

Treatment of the Acute Attack of Malaria Caused by
Plasmodium vivax: A Comparison of Mefloquine
with Standard Therapy

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OBJECTIVE : To compare the effect of several antimalarials upon sexual and asexual parasitemia with *P. vivax* in naturally infected individuals.

BACKGROUND : Standard therapy of *P. vivax* infections in Thailand consists of 1,500 mg. of chloroquine administered over the course of three days in G-6-PD normal individuals. Other therapy occasionally used includes Fansidar (sulfadoxine-pyrimethamine), and in some cases pyrimethamine. Mefloquine hydrochloride, a new antimalarial developed by the U.S. Army's Antimalarial Drug Development Program, has been shown to be useful in the therapy of the acute vivax attack in American volunteers (1). It had no effect in the prevention of relapse, however. Mefloquine has also been shown in several studies to be highly effective both in laboratory-induced and naturally acquired infection of *P. falciparum*.

Primaquine, aside from its activity in the prevention of relapse of infections with *P. vivax*, is also gametocytocidal against the sexual forms of both *P. vivax* and *P. falciparum*. The gametocytocidal effect is apparent after very small doses of the preparation.

METHODS : The study has been underway at two malaria-endemic areas in Thailand. The project was initiated at the Phrabuddhabat Hospital, in Saraburi Province and later moved to the Phraya Paholpolpayuhasena Hospital, the Kanchanaburi Provincial Hospital. Patients were admitted either from the out-patient department of the hospital or from the passive detection center of the National Malaria Eradication Project. The usual conditions for acceptance of subjects to chemotherapeutic trials were applied. Patients were randomly assigned to one of the following therapeutic regimens :

1. Mefloquine hydrochloride, single dose 1,500 mg., p.o.
2. Fansidar, single dose : a) two tablets, b) three tablets.
3. Chloroquine 1,500 mg. Total dose p.o., administered over three days.
4. Chloroquine, 1,500 mg., as above plus primaquine 15 mg. daily for five days.

5. Pyrimethamine, in dosages ranging between 50 and 150 mg.

Patients were normally retained in the hospital until clearance of parasitemia and clinical symptoms. They were followed weekly for 28 days, and at their final visit, they were given primaquine 15 mg. daily for 14 days.

RESULTS : One hundred thirteen patients have been studied (Table 1). It soon became apparent that Fansidar, in either dosage was ineffectual treatment for vivax malaria. The cure rate for the two-tablet dose was unacceptable and parasite clearance time for the three-tablet dose was markedly longer than that for mefloquine or chloroquine. This is the subject of a subsequent report. Pyrimethamine was studied in order to document the resistance of the parasite to this component of Fansidar. Mefloquine was found to be effective in the elimination of parasites and fever in the 31 patients studied. Fever and parasite clearance times obtained with mefloquine were similar to those associated with chloroquine. Pyrimethamine in several dosages was found to be ineffective, confirming pyrimethamine resistance in the strains studied.

Since no well-documented evidence of chloroquine resistance in *P. vivax* has appeared, chloroquine remains the drug of choice for the termination of the acute attack of vivax malaria. Primaquine must be used subsequently in order to prevent relapse.

When mefloquine is available, it may be useful in the treatment of acute vivax malaria, although its structural similarity to primaquine may make combination therapy with these two agents hazardous, since toxicity may be expected to be additive.

The prolonged half-life of mefloquine in man is currently being evaluated using specimens collected in Bangkok. Patients with *P. falciparum* infections were treated with mefloquine and then subjected repeated venipuncture in order to determine the pharmacokinetics of this preparation (Cf. AFRIMS Annual Report 1976-1977). Mefloquine blood levels are currently being estimated on these specimens at the Walter Reed Army Institute of Research.

REFERENCE :

1. Trenholme, G.M., Williams, R.L., Desjardins, R.E., Frischer, H., Carson, P.E., and Rieckmann, K.H. "Mefloquine (WR 142,490) in the treatment of human malaria". Science, 190:792-794, 1975.

Table 1. Therapy of the acute attack of vivax malaria

Therapy	Number	Mean initial asexual parasite ₃ count/mm	Mean fever clearance time in hrs.	Mean parasite clearance time in hrs.	Number of treatment failures*
Mefloquine	31	5885	37	48	0
Fansidar (2 tablets)	10	7441	68	77	4
Fansidar (3 tablets)	11	7342	49	93	0
Chloroquine	24	10889	39	53	0
Chloroquine + primaquine	26	7813	42	42	0
Pyrimethamine	6	5233	26	90	4

* Failure to clear parasitemia within 7 days of the initiation of treatment. Fever and parasite clearance times for these patients were not included in the computation of mean values.