Single-Dose Therapy of Falciparum Malaria with Mefloquine or Fansidar(R) (pyrimethamine-sulfadoxine)

Investigators : Edward B. Doberstyn, LTC, MC
Phung Phintuyothin, MG, MC, RTA, (Ret.)
Suphat Noeypatimanondh, M.D.
Chaiphorn Teerakiartkamjorn, M.D.

OBJECTIVE : To further evaluate the therapeutic efficacy of mefloquine hydrochloride given as a single dose to patients with acute falciparum malaria. To compare its effect and toxicity with that of Fansidar, the current single-dose drug of choice.

BACKGROUND : Mefloquine hydrochloride (WR142490) is an analog of quinine and of the investigational drug WR30090 which was used successfully to treat cases of chloroquine-resistant falciparum malaria in American servicemen returning from the Vietnam war as well as indigenous cases in Thailand. Mefloquine has been studied in Thailand both as a single regimen and in combination with quinine. It also has been studied as a suppressant of falciparum and vivax infections in the Bu Phram Valley, Prachinburi Province. It has been known to be highly effective both as therapy and prophylaxis.

METHOD : The study was carried out at Phrabuddhabat Hospital in Saraburi Province, Central Thailand. This area is known to be endemic for chloroquine-resistant falciparum malaria. Current in vitro data confirm the high level of chloroquine resistance of parasites in the patients reporting for treatment in this area. Patients were selected from those presenting to the hospital outpatient department and the Passive Detection Center of the National Malaria Eradication Project Regional Headquarters in Phrabuddhabat.

Criteria for selection of patients included the following :

1. Males at least 18 years of age (possible side effects of neither drug have been completely evaluated in pregnancy or in young children).

2. Moderate parasitemias. Patients were generally not admitted to the study if the asexual count was less than 1,000 or more than 100,000/cu.mm.

3. Uncomplicated disease. Patients in coma, with severe jaundice, uncontrollable vomiting or with evidence of renal, pulmonary, or cardiac complications were not admitted to the study.

4. Willingness to sign a consent form after details of the study had been explained. The use of a new drug, the need for prolonged follow-up and repeated venipuncture were described to the patients before the signature was requested. A Thai language information sheet containing details of the study was given to the patients. Patients considered eligible for the study were admitted to the male medical ward of the hospital and were followed by one of the investigators with clinical rounds conducted at least twice daily.

Quantitative parasite counts by the technique of Earle & Perez were performed eight hourly until asexual parasitemia had disappeared, and at each follow-up visit. A detailed record of symptoms and physical signs was kept by the physician during hospitalization and at follow-up visits. In addition, clinical laboratory examination of hematologic, renal and hepatic function were performed on admission and at intervals during hospitalization and follow-up. Serum screening for quinine and sulfonamide was performed at AFRIMS, Bangkok, on specimens obtained on admission and at follow-up visits in order to detect additional antimalarial self-treatment.

Patients were kept in the hospital an average of four days and then followed as out-patients on days 10, 15, 21, 28, 38, 50 and 60 after admission. Upon discharge, patients were driven home and a record was kept of their home address. If a patient failed to keep a follow-up appointment, an attempt was made to follow him at home. Mefloquine was supplied by the Walter Reed Army Institute of Research and the Fansidar* was purchased locally. Drugs were administered by an investigator and patients were checked to assure that they had swallowed the tablets. Alternate patients were assigned to one of the following single-dose regimens :

1. Fansidar three tablets (pyrimethamine 75 mg., Sulfadoxine 1.5 gm.)

2. Mefloquine hydrochloride six tablets (1.5 gm.)

In addition, antipyretics and analgesics, intravenous fluids and suppressants of nausea and diarrhea were used as clinically indicated.

Treatment results were evaluated according to the WHO criteria originally conceived to evaluate chloroquine resistance : "S" indicates clearance of asexual parasitemia and maintenance of a negative blood film for 28 days after therapy. "RI" refers to initial clearance of parasitemia followed by recrudescence within 28 days after treatment, "RII" indicates initial reduction in the level of parasitemia, but failure to clear in seven days. "RIII" indicates no reduction in parasitemia following treatment.

RESULTS : Ninety-one patients were admitted to the study and followed for at least seven days. Of these, 75 were followed for at least 28 days (82%) and 50 (55%) were followed for 60 days.

There was no significant difference between the two groups in regard to age, initial parasite count or percentage returning to areas of transmission during the period of follow-up.

In patients followed at least 28 days, 100% of the mefloquine group (37/37) were radically cured ("S" response). Of the Fansidar group, 89% were cured (34/38); there were two RI failures and two RII failures (Table 1). RI recrudescence were detected on Day 21 and Day 28 of follow-up respectively, and may

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have been due to reinfection, although the patients denied having returned to areas of malaria transmission. After recrudescence, treatment with mefloquine resulted in radical cure in both cases. Patients described as experiencing RII failures were retreated with mefloquine after Fansidar had failed to clear parasitemia in seven days. Both of these patients cleared their parasitemia rapidly and remained well for an additional 60 days of follow-up.

Table 1. Results of Treatment

Regimen	Number of Patients	Mean Asexual Parasite Count	Mean Fever Clearance Time (hours)	Mean Parasite Clearance Time (hours)	Therapeutic Result				Cure Rate
					RI	RII	RIII	S	
Fansidar	38	25,770	64	67	2	2	0	34	89%
Mefloquine	37	24,750	58	62	0	0	0	37	100%

Fever and parasite clearance times for mefloquine (58 and 62 hours, respectively) were shorter than those for Fansidar (64 and 67 hours) but the difference was not significant. The fever and parasite clearance times associated with mefloquine were slightly better than those obtained when quinine is used alone, (64 and 70 hours, respectively). Fansidar rates were almost identical with those for quinine.

The regimens were alike in their association with symptoms of malaria; e.g., headache and dizziness, but differed in regard to the presence of gastrointestinal complaints (Table 2). Nausea, vomiting and diarrhea were more common in the mefloquine group than in the Fansidar group. However, no patient had severe vomiting or diarrhea, and these symptoms were easily managed with routine medication.

There was no significant difference between the two groups either before or during therapy, in routine hematologic or biochemical parameters.

Abnormalities which did occur were more likely related to malaria than to either therapeutic regimen, and most had cleared by the end of the follow-up period.

This study is now complete and the manuscript has been submitted for publication.

Table 2. Symptoms Encountered During Initial Four Days of Hospitalization.

Symptom	Regimen			
	Fansidar (48 pts.)		Mefloquine (49 pts.)	
	Number	Percent	Number	Percent
Headache	45	94	46	94
Dizziness	44	92	47	96
Nausea	28	58	41	84
Vomiting	14	29	25	51
Diarrhea	8	17	13	27