

Comparison of Mefloquine (WR 142490) and Pyrimethamine with
Sulfadoxine for the Single-Dose Treatment of Falciparum Malaria

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OBJECTIVE: To compare the efficacy of mefloquine and Fansidar in the treatment of falciparum malaria.

BACKGROUND: Mefloquine (WR 142490) is ∞ - (2-piperidyl)-2, 8-bis (trifluoromethyl)-4-quinoline methanol hydrochloride. Mefloquine, given as a single dose, has been very effective in the treatment of induced falciparum malaria in prison volunteers in the United States (1). It is a long acting chemical analogue of WR 30090. In Thailand WR 30090 was as effective as quinine when administered every 8 hours for 6 days in the treatment of falciparum malaria.

Fansidar (a 20:1 combination of sulfadoxine and pyrimethamine) has been extensively studied as a single dose for the treatment of falciparum malaria. In Thailand Fansidar was 85% curative in Trad Province and 82% curative in Prachinburi Province in the SEATO studies.

DESCRIPTION: The study was begun at the Chao Phya Abhai Bhu Bejhr (Prachinburi Provincial Hospital) on 24 February 1975. Male patients who volunteered were selected for study if they were aged at least 15 years. Other criteria were an asexual parasite density of *P. falciparum* of at least 1,000 per cu.mm. and the ability of the patient to return for follow-up examination on days 14, 21 and 28 after therapy. Also the patients were asked to sign a written consent after being informed of the nature and potential hazards of the study. Thirty patients will be treated in each group.

Direct estimations of the parasite density were made on admission, twice daily in hospital and once at follow-up examination on days 14, 21 and 28. Determinations of the hematocrit and WBC count were made daily in hospital and at the follow-up examinations. Urinalysis was performed on admission and whenever subsequently indicated.

The medications were administered by the nursing staff in the presence of a study physician. Mefloquine was supplied as plain tablets each containing 250 mg of the drug. The dose was 1.5 g (six tablets).

Sulfadoxine-pyrimethamine was prescribed as plain tablets each containing 500 mg sulfadoxine and 25 mg pyrimethamine. The dose was three tablets.

PROGRESS: MEFLOQUINE acted more quickly against falciparum malaria than did Fansidar (Tables 1 and 2). However, even with mefloquine, the patients' symptoms did not always respond as quickly as the parasite and fever clearance time would suggest.

The parasite clearance time for mefloquine was 59 hours which is shorter than for the 12 other regimens that we have tested. For example, the parasite clearance time for quinine, in a group of patients of similar clinical severity, was 69 hours. The average fever clearance time for mefloquine was 46 hours.

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Only amodiaquine had a shorter fever clearance time (36 hours). In most patients who received mefloquine, fever cleared rapidly, but in two it was more prolonged (Cases 3 and 5).

One patient showed clinical deterioration during the first few hours after the dose of mefloquine and an RIII failure was diagnosed. The patient responded to quinine and the case history is given below. Follow-up has been completed on nine other patients and all achieved radical cures of their infection.

Patient No. 1. was an 18 year old laborer with a history of headache and fever for five days. He complained of a bitter taste in his mouth but was not thirsty. He was afebrile on admission (temperature 37.2°C) and the pulse rate was 90 per minute. The blood pressure was 90/50. He looked slightly anemic but was not jaundiced. His abdomen was soft and the liver and spleen were both moderately enlarged. He could stand and stagger about but he preferred to lie down. He was alert and signed the consent form. His skin was cool without perspiration. The initial parasite density (5 minute stain) was 96,000 per cu.mm. He was diagnosed as having moderately severe falciparum malaria. Because he was afebrile and hypotensive, the old term "algid malaria" was probably appropriate. The hypotension was probably due to salt depletion or possibly dehydration. Mefloquine 1.5 g orally was administered at 0945 hours and 500 ml normal saline was infused over a four hour interval. The Accurate Count (30 minute stain) was 171,000 per cu. mm. At 1330 hours the parasite count was 208,000 per cu.mm., but the patient had a large lunch. At 1600 hours the patient sat on the floor (as was his custom) and had a large meal. He then developed severe abdominal pain. On examination the patient was groaning and writhing in agony. An infusion of quinine (500 mg in 500 ml normal saline) was begun at 1650 hours and was infused in 3.5 hours. The serum quinine concentration increased from 0 to 13.3 mg per liter during the infusion.

