

Falciparum Malaria Cured by Quinine Followed by Fansidar  
(Sulfadoxine with Pyrimethamine)

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**OBJECTIVE:** To determine the efficacy of a short course of quinine (about three days) followed by a single dose of sulfadoxine with pyrimethamine against falciparum malaria in Thailand.

**BACKGROUND:** The treatment of chloroquine-resistant falciparum malaria has hitherto been confusing. No clearcut regimen has yet emerged (1). The World Health Organization (2) mentions 16 different regimens involving 12 drugs administered over 1 to 14 days. Based upon the results of this study we recommend one regimen involving three drugs given in about three days.

In Southeast Thailand a six day course of quinine cured 85% of patients with falciparum malaria (3); a single dose of Fansidar (sulfadoxine with pyrimethamine) was also 85% curative (4). Therefore we tested a short course of quinine (average 3 days) followed by Fansidar in about 400 patients.

**DESCRIPTION:** The Trad Provincial Hospital is in southeast Thailand 400 Km from Bangkok. Malaria is endemic in the area throughout the year. Volunteers were selected for the study if their asexual parasitemia of *P. falciparum* was at least 1,000 per cu.mm. Initially only adult males were studied. When quinine—Fansidar was shown to be the most effective therapy, it was used routinely on adults and children. Patients with coincident vivax malaria were treated but not included in this study.

Quantitative parasite counts (5) were performed at least twice daily in hospital on finger—stick specimens taken at 0800 and 1400 hours and at follow-up examinations on days 14, 21 and 28. Hematocrit levels (packed cell volume) and leukocyte counts were made on admission and whenever clinically indicated.

The drugs were administered by the study physicians during ward rounds usually conducted at 0600, 1400 and 2200 hours. Intravenous quinine was administered as the dihydrochloride salt. The standard dose in adults was 490 mg quinine base in 500 ml normal saline infused over a four hour interval. Oral quinine was prescribed as tablets of quinine sulfate each containing 270 mg base. The routine formulation was a sugar-coated tablet, but plain tablets were occasionally used especially in small children. The standard dose in adults was 540 mg (two tablets) every 8 hours. Each plain tablet of Fansidar (Hoffman—La Roche) contained 25 mg pyrimethamine and 500 mg sulfadoxine. The standard dose in adults was three tablets given with or eight hours after the last dose of quinine.

Quinine concentrations on random sera were determined by the benzene extraction method of Brodie and Udenfriend (6). This is an accurate technique (7).

Parasite and fever clearance times were determined in hours. The patients' temperature charts were retained for analysis. Patients were considered radically cured (S response) if the parasitemia was cleared by treatment and had not reappeared before day 29 (the day of admission being called day 0). The WHO (8) classification was used (Table 2).

**PROGRESS:** Four hundred and fourteen patients were admitted to the study. Nine patients left the hospital after clinical improvement but before receiving Fansidar. Therefore 392 patients received

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quinine—Fansidar therapy. The average age of the group was 23.9 years (range 1—73) and average weight 45.4 Kg (range 5—80). Only 14 patients were female since we usually confined our studies to male patients.

Most patients were fairly seriously ill on admission. The average parasite count (90,676 per cu.mm.) was much higher than in our other therapeutic studies (3) and the average parasite clearance time of 77.3 hours indicates a satisfactory response (Table 1). Clearance of parasitemia was slow in a few patients, especially those with high parasite counts (e.g. over 200,000 per cu.mm.) and was possibly due to partial resistance to quinine. A typical patient was No. 391 with a parasite count of 252,720 per cu.mm. He received 18 doses (six days) of quinine (Table 1) before the Fansidar. His parasite clearance time was prolonged at 147 hours. Despite the slow clinical response, his blood was free of parasites on days 14, 21 and 28 and so he was accredited with a radical cure.

The average fever clearance time was 61.5 hours. In a few patients a persistent fever was probably caused by the quinine. Since the average course of quinine was short; quinine fever was not so frequent a problem as with longer courses in previous studies (9). In some patients, who received only a few doses of quinine, a rising temperature on day 1 or day 2 was probably caused by the Fansidar, since the fever patterns were similar to those found in patients receiving Fansidar alone (4). Many patients were discharged when they felt better but before the fever and parasitemia had cleared.

Eighty two percent (322/392) of the patients received at least one dose (average 1.5 doses, range 1—7) of quinine as a continuous intravenous infusion. The standard dose of quinine base was 10 mg per Kg but in small children a lower dose was often used to prevent toxicity. The adult intravenous dose (490 mg quinine base in the dihydrochloride salt) was usually given in 500 ml normal saline. The optimum infusion time for a rapid response and avoidance of toxicity was four hours. Half strength solutions (0.5 mg quinine base per ml) were administered, especially in children, if quinine toxicity was suspected. In comatose adults optimum therapy was not more than 1,000 mg quinine base (two doses) per 24 hour interval given in 1000—1500 ml fluid intravenously. Quinine metabolism is impaired in severe falciparum malaria and the half—life of the drug is prolonged. Thus lower or less frequent doses are needed to prevent overdosage. In several of our patients toxic levels of serum quinine (concentration over 10 mg/L) occurred despite subnormal doses of the drug. Nevertheless quinine is the only drug that brings severe falciparum infections under satisfactory control in Southeast Thailand.

