

Single-Dose Therapy of Falciparum Malaria Using Pyrimethamine
In Combination with Diformyl-dapsone or Sulfadoxine

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OBJECTIVE: To compare the efficacy of diformyl-dapsone and sulfadoxine used with pyrimethamine in the treatment of falciparum malaria.

BACKGROUND: Weekly administration of pyrimethamine and diformyl-dapsone (DFD) has proved to be an effective chemosuppressant against drug-resistant *P. falciparum* malaria in both induced infection in volunteers (1) and in field populations (2).

In a trial of DFD alone as therapy for falciparum malaria, Clyde, et al, found that single dose treatment was slowly effective in clearing 15 of 23 episodes of asexual parasitemia in volunteers; however, recrudescence occurred in all but one patient (3).

The combination of pyrimethamine with sulfadoxine (Fansidar) has been reported to be highly effective both for treatment (4) and prophylaxis (5) of drug-resistant falciparum malaria.

Pyrimethamine-DFD, like pyrimethamine-sulfadoxine, is a single-dose preparation, and the therapeutic potency of the two combinations was compared.

DESCRIPTION: The patients to be studied were selected from males presenting at the Trad Provincial Hospital in Southeast Thailand with an asexual parasite count of *P. falciparum* greater than 1000 per cu. mm. The patients also had to agree to be hospitalized and followed during the study period, and be willing to signify consent after being informed of the nature and potential hazards of the study. Since pyrimethamine with sulfadoxine is known to be therapeutically effective, 45 patients were selected who had clinically moderate disease. Their average age was 22.7 years and average weight 47.3 kg. Since the therapeutic potency of pyrimethamine with DFD was not known, most of the patients selected had clinically mild disease. Thirty three patients received pyrimethamine with DFD. Their average age was 23.6 years and average weight 51.5 kg.

Direct quantitative parasite counts (6) were performed on admission and thereafter twice daily in hospital and 14, 21 and 28 days after admission. Hematocrit, white cell count, and urinalysis were performed on admission, and whenever subsequently indicated. Patients were taken home by a member of the study team, and follow-up examinations were made either at the clinic or at the patients' homes. Other details of the study procedure are described elsewhere (7).

All medications were administered by one of the study physicians, and patients were seen on clinical rounds made three times daily. The drugs used were combination tablets of pyrimethamine 25 mg and sulfadoxine 500 mg (Fansidar, Hoffmann-LaRoche) or pyrimethamine 12.5 mg and diformyl-dapsone 200 mg (supplied by the Walter Reed Army Institute of Research). Both were supplied as uncoated white tablets. The dosage of pyrimethamine-sulfadoxine used in adults was pyrimethamine 75 mg and sulfadoxine 1500 mg (3 tablets). This is the maximum dose recommended by the manufacturer. Seven boys weighing between 20 and 36 kg received two tablets. One boy weighing 18 kg received one tablet. Two dosages of the pyrimethamine-DFD combination were tested: pyrimethamine 25 mg, DFD 400 mg (2 tablets) and pyrimethamine 50 mg, DFD 800 mg (4 tablets).

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Therapeutic responses were classified according to WHO criteria (8). Parasite clearance times and fever clearance times were determined for each patient. Fever was considered to be "cleared" if it remained at or below 37.2°C for at least 12 hours. Patients in whom asexual parasitemia was cleared by treatment and had not reappeared for 28 days following therapy were considered radically cured.

PROGRESS: PYRIMETHAMINE 75 MG, SULFADOXINE 1500 MG.

Forty-five patients were treated with the combination pyrimethamine-sulfadoxine (Table 1). Patients in this group had a high average parasitemia (60,000 per cu.mm.) and were moderately or severely ill. The mean parasite clearance time was 73 hours and the mean fever clearance time was 63 hours.

Thirty-nine of the forty-five men were followed for the 28 day observation period and radical cure was attained in 33 (85%). All patients with parasite counts below 30,000 per cu.mm. were cured. A typical successful response to pyrimethamine-sulfadoxine is described below.

Patient No. 5: This 18 year old farmer was admitted with a three day history of fever, insomnia, and backache. He gave a history of malaria one year previously. On physical examination, he was found to have a temperature of 39.2°C, but no other positive findings. The asexual parasite density of *P. falciparum* was 115,900 per cu.mm. on admission. He remained febrile for 51 hours following treatment and complained of continuing backache, but his parasitemia steadily decreased. There were rare ring forms 48 hours after therapy, but smears were negative thereafter. He remained well throughout the follow-up period.

Two patients exhibited recrudescence of asexual parasitemia and malaria symptoms before the end of the 28 days and were considered RI treatment failures. Six patients required intravenous quinine after the initiation of the pyrimethamine-sulfadoxine therapy because of rising parasitemia and worsening clinical state. However, to bring the infection under control, four patients required only one dose of quinine one received two doses and another five doses. Some of the patients may indeed have eventually responded to the single dose of Fansidar, but in the judgement of the attending physicians, withholding the faster acting drug of known effectiveness was not warranted. Four patients were diagnosed as RIII treatment failures. In two patients (Numbers 1 and 4), it was later considered that the quinine therapy may have been given prematurely, so no result was recorded.