The severe abdominal pain disappeared within 30 minutes of the beginning of the infusion and overall the patient greatly improved. The parasite density, however, was 407,000 per cu.mm. at 1745 hours and 468,000 at 2020 hours. A fever of 39.1°C developed during the day.

The patient's condition was satisfactory the next morning but the parasite density was still 450,000 per cu.mm. A second infusion of quinine 500 mg in 500 ml normal saline was infused over a four hour interval. At the end the patient had tinnitus indicating quinine toxicity. However at 1300 hours the parasite density had decreased to 141,000 per cu.mm. A third and smaller dose of quinine (270 mg orally) was given at 1800 hours. Thereafter the patient made a steady recovery and remained free of parasitemia on days 14, 21 and 28.

The parasitemia cleared in 99 hours and the fever in 88 hours. During the initial 24 hours the hematocrit (packed cell volume) decreased from 40 to 26 per cent. Thereafter, coincident with the eradication of his disease, the hematocrit increased to 41 per cent on day 28 without any hematinic therapy.

FANSIDAR: The single dose combination of pyrimethamine with sulfadoxine (Fansidar) cleared parasitemia on average more slowly (76 hours) than did mefloquine (59 hours). Clinically Fansidar acted slowly in many patients (case histories given below). The fever clearance time (62 hours) was longer than that for mefloquine (46 hours). The differences between the clearance times are not statistically significant but probably will be when more patients have been studied. So far, 6 out of 8 patients have been cured.

Patient No. 16. This 35 year old laborer had headache and myalgia for four days. There was no history of previous malaria. His temperature was 40.0°C, pulse rate 90, blood pressure 120/80 and weight 46 kg. He appeared mildly jaundiced but not anemic. He was alert but tired and could only walk with assistance. The parasite density was 100,000 on the slide stained for five minutes and 78,000 on the 30 minute slide. The dose of Fansidar was given at 1530 hours. Because his lips were dry, dehydration was diagnosed. One thousand milliliters 5% dextrose in saline were infused over a four hour interval. On day 1 the parasite density decreased to 12,000 but his fever resurged to 40.5°C on day 1 and to 41.0°C on day 2. The patient was observed carefully and he improved; however, anorexia persisted. His parasitemia cleared on the morning of day 6 (135 hours) but reappeared in the afternoon.

Therefore a treatment failure was diagnosed, either RI or RII. The patient received four doses of oral quinine and the parasitemia cleared. He was discharged. On day 28, the patient returned with a parasite count of 1000. Again he received four doses of quinine. On day 42 the patient returned with a count of 2,000. Six days of oral quinine therapy was prescribed as an outpatient. One week later the patient was free of parasitemia.

Patient No. 20. This 36 year old farmer had a history of headache and fever for three days. His temperature was 39.5°C and pulse rate 90 per minute. He was walking and alert. The liver and spleen were not palpable. The parasite density was 31,000 per cu.mm. Fansidar was given at 1730. The parasitemia decreased to 20 per cu.mm. by the afternoon of day 2, at which time the fever resurged to 39.9°C. On day 3 the patient felt better and the fever decreased to 37.8°C at 0600 hours. During the day the parasitemia increased from 20 (overnight) to 900 to 2200 per cu.mm. An RII response was diagnosed. One dose of oral quinine was given at 0900 hours. The parasitemia decreased to 0 by day 6; however, the patient developed a persistent headache and a parasite count of 10 per cu.mm. was again noted on day 9. A six dose course of quinine was now given and another dose of Fansidar. The patient was cured.

The therapeutic result in this patient is somewhat difficult to assess. On day 3 the parasite count increased but the fever decreased and the patient felt better. It could be argued that the quinine was given prematurely. However despite one dose of quinine, the parasitemia returned on day 9. The patient therefore had either an RII or an RI response.

Patient No. 22. This 38 year old laborer had received two shots (probably an antipyretic) two days previously. He did have a history of malaria eight years ago. His temperature was 38.6°C, pulse 104, blood pressure 90/60 and weight 55 kg. The spleen was enlarged. The parasite count was 13,000 per cu.mm. The dose of Fansidar was administered at 1115 hours. At 1300 hours the parasite count was 62,000 but the patient had improved clinically. At 1930 the parasite count had increased slightly to 90,000. The patient felt better and the temperature had decreased from 40.2°C. to 37.2°C. Because of the increase in parasitemia, quinine therapy was begun. The fever cleared in 63 hours. The patient received oral quinine every 12 hours, but the parasitemia persisted at 10-60 per cu.mm. for three days. Therefore the quinine dosing was increased to every 8 hours. The patient finally received 18 doses of quinine. It was later decided that quinine therapy had been instituted prematurely on day 0, so no therapeutic result could be recorded.

DISCUSSION: Fansidar (a 20:1 combination of sulfadoxine with pyrimethamine) has been extensively studied both for the treatment and prevention of malaria. At Prachinburi Hospital in Northeast Thailand in 1972, a single dose of Fansidar cured 82% of a group of patients with falciparum malaria; in Southeast Thailand in 1974 the cure rate was 85%. However it is well known that Fansidar is often slow to bring an infection under control and some infections are resistant to the drug. The preliminary results of this study suggest that a lower cure rate will be found at Prachinburi Hospital in 1975.

In the initial group of patients, mefloquine cleared parasitemia and fever more quickly than did sulfadoxine with pyrimethamine. Clinically mefloquine acted more quickly and appears to be a very effective antimalarial drug; however quinine by intravenous infusion is still required for severe infections. The current recommended treatment for chloroquine resistant falciparum malaria is a course of quinine followed by a single dose of sulfadoxine with pyrimethamine. Mefloquine can be considered a superior substitute for Fansidar in this regimen. A short course (e.g. 2-6 doses) of quinine will probably usually suffice in severe cases and in mildly ill patients, the mefloquine can be given alone.

SUMMARY: Mefloquine 1.5 g (a 4-quinoline methanol) was compared with pyrimethamine 75 mg and sulfadoxine (Fansidar) 1500 mg for the single dose treatment of falciparum malaria. The study is still in progress. So far, mefloquine has cured 90% (9/10) of patients; the average parasite clearance time has

been 59 hours and the average fever clearance time 46 hours. With Fansidar the cure rate has been 75% (6/8), the parasite clearance time 76 hours and the fever clearance time 62 hours.

REFERENCES:

1. Canfield, C.J., and Rozman, R.S.: Clinical Testing of New Antimalarial Compounds, Bull Wld. Hlth. Org. 50, 203, 1974.

Table 1. Falciparum Malaria Treated with Mefloquine (WR 142490)

Patient Number	Initial Asexual Count <i>P. falciparum</i> (per cu.mm.)	Parasite Clearance Time (Hours)	Initial Fever (°C)	Fever Clearance Time (Hours)	Result*
1	171000	—	37.2	—	RIII
2	130000	62	38.2	28	
3	68000	67	39.0	46	S
4	28000	68	40.0	79	S
5	27000	44	38.8	31	
6	16000	43	39.8	10	S
7	15000	62	39.1	101	S
8	11000	88	39.8	38	S
9	8000	91	40.4	104	
10	7000	76	38.5	61	S
11	5000	66	39.6	32	S
12	4000	22	39.2	15	S
13	2000	19	39.4	10	S
Mean	38,000	59	39.2	46	

* In no result given, follow-up had not yet been completed.

Table 2. *Falciparum* Malaria Treated with Fansidar
(Pyrimethamine with Sulfadoxine)

Patient Number	Initial Asexual Count <i>P. falciparum</i> (per cu.mm.)	Parasite Clearance Time (Hours)	Initial Fever (°C)	Fever Clearance Time (Hours)	Result
14	104000	91	40.1	110	S
15	81000	—	39.7	—	
16	78000	135	40.0	114	RI
17	56000	73	41.0	104	
18	41000	86	40.5	37	S
19	35000	73	40.0	52	
20	31000	—	39.5	—	RII
21	15000	87	39.9	61	
22	13000	—	40.2	—	See Text
23	13000	67	36.5	—	
24	7000	71	40.0	40	
25	6000	90	37.5	—	S
26	5000	69	39.0	64	
27	4000	88	38.0	104	S
28	4000	67	40.2	58	
29	4000	64	39.6	47	
30	3000	43	38.0	17	S
31	2000	42	38.5	13	
32	1000	68	39.0	43	S
Mean	26,000	76	39.3	62	