of its long half-life, it is also not a good solution, when the risk of drug resistance is a major concern. It is therefore necessary to look for other suitable drugs that can be combined with drug to provide high effectiveness.

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