Patient No. 11 was an example of an RIII response. An 18 year old farmer was admitted with a two day history of headache, muscle pain, fever, and thirst. Admission temperature was 40.4°C. His spleen was not palpable and there were no abnormalities on physical examination. The asexual parasite count on admission was 79,800 per cu.mm. and he was treated with three tablets of Fansidar. By the afternoon of admission, he was in severe distress with headache, abdominal pain, restlessness, and his fever was still 40°C. The parasite count seven hours after treatment had risen to 366,000 and it was decided to infuse 500 mg quinine. A second infusion of 500 mg quinine was given the following morning when the parasite count was 236,000. The patient did not require additional therapy, and attained a radical cure of his malaria. Despite the fact that the elapsed time between treatment with the drug under evaluation and the initiation of quinine therapy was only eight hours, it was felt that this patient represented a failure of the pyrimethamine-sulfadoxine combination in view of his worsening clinical condition and progressive rise in parasitemia.

Toxicity: Two patients developed rashes after the pyrimethamine-sulfadoxine combination which were considered to be related to the administration of the drug. In one patient the rash consisted of giant urticaria, appearing 34 hours after dosing, which resolved after treatment with antihistamines and dexamethasone. Another patient developed a pruritic erythematous rash four days after therapy, which disappeared spontaneously without additional treatment. Neither patient had mucous membrane lesions, and aside from multivitamins, neither had received additional medication. Radical cure was achieved in both patients.

PYRIMETHAMINE 50 MG, DFD 800 MG.

Thirty patients received a single four tablet dose of the combination. Fever clearance time (mean 59 hours) and parasite clearance time (mean 60 hours) were short. However this group of patients had a low mean

Initial parasite count (17,000 per cu.mm.), and were, usually, clinically mild cases. Twenty-three patients were followed throughout the 28 day period (Table 2); only ten were cured. Of the failures, two had RIII responses and two exhibited RII responses. Nine had recrudescences of parasitemia before the end of the 28 day observation period, and were considered RI failures. The over-all cure rate for pyrimethamine-DFD at this dosage was 43%. There was no evidence of hematologic or other toxicity.

The case-history of a patient with an RII response is given below.

Patient No. 50: A 42 year old tailor presented with a four day history of fever, headache, anorexia and vomiting. A cough had been present for six days. He gave a history of malaria 10 years previously. Examination showed a temperature of 40.0°C and rhonchi in the chest. The asexual density of *P. falciparum* was 40,700 per cu.mm. The four tablet dose was administered at 1100 hours. The patient felt better in the evening. By 1400 hours the following day, the parasite density had decreased to 400 per cu.mm. and the patient had a temperature of 38.0°C. He developed fever and chills at 2000 hours, his temperature rose to 39.6°C and his parasite count increased to 10,800 per cu.mm. An RII response was diagnosed and 500 mg quinine was administered intravenously in 500 ml saline over four hours. Altogether nine doses (eight oral) of quinine were given, followed by a single dose of pyrimethamine-sulfadoxine. The patient made a rapid recovery.

PYRIMETHAMINE 25 MG WITH DFD 400 MG, AND PYRIMETHAMINE ALONE.

Early in the study, three patients were treated with the pyrimethamine-DFD combination at this lower dosage (two tablets). Of the three, one responded promptly (S), and two were RII failures. Because of the apparently unacceptable therapeutic action of the combination at this dosage, no further patients were studied.

Three patients with mild illness and low parasitemias were treated with 50 mg pyrimethamine daily for three days. In all three, only a temporary reduction in parasitemia resulted (RII), and symptoms persisted, supporting an earlier impression of resistance of the local strain of *P. falciparum* to this drug.

DISCUSSION: Pyrimethamine 50 mg with DFD 800 mg is only partially effective as an antimalarial, since only 43% of mildly ill patients were cured. This cure rate is similar to that for a pyrimethamine-dapsone (DDS) combination, which was 19% effective (chi square=2.0, $p > 0.05$) (9). DFD has a metabolic half-life of 30 hours, (10) compared with 21 hours for DDS (11). Pyrimethamine, which has a half-life of 96 hours (12), used with either DFD or DDS leads to an unbalanced synergistic combination. Obviously at certain times only an effective dose of pyrimethamine is present in the blood. Since pyrimethamine resistance was demonstrated in this study, the partial therapeutic efficacy of pyrimethamine with DFD may be explicable on this basis. Conversely, pyrimethamine-sulfadoxine is a balanced combination since the half-life of sulfadoxine is 200 hours, (13), and of pyrimethamine about 96 hours.

In this study, pyrimethamine with sulfadoxine cured 85% of patients with an average parasite count of 60,000 per cu.mm., when administered in an adult dose of three tablets (pyrimethamine 75 mg, sulfadoxine 1500 mg.). Thus the combination (Table 3) was twice as effective as pyrimethamine-DFD ($p < 0.01$) in patients whose average parasite count was three times greater ($p < 0.001$).

