

Treatment of Vivax Malaria with Sulfadoxine-Pyrimethamine and with Pyrimethamine Alone

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OBJECTIVE : To evaluate the activity of pyrimethamine alone and in combination with sulfadoxine against acute malaria due to *P. vivax*.

BACKGROUND : Sulfadoxine-pyrimethamine (Fansidar, Roche Laboratories) is used in increasing quantities for the therapy of malaria in areas where *P. falciparum* is resistant to chloroquine. The combination remains highly effective against asexual forms of *P. falciparum*. Field studies of hospitalized patients carried out by this Laboratory over the past five years have shown virtually no change in the efficacy of sulfadoxine-pyrimethamine. Radical cure rates for *P. falciparum* have ranged between 80 and 91%. Two tablets and three tablets administered as a single dose appear to have equal activity in the adult Thai populations studied (a tablet includes sulfadoxine 500 mg., and pyrimethamine 25 mg.). In view of its efficacy and lack of toxicity, the value of this preparation as a single-dose regimen for mild to moderately severe falciparum malaria is undisputed.

Fansidar has not generally been recommended for the therapy of *P. vivax* infections although the package insert lists this parasite as one of the indications for use of the combination, along with *P. falciparum* and *P. malariae*. However, in areas endemic for chloroquine-resistant falciparum malaria, sulfadoxine-pyrimethamine is widely used for the treatment of fevers presumed to be malaria when microscopic diagnosis is either not available or not convenient. Malaria eradication programs often use sulfadoxine-pyrimethamine as presumptive therapy for fevers assumed to be malaria in areas of known *P. falciparum* drug resistance, where follow-up is difficult or impossible. In addition, clinics without adequate laboratory support often treat all cases of suspected malaria with sulfadoxine-pyrimethamine. In Thailand, the combination can be purchased by the patient at drug stores and self-treatment may be extremely common. The fact that more than sixteen million tablets of Fansidar were imported into Thailand over a recent one-year period reflects the wide use of the drug.

Vivax malaria has increased in incidence dramatically over the last several years in Thailand. In the Bhu Phram Valley, the proportion of new vivax infections increased from 44% of the population infected in 1972 to 80% in 1976, whereas falciparum infection rates remained nearly unchanged (2, 3). In an attempt to delineate factors which may have contributed to this increase, our laboratory has considered the possibility that treatment with Fansidar may be implicated. Since sulfonamides appear to stimulate the production of infectious gametocytes in *P. falciparum*, the effect of sulfadoxine-pyrimethamine on vivax gametocytemia is being evaluated. During the course of this investigation it

became apparent that the combination is not effective therapy for the acute episode of vivax malaria.

METHODS AND RESULTS : In Phrabuddhabat Hospital, Saraburi Province, Central Thailand, ten patients with peripheral smears positive for *P. vivax* were treated with two tablets of Fansidar (sulfadoxine 1.0 gm., pyrimethamine 50 mg.). Patients were all males, ranging in age from 19 to 33 years (mean 25 years) (Table 1). Of the ten patients, only six cleared their asexual parasitemia by day 7 following therapy, and mean fever and parasite clearance times were prolonged at 63 and 73 hours respectively. The remaining four patients, although they had a reduction in the level of parasitemia and clearance of fever, still had asexual parasites on their peripheral blood films seven days after treatment. Active sulfanamide was detected in the serum of all patients, indicating adequate drug absorption.

Eleven patients, ranging in age from 19 to 46 years, with a mean of 27 years, were treated with three tablets of the combination, (pyrimethamine 75 mg., sulfadoxine 1.5 gm.). All patients in this group cleared parasitemia within seven days; however, mean parasite and fever clearance times were prolonged at 90 and 50 hours respectively (mean values for 18 patients treated with chloroquine were 52 and 40 hours respectively).

In addition, six patients aged from 19 to 38 years (mean 25 years) were treated with pyrimethamine alone in dosages ranging from a single 50 mg. dose to 50 mg. daily for three days. Of this group, only two had cleared parasitemia by day 7, one patient treated with 50 mg. dose and one patient treated with 50 mg., daily for three days. Parasite clearance times for these two patients were long, 113 and 66 hours. Fever, however, was not prolonged - 32 and 20 hours.

Patients whose parasitemia failed to clear or relapsed were treated with chloroquine 1.5 gm. over three days, followed in G-6-PD normal individuals, by primaquine 15 mg. daily for 14 days. All patients so treated were cured. At the end of the 28-day follow-up period, all G-6-PD normal patients were given a 14-day course of primaquine.

In most cases gametocytes infectious to mosquitoes were present in the peripheral blood as long as the asexual parasites. Therefore, patients treated with sulfadoxine-pyrimethamine are carriers of gametocytes available to infect vector mosquitoes for a longer period of time than patients treated with more effective therapy, e.g., chloroquine. Whether this fact has a significant effect upon the transmission of the parasite is not clear.

Pyrimethamine, and pyrimethamine combined with sulfadoxine, appear to be inappropriate therapeutic regimens for vivax malaria in Thailand. Pyrimethamine alone and the two-tablet dose of sulfadoxine-pyrimethamine have unacceptable activity in terminating the acute attack. The three-tablet dose of the combination provides clearance of fever and parasitemia, but acts very slowly and cannot be recommended.

Children with *P. vivax* studied in Bangkok have shown even higher failure rates after treatment with sulfadoxine-pyrimethamine (1). Our higher success rate may