

Mefloquine and Fansidar Alone and in Combination with Quinine
for the Treatment of Falciparum Malaria

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OBJECTIVE : To determine the efficacy of mefloquine in naturally-acquired falciparum malaria.

BACKGROUND : Mefloquine hydrochloride is an analogue of quinine and of WR 30090, an antimalarial which was developed during the Viet Nam war and was used effectively in the treatment of military personnel with falciparum malaria unresponsive to other drugs. It is a 4-quinoline-methanol containing a 2-trifluoromethyl group which blocks ring oxidation at that point, a major site of enzymatic inactivation of quinine.

Fansidar, a 20:1 combination of sulfadoxine and pyrimethamine has been used widely for the single-dose therapy of falciparum malaria, and has been shown to be 85% and 82% successful in SMRL studies in Trat and Prachinburi provinces respectively.

Recent SMRL studies have shown the most effective therapeutic regimen for drug resistant malaria in Thailand to consist of a short course of quinine followed by a single oral dose of Fansidar. Four doses of quinine, 10 grains every eight hours, followed by a single dose of Fansidar produced a cure rate of 96% (1).

DESCRIPTION : The study was opened at the Chao Phya Abhai Phu Bejr Hospital (Prachinburi Provincial Hospital). In the early phase of the study, only patients with clinically mild and moderate infections were considered eligible. Male volunteers over 15 years of age with *P. falciparum* asexual parasitemias of more than 1,000/cu.mm., were admitted to the study and assigned randomly to single dose oral therapy with either Fansidar, three tablets (total 75 mg. pyrimethamine and 1.5 gm. sulfadoxine) or mefloquine, six tablets (1.5 gm.).

Parasite counts were performed twice daily in the hospital and on days 14, 21 and 28 following therapy, at follow-up visits. Hematocrit, WBC count, urinalysis and liver function studies were also performed.

In the later phase of the study, patients of all degrees of severity were admitted to the study; they were treated with quinine, administered either orally or intravenously, 10 grains every eight or twelve hours, followed by a single dose of either mefloquine or Fansidar when their clinical condition had improved.

Therapeutic response was judged by a modification of the WHO criteria (2). An RIII response was diagnosed if the patient's clinical condition and/or parasitemia failed to improve or worsened within

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a few hours after administration of the test medication. An RII response indicated reduction but not elimination of asexual parasites following therapy, and an RI response was arbitrarily diagnosed if asexual parasites reappeared on or before the 28th day following the initiation of therapy, whether or not the patient had returned to an endemic area.

In some patients, it was later decided that an RIII response was diagnosed prematurely, and that the test regimen may have proven effective on its own. These cases were classified as undetermined results.

An S response (radical cure) was diagnosed in patients in whom asexual parasitemia cleared promptly and did not reappear during the 28-day follow-up period.

PROGRESS : Fansidar — Thirty-six patients were treated with Fansidar (Table 1). All patients received three tablets except one boy weighing 31 kg., who received two. In four patients, RII or RIII early failures were diagnosed, and quinine was added. In two additional patients, increases in parasitemia occurred, but by the time quinine was added, improvement in the clinical picture and fever had already occurred. It was considered that quinine was given prematurely, and treatment failures were therefore not diagnosed. Two patients responded in hospital, but recrudesced before the end of the 28-day follow-up period, and were considered RI failures. Six patients did not complete follow-up. The overall cure rate was 80%. Parasite and fever clearances were 76 and 61 hours respectively (Table 2).

Mefloquine — Thirty-two patients received a single oral dose of mefloquine. Four patients weighing between 30 and 40 kg. received 1.25 gm.; the others were treated with 1.5 gm. One patient did not complete follow-up; one patient had a recrudescence on the 24th day following treatment, after having returned to an endemic area; and one patient was given quinine seven hours after the oral dose of mefloquine because of an increasing asexual parasite count. In retrospect, this last patient probably should not have been a candidate for oral therapy on admission because of the symptom combination of borderline hypotension, lack of fever, and prostration; the complex known as "algid malaria". Drug absorption in such a patient would be expected to be slow, and effective blood levels of the drug difficult to obtain. It is likely that the drug was eventually absorbed since the patient went on to complete recovery following only three doses of quinine. Eliminating this last patient from consideration, mefloquine produced a 97% cure rate. Parasite and fever clearance times were 66 and 48 hours respectively.

Quinine-Fansidar — Forty-four patients were treated with from one to eleven doses of quinine followed by a single dose of Fansidar (average 4.7 doses of quinine). Three patients developed RI recrudescences, making the overall cure rate 92% (36 of 39 patients followed up).

Quinine-Mefloquine — Forty patients were treated with quinine, one to eleven doses (average 4.3) followed by a single oral dose of mefloquine. Complete follow-up was achieved in 35 patients, all of whom were radically cured.

Gastrointestinal side-effects were most often seen in patients receiving the quinine-mefloquine regimen. This is not surprising, since the drugs are similar and would be expected to produce additive toxicity. Mefloquine alone was occasionally responsible for protracted vomiting and diarrhea. These side-effects were controlled with symptomatic medication and none were considered severe. Fansidar alone was not associated with any drug-related side effects. Quinine-Fansidar patients showed only side effects related to quinine therapy; tinnitus, dizziness and nausea. (There were no side effects attributable to Fansidar).

A method of determination of serum levels of mefloquine has recently been developed and specimens from this study are currently being analyzed. In view of the relatively small numbers of patients who received single oral doses of mefloquine and Fansidar, the study is being continued at the Phrapphattabat Hospital, Saraburi Province.

REFERENCES :

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2. Doberstyn, E.B., Hall, A.P., Vetvutanapibul, K., and Sonkom, P. Single-Dose Therapy of Falciparum Malaria using Pyrimethamine in Combination with Diformyldapsone or Sulfadoxine. Am. J. Trop. Med. Hyg., 25, 14-19, 1976.

Table 1. Therapy of *P. falciparum* Malaria, Prachinburi 1975

Regimen	Total Patients Studied	Initial Parasite Count (Average/Range)	Response*				Total Patients Followed-up	Cure-Rate
			RIII	RII	RI	S		
Quinine : Mefloquine	40	58,000 (1,700 - 750,000)	0	0	0	35	35	100% (35/35)
Mefloquine	32	47,000 (1,440 - 177,000)	0	0	1	29	30	97% (29/30)
Quinine : Fansidar	44	56,000 (1,100 - 656,000)	0	0	3	36	39	92% (36/39)
Fansidar	36	42,000 (1,200 - 134,000)	1	3	2	24	30	80% (24/30)

- * RIII, no marked reduction of asexual parasitemia;
 RII, marked reduction of asexual parasitemia, but no clearance;
 RI, clearance of asexual parasitemia, followed by recrudescence;
 S, clearance of asexual parasitemia, without recrudescence (radical cure).

Table 2. Average Parasite and Fever Clearance Times
for Mefloquine and Fansidar^R

	Number Patients	Average Parasite Count	Parasite Clearance Time in Hours (Average/Range)	Average Initial Temperature (°C)	Fever Clearance Time in Hours (Average/Range)
Mefloquine	32	47,000	66* (19 - 116)	39.4	48** (10 - 104)
Fansidar	36	42,000	76* (42 - 135)	39.5	61** (9 - 114)

* t = 1.06, p > 0.1

** t = 1.11, p > 0.1