Follow—up examinations were completed in 314 patients, of whom 302 (96%) were radically cured (Table 2). The quinine—Fansidar regimen was more effective than a six day course of quinine, or Fansidar alone, in our test system.

Initially all patients received nine doses of quinine. The questions arose whether a shorter course of quinine would be equally effective and whether, in severe cases, a longer course of quinine would be more effective. Therefore, additional patients received from 1 to 18 doses of quinine before the single dose of Fansidar. To our surprise the cure—rate was about 96% throughout the range (Table 1). However the cure—rate of 98% (43/44) with 10 to 18 doses was impressive since the patients were mostly seriously ill and their average parasitemia was high (166,000 per cu.mm.).

If the course of quinine was very short (less than four doses), then the initial clinical improvement was not always maintained and a temporary resurgence of fever and other symptoms often occurred on about the second day. If at least four doses of quinine were given, optimal clinical improvement usually resulted. Table 1 shows that the shortest fever clearance time occurred with the four dose course. Longer courses of quinine appeared to be indicated in patients with high initial parasite counts or evidence of chronic disease (e.g. large spleens).

Quinine caused typical mild side-effects in most patients (e.g. nausea and tinnitus). If blurred vision or other serious symptoms occurred, the dose of quinine was reduced. Serious side-effects were more frequent in children than in adults (e.g. coma, convulsions). Reduction or deletion of dosage usually resulted in a rapid decrease in toxicity.

Serious toxicity attributable to the Fansidar did not occur in any of the 392 patients who received the the quinine-Fansidar regimen. However Fansidar as solo therapy often causes fever and less often urticarial rashes (4).

The cost of treatment comprises the hospital costs (if the patient requires admission) plus the cost of the drugs. The 392 patients were in hospital for an average of only 3.8 days which was brief in relation to the average clinical severity of the group, and reflects the fact that quinine usually acts rapidly.

We determined that the minimal effective regimen was four doses of quinine plus Fansidar. At the time of the study quinine cost the hospital pharmacy about U.S. \$0.04 per tablet and Fansidar about \$0.15 a tablet. Thus the cost of the regimen orally was at least \$0.77. This was less expensive than any other effective regimen. Intravenous therapy was much more expensive because units of intravenous fluid were relatively costly.

Other relevant factors are the duration of therapy, the total number of doses and the frequency of dosing. Optimal quinine-Fansidar therapy comprises at least five doses (four quinine, one Fansidar) given over two days at eight hour intervals. These parameters are less than for any other effective regimen.

**DISCUSSION:** This study has established that quinine followed by Fansidar is the treatment of choice for chloroquine-resistant falciparum malaria. The regimen is theoretically sound because it comprises the rapidly acting drug quinine, followed by the long acting combination of sulfadoxine and pyrimethamine (Fansidar). The quinine brings the infection under control and the Fansidar assists in its eradication. This regimen is useful because we found that Fansidar is non-toxic when given at the end of a course of quinine; It is practical because it is completed in about three days, thus allowing the patient to be discharged promptly.

The value of an antimalarial regimen may be determined by five criteria viz., efficacy, toxicity, cost, duration of therapy and length of hospital stay. These criteria must be judged in relation to the average severity of the cases being treated, which is indicated by the clinical severity and the average parasite count. Considering all these factors, the quinine-Fansidar regimen is the best that we have tested.

The components of the quinine-Fansidar regimen are more powerful antimalarials than any alternative drugs. For chloroquine-resistant falciparum malaria, quinine is the only rapidly acting drug currently available. The components of Fansidar are longer acting than any other similar drugs (Table 3). Fansidar is more effective in the radical cure of *P. falciparum* than pyrimethamine with DDS (10) or pyrimethamine with DFD (4). Single dose Fansidar is more effective than multi-dose clindamycin or tetracycline (11). It should be stressed that Fansidar alone is often toxic (e.g. fever, urticaria) and slow acting, but when given at the end of a course of quinine, it caused no serious toxicity in over 300 patients. Sequential quinine-Fansidar is also more logical than combination therapy because antimalarial activity in the blood is obviously maintained for a longer period.

Quinine has, of course, been used for malaria for several hundred years. Sulfadoxine was introduced for malaria by Laing (12). Chin (13) discovered the antimalarial potentiation of sulfadoxine and pyrimethamine. The U.S. Army found that a 14 day course of quinine with an initial dose of sulfadoxine and pyrimethamine was effective against falciparum malaria (14, 15). However the official U.S. Army regimen is still quinine for 10 days, pyrimethamine for 3 days and DDS for 29 days (16). In Laos a 7-10 day course of quinine plus an initial dose of Fansidar was found to be effective (17). However quinine with Fansidar is not mentioned in the regimens recommended by W.H.O. (2) nor in the latest addition of a leading textbook of medicine (18).

There is evidence that quinine is more effective than chloroquine against chloroquine-sensitive falciparum malaria from Africa (19). Therefore comparative studies of quinine and chloroquine with and without terminal Fansidar for African falciparum are obviously indicated.

**RECOMMENDATIONS:** The following is the recommended treatment of falciparum malaria in Thailand based on all completely tested drug regimens to date:

1. At least four doses of quinine (540 mg base each dose in adults) usually given at 12 hour intervals followed by a single dose of Fansidar (sulfadoxine 1.5 g with pyrimethamine 75 mg in adults). Proportionately smaller doses are given to children.
2. Quinine dosage should not exceed 20 mg/kg daily. The first and sometimes subsequent doses of quinine should often be administered as an intravenous infusion usually in four hours. The standard dose in adults is 500 mg (10 gr) in 500 ml normal saline.
3. In order to prevent pulmonary edema, Thai adults with falciparum malaria should not receive more than 1500 ml fluid (including blood transfusion) every 24 hours. Children should receive proportionately smaller volumes.
4. Blood transfusion is rarely indicated in falciparum malaria and antimalarial therapy is usually sufficient. Blood transfusion should be considered if the hematocrit falls below 15%.

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Table 1. Relation of the Number of Quinine Doses to the Falciparum Malaria Cure Rate.

No. Doses Quinine	Average Parasite Count For Group	Average Parasite Clearance Time (Hrs)	Average Initial Fever (°C)	Average Fever Clearance Time (Hrs)	Treatment Failures (RI-III)	Cure (S)	Cure Rate
0*	60230	73.0	39.5	62.6	6	33	85 %
1	57742	67.3	39.1	50.7	0	21	
2	65510	71.6	39.5	57.5	2	22	
3	71719	67.7	39.3	55.6	0	24	
4**	124624	72.4	39.4	43.4	0	22	
5	76385	67.4	39.5	54.5	2	22	
6	81481	73.8	38.8	62.5	1	21	
7	114285	75.3	39.4	58.0	0	23	
8	99600	78.2	39.3	70.3	1	21	
9	64067	76.6	39.2	59.5	5	83	
10	98651	81.5	38.5	69.5	0	20	
11	66949	91.8	39.6	102.0	0	7	
12	285057	88.0	39.0	74.8	1	6	
13	242345	92.5	39.2	93.5	0	3	
14	269754	108.8	38.7	91.0	0	3	
15	138340	117.0	40.3	109.5	0	2	
16	—	—	—	—	—	—	
17	515060	130.0	40.1	82.0	0	1	
18	252720	147.0	40.2	137.0	0	1	
Average 1-18 Doses (Total Quinine-Fansidar Group)	90676	77.3	39.2	61.5	12	320	96 %

\* Study reported in detail elsewhere (4)

\*\* For optimum clinical response at least 4 doses of quinine should be given before the Fansidar.

Table 2. Falciparum Malaria in Thailand 1973-1974.  
Cure Rates with 4 Different Regimens.

Drug Regimen	Average Duration Therapy	Average Parasitemia (per cu.mm.)	RIII*	RII	RI	S	Cure Rate (%)
Quinine+Fansidar	3 days	90,000	0	0	12	302	96
Quinine**	6 days	28,000	1	0	9	55	85
Fansidar***	1 dose	56,000	4	0	2	33	85
Chloroquine	3 days	15,000	2	8	1	0	0

\* 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).

\*\* Study reported in detail in Hall, A.P. et al. (3)

\*\*\* Dose in adults 1.5 g sulfadoxine and 75 mg pyrimethamine.

Table 3. Dihydrofolate Reductase Inhibitors, Sulphonamides and Sulphones Used in Malaria - Half-life (t/2)

Drug	Half-life (T/2 in Hours)	Reference
Sulfadoxine*	200	Brooks, M.H. et al. (15)
Pyrimethamine*	96	Smith, C.C., and Ibrig, J. (20)
Sulfalene	65	Seneca, H. (21)
DFD	30	Sonntag, A.C, et al. (22)
DDS	21	Glazko, A.J. et al. (23)
Sulfadiazine	17	Richards, W.H.G. (24)
Sulfamethoxazole**	9	Schwartz, D.E., and Rieder, J. (25)
Trimethoprim**	9	Schwartz, D.E., and Rieder, J. (25)

\* Sulfadoxine with pyrimethamine is marketed as Fansidar.

\*\* Sulfamethoxazole with trimethoprim (co-trimoxazole) is marketed as Bactrim or Septrin.