In Northeast Thailand, a two tablet dose (pyrimethamine 50 mg, sulfadoxine 1000 mg.) cured 82% of patients with an average count of 28,000 per. cu.mm. (9).

Pyrimethamine-sulfadoxine alone is an effective and convenient antimalarial. However, in the opinion of the authors, its major limitation is the somewhat slow control of fever and clinical symptoms (viz patients No. 5 and 11 above). The prolonged activity of the drug, when preceded by the rapid action of quinine, results in the currently optimal therapy for drug-resistant *falciparum* malaria (14).

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Table 1. Falciparum Malaria in Thailand. Single Dose Therapy with Pyrimethamine 75 mg. and Sulfadoxine 1.5 gm. (Smaller Dose in Children)

Patient Number	Initial Asexual Count <i>P. falciparum</i> (per. cc. mm.)	Parasite Clearance Time (Hours)	Initial Fever (°C)	Fever Clearance Time (Hours)	Result
1	314500	—*	39.4	—*	—*
2	286900	—	39.3	—	RIII***
3	258400	—	41.0	—	RIII
4	179600	—	38.5	—	—
5	115900	65	39.2	51	S
6	111000	88	37.0	—	S
7	98000	66	39.9	—	S
8	93300	118	40.4	69	RI
9	92200	—	40.0	67	S
10	90300	76	38.1	68	S
11	79800	—	40.4	—	RIII
12	71300	88	40.3	87	S
13	65300	113	40.2	88	S
14	65000	—	39.7	—	RIII
15	63100	68	39.8	55	S
16	61800	69	40.0	61	S
17	58900	—	39.3	66	S
18	58700	—	40.1	63	S
19	58700	—	40.1	66	S
20	56200	—	39.9	64	S
21	50400	70	40.9	74	S
22	44200	—	39.4	66	S
23	36100**	—	39.8	42	S
24	30400	—	39.6	—	RI
25	27200	76	40.1	68	S
26	26100	62	39.4	37	S
27	24500	—	39.5	64	S
28	23400	66	39.0	41	S
29	21300	75	40.4	83	S
30	19400	63	40.3	62	S
31	17300	61	38.2	84	S
32	17200	—	37.3	—	S
33	16200	—	40.2	66	—
34	13400	—	39.4	—	S
35	10900	117	39.1	37	—
36	10100	93	40.0	109	S
37	9400	39	39.4	—	S
38	8600	—	40.3	—	—
39	6800	—	39.6	35	S
40	6400	70	39.9	57	S
41	4900	—	39.0	42	—
42	4800	45	38.7	44	S
43	3000	52	39.2	—	S
44	2300	—	37.3	—	S
45	1700	38	37.0	—	S
Mean	60300	73	39.5	63	Cure Rate = 85% (33/39)

* If period of observation not adequate, no result given.

** Median count.

*** If no symbol, final result could not be determined.

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).

World Health Organization (1967) Tech. Rep. Ser. No. 375, p. 42.

Table 2. Falciparum Malaria In Thailand.
Single Dose Therapy with Pyrimethamine 50 mg and DFD 800 mg

Patient Number	Initial Asexual Count <i>P. falciparum</i> (Per cu. mm.)	Parasite Clearance Time (Hours)	Initial Fever (°C)	Fever Clearance Time (Hours)	Result
46	95600	93	39.0	84	RI
47	63700	—*	39.2	—*	—*
48	46100	43	39.2	42	—
49	41000	—	38.4	—	RII
50	40700	—	40.0	—	RII
51	30300	69	39.1	69	S
52	20200	44	39.0	50	S
53	18400	117	37.8	—	RI
54	13000	52	40.5	—	—
55	13000	62	38.3	12	—
56	12400	45	37.3	—	S
57	12300	70	40.4	93	RI
58	12200	67	36.9	—	S
59	11700	84	39.8	71	S
60	11200	—	40.5	—	RIII
61	10000**	—	40.4	—	RIII
62	7300	66	37.7	—	—
63	7200	60	39.3	59	RI
64	7200	44	37.1	—	S
65	6900	43	37.8	—	S
66	5700	40	37.0	—	S
67	5400	92	39.2	67	RI
68	4900	72	40.3	40	RI
69	2600	41	38.6	160+	RI
70	1800	61	39.6	12	—
71	1600	45	38.7	37	RI
72	1400	61	38.8	36	S
73	1200	14	39.8	—	S
74	1100	—	40.0	—	—
75	1000	61	38.7	60	RI
Mean	16,900	60	38.9	59	Cure Rate = 43 % (10/23)

* If period of observation not adequate, no result given.

** Median count.

Table 3. Comparison of Cure Rates*

Drug	Average Initial Parasite Count (Per cu.mm.)	RIII	RII	RI	S	Cure*** Rate (%)
Pyrimethamine+Sulfadoxine	60,300**	4	0	2	33	85 %
Pyrimethamine+DFD	16,900**	2	2	9	10	43 %

* Patients who did not complete follow-up examinations were not included in this table.

** The average initial parasite counts were significantly different ($t=8.4$, $p<0.001$)

*** The difference in cure rates was statistically significant ($\chi^2=9.67$, $p<0.01$)