FANSIMEF FOR PROPHYLAXIS OF MALARIA: A DOUBLE-BLIND RANDOMIZED PLACEBO CONTROLLED TRIAL

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Abstract. At a time when Fansimef®, the fixed combination of mefloquine, sulfadoxine and pyrimethamine was considered for prophylaxis of falciparum malaria, a randomized double-blind study comparing the efficacy and tolerability of Fansimef® with that of Lariam® (mefloquine), Fansidar®, chloroquine and placebo in malaria prophylaxis was performed in Thailand from July 1987 to January 1988. The study population of 602 adult males was recruited in Pak Tongchai District, some 360 km North-East of Bangkok, where multiresistant *P. falciparum* is endemic. All active treatments and placebo were given once weekly for 24 weeks with doses as follows: Fansimef: 125 mg mefloquine + 250 mg sulfadoxine + 12.5 mg pyrimethamine (1 half-strength tablet); Lariam: 125 mg mefloquine (1 half-strength tablet); Fansidar: 500 mg sulfadoxine + 25 mg pyrimethamine; chloroquine; 300 mg. A loading dose of 2 half-strength tablets was given in the Fansimef group in weeks 1 and 2 and in the Lariam group in weeks 1 to 4. The incidence of acute episodes of *P. falciparum* per 100 person months of prophylaxis was 0.17 each in the Fansimef and the Lariam groups, 1.18 in the Fansidar group, 0.69 in the chloroquine group and 0.64 in the placebo group (differences statistically not significant). Clinically adverse events were reported by 170 subjects (Fansimef 28, Lariam 29, Fansidar 41, choroquine 43, placebo 29; differences statistically not significant). The most frequent adverse events in all groups were headache, sleepiness, dizziness and weakness. There were five adverse events that led to premature discontinuation: 1 each in the placebo, chloroquine and Fansidar groups and 2 in the Lariam group (breathing difficulties, dizziness, dull head, feeling feverish, weakness and "less active"). In this setting Fansimef and Lariam offered an approximately four-fold higher protection than Fansidar or chloroquine which resembled placebo in their effect. The safety of low Fansimef and Lariam prophylactic doses was similar to placebo.

INTRODUCTION

Resistance of *Plasmodium falciparum* to almost all current antimalarials is an increasing problem for prophylaxis and treatment of malaria. Mefloquine has been shown to be effective in treatment of mutiresistant *P. falciparum* malaria. However, *in vivo* resistance to mefloquine has appeared in Thailand (Boudreau *et al,* 1982; Webster *et al,* 1985), the Philippines (Smrkovski *et al,* 1982) and East and West Africa (Bygbjerg *et al,* 1983).

A fixed combination of mefloquine (M) with sulfadoxine (S) and pyrimethamine (P) in the ratio of 250:500:25 mg (Fansimef®) was introduced with the aim of delaying the development of resistance to the single components shown in the *P. berghei* mouse model (Peters and Robinson, 1984, Merkli *et al,* 1980).

In Thailand in 1984, 2 and 3 tablets of Fansimef gave cure rates of 93 and 98% respectively in acute falciparum malaria (Harinasuta *et al,* 1983). In 1986 and 1987, cure rates of > 98% were published (Meek *et al,* 1986; Nosten *et al,* 1987). In a recent study, carried out in an area where mefloquine resistance occurred, 3 tablets of MSP (M dose of 750 mg) and 5 tablets of Lariam (M dose of 1,250 mg) gave equivalent cure rates (Roche internal report 1989), thus demonstrating superiority of MSP over M alone. In Vietnam, MSP continues to be highly effective (Anh *et al,* 1990).

Since the late 1950s, the incidence of chloroquine resistant falciparum malaria in Thailand has increased rapidly to over 90%. Resistance to sulfadoxine-pyrimethamine and quinine has followed closely to over 90% and 25% respectively (Bunnag and Harinasuta, 1987). For special groups of personnel at high risk of falciparum infection such as Military Rangers of Border Patrol Police in need of prophylaxis, MSP could be deployed. This was considered when a study was performed with the

aim to evaluate efficacy and tolerability of a half-strength tablet of Fansimef (125 mg M, 250 mg S + 12.5 mg P), compared to Lariam®, Fansidar®, chloroquine and placebo for malaria prophylaxis in an endemic area of multi-drug *P. falciparum* malaria.

MATERIAL AND METHODS

Study site

The project was jointly organized and conducted by the Malaria Division, Department of Communicable Disease, Ministry of Public Health; the Hoffmann-La Roche company, Basel, Switzerland; and The Faculty of Tropical Medicine, Mahidol University, Bangkok. A malaria endemic area of 150 km^2 at Pak Thong Chai District, Nakhon Ratchasima Province, Thailand was selected as the field study site. It is 400 km (National Highway) northeast of Bangkok on a high plateau (200 m above sea level), with mountains and streams. This area was a forest 20 years ago, but at the time when the study was conducted held 16 villages with a population of about 20,000. Most of the villagers are paddy farmers and planters (tapioca, maize, sugar cane, etc). The rainy season extends from June to November with annual temperatures between 13°C and 34°C.

Design

The study was designed as a single center, randomized double-blind trial with five parallel groups, receiving either Fansimef®, Lariam®, Fansidar®, chloroquine or placebo once weekly for 24 weeks, with a follow-up period of 4 weeks. For dosages see Table 1. The tablets were identical in appearance; they were packed in numbered blister packs and were in addition labeled weeks 1-24. The study was conducted between July 1987 and January 1988 (malaria transmission season: July-December), *ie* one month after start of the rainy season.

Procedure

The trial was performed by two research teams: 17 local Malaria Field Workers who were familiar with the area and were well-known to the villagers were provided by the Malaria Division; 12 other people, including investigators and monitors, came from the Bangkok Hospital for Tropical Diseases. A laboratory was set up, two 1 kw electricity generators and lighting equipment were supplied by the Malaria Division. Thee Field Workers travelled by their own motor cycles to visit each volunteer at the residential and field sites.

Table 1

Dosages of drugs given to 5 groups of volunteers for malaria prophylaxis of 24 weeks duration.

Drug	Dose/week
Fansimef®*	125 mg M + 250 mg S + 12.5 mg P
Lariam®**	125 mg M
Fansidar®	500 mg S + 25 mg P
Chloroquine	300 mg
Placebo	1 tablet

* at first 2 weeks double dose was given
** at first 4 weeks double dose was given

Healthy male volunteers, aged between 16 and 60 years, living in this area, were recruited. Persons with a known history of allergy against sulfonamides, with an evident illness of fever, or with a positive malaria blood film (with or without symptomatic malaria) were excluded. After having given oral informed consent (which was recorded in the English/Thai Clinical Case Report Form and signed by a witness), eligible volunteers were randomly assigned to treatment groups.

During the week prior to start of the drug administration a running number was given to each volunteer. The demographic data, past history of malaria, mosquito exposure prevention (use of bed nets, incense, or repellent), wearing long trousers or long garments, outdoors at evening, allergies, and concomitant diseases were recorded by the Field Workers. Fingertip capillary blood was obtained in three capillary tubes for a thin/thick malaria film, and for the determination of hematocrit, white blood cell count and white cell differential count. In the first week, after a snack (cookies and Thai sweets) the coded test drugs for weeks 1-4 were given to every subject and the swallowing of the first dose was observed by one of the personnel. Subsequent visits were performed by the

Table 2

Schedule of assessment at baseline, during the 24 weeks treatment phase and the 4 weeks wash-out period.

	Baseline	Follow-up during prophylaxis	Follow-up during wash-out
Medical history	×		
Physical examination	×		
Clinical signs for malaria		× if any	× if any
Adverse events		× if any	× if any
Parasitology			
Thin smear	×	every four weeks	week 28
Thick smear	×	every four weeks	week 28
Laboratory parameters			
Hematocrit	×	week 4 and 24	week 28
WBC	×	week 4 and 24	week 28

field workers during treatment in weeks 4, 9, 14, 19, 24 and, after the end of suppressive treatment, during week 28 (follow-up visit) (for schedule of assessments see Table 2). In weeks 4, 24 and 28 laboratory tests (hematocrit, WBC differential count) were repeated, in addition to thin/thick malaria smears. At weeks 9, 14, 19 only malaria blood films were obtained. At each visit, all volunteers were asked about the dates of tablet intake, the expericence of acute attacks of malaria and adverse events or concomitant diseases. Malaria episodes were defined by a history of symptoms suggestive of malaria including fever and malaise and diagnosis was confirmed with a blood smear. Adverse events were defined clinically, and, starting week 14, volunteers reporting adverse events were interviewed by members of the Hospital team; most of them were also seen by principal investigators (DB and TH). To detect parasitemia without clinical symptoms thick-thin malaria films were checked. Blood films were stained with Giemsa. Examination of 200 negative oil fields constituted a negative slide.

Statistical analysis

For statistical analysis of efficacy the proportion of confirmed cases of *P. falciparum* malaria within 24 weeks of prophylactic treatment per 100 person-months was calculated. Person weeks were computed for each individual by summarizing the number of weeks the individual remained in the study. Fansimef® was compared to the other four treatments by Fisher's exact tests, using the Bonferroni-Holm adjustment for multiple comparisons.

The numbers of subjects who suffered one or more adverse events were compared using the closed test procedure for a one to many comparison. According to the protocol the Chi Square test was applied for all comparisons.

RESULTS

Demographic data

The agregate mean age of participants was 34-35 years, the aggregate average weight and height 53-54 kg and 161-163 cm, respectively. The 5 groups were comparable with regard to age, weight and height (Table 3).

Efficacy data

Of the 605 subjects originally randomized, 3 were excluded because of baseline parasitemia.

Table 3

Demographic data of 5 prophylactic groups (in bracket: medians).

	Fansimef® N = 120	Lariam® N = 123	Fanidar® N = 119	Chloroquine N = 119	Placebo N = 121
Age (years)	16-59 (31)	16-60 (30)	16-56 (31)	16-60 (31)	16-60 (34)
Weight (kg)	40-71 (53)	39-69 (54)	40-74 (53)	38-84 (54)	36-85 (54)
Height (cm)	150-178 (162)	145-185 (162)	148-180 (162)	148-177 (163)	149-180 (162)

Table 4

Episodes of malaria, person weeks of prophylaxis and incidence, per group.

Prophylactic Drugs	Number of acute episodes of malaria	Personweeks of prophylaxis	Incidence per 100 person months
Fansimef®	1	2,591	0.17
Lariam®	1	2,550	0.17
Fansidar®	7	2,545	1.18
Chloroquine	4	2,469	0.69
Placebo	4	2,663	0.64

Table 5

Number of participants who reported adverse events (AEs), number of AEs and number of AEs leading to premature stop of tablet intake.

Group	Subj with AEs/ subj in group	% of subj with AEs	No of all AEs	AEs leading to premature stop	week when last dose was taken
Fansimef®	28/116	24	38	-	-
Lariam®	29/116	25	36	2	3/11
Fansidar®	41/115	36	53	1	4
Chloroquine	43/112	38	58	1	14
Placebo	29/119	24	44	1	1

Table 6

Occurrence of acute episodes of malaria.

● *P. falciparum* ○ *P. vivax*	July	Aug	Sept	Oct	Nov	Dec	Jan
Fansimef® (N = 120)						●	
Lariam® (N = 123)				●*)			○
Fansidar® (N = 119)	● ○	● ●	●		● ●	●	○
Chloroquine (N = 119)	●	● ○	●	●			
Placebo (N = 121)		○	● ○	●		● ●	
	◄ = = = = = = Treatment phase = = = = = = ►						◄ = = ►
							Follow-up

* tablets not taken in weeks 5, 6, 7 and 8

The remaining 602 constituted the total. The number of participants in groups 1 to 5 was 119, 119, 120, 123 and 121 respectively. Of these, 17 suffered an acute episode of *P. falciparum* malaria (Table 4, 6). No significant differences could be detected between Fansimel® and the other treatments (including placebo). The malaria incidence was low during the study period, but cases occurred evenly between July and December Table 6.

Safety data

Clinical adverse events were reported by 170 subjects. The frequency of adverse events was similar in the placebo (29 or 24%), Lariam® (29 or 25%) and Fancimef® groups (28 or 24%), and somewhat higher in the Fansidar® (41 or 36%) and chloroquine group (43 or 38%) (Table 5, 6). The trend for better tolerability of Fansimef® compared to chloroquine and Fansidar® was, however, statistically not significant.

Most adverse events were mild and involved the nervous system (headache, sleepiness, dizziness). Five volunteers, one each from placebo (after dose 1), chloroquine (after dose 14), and Fansidar® groups (after dose 4), 2 from the Lariam® group (after doses 4 and 12 respectively), and none from the Fansimef® group left the trial prematurely because of adverse effects. These were breathing difficulty, fainting, and legs shaking (placebo group), dizziness (choroquine group), dull head (Fansidar® group), feverish, weakness, and "less active" (Lariam® group). This last subject refused to be re-interviewed by the investigators (DB and TH).

Hematological results

The results of hematocrit, WBC count and neutrophil count were within normal limits at baseline and did not change relevantly during the study.

DISCUSSION

During the 6-month study period (July-December 1987), 384 malaria cases were registered in the six malaria clinics located in the study area. 66% of the cases were due to *P. falciparum*. For an estimated catchment population of 20,000 extrapolation to a year would give an estimated incidence of clinical falciparum malaria of 25/1,000/year, which is rather low. We considered it essential to include a placebo group in the trial. Since the study population usually did not use any malaria prophylaxis, the ethical issue did not arise. The placebo group allowed us conclusions on the type and true incidence of adverse events. In this study only headache was found slightly more often in the Fansimef® group than in the placebo group. Other adverse events occured in the active treatment groups to the same or even lower extent than in the placebo group. One of the volunteers, who complained about severe adverse events and left the study for this reason, was in the placebo group. Although some of the volunteers left the

study for personal reasons (moving away from the area) and some of them missed drug-taking (three doses and more), compliance and cooperation in general was good; as an expression of satisfaction with the general medical care as well as with the prophylaxis program the volunteers also agreed to participate in future studies. Fansimef® and Lariam® were effective in the prophylaxis of falciparum malaria. During medication weeks, one case of breakthrough was observed in either group as compared to four each in the placebo and chloroquine group and seven in the Fansidar® group.

In conclusion, in this study Fansimef® half dose (125 mg mefloquine, 250 mg sulfadoxine, 12.5 mg pyrimethamine) once weekly and Lariam® half (125 mg mefloquine) once weekly exhibited adequate protection against *P. falciparum* and safety of these prophylactic regimens was similar to placebo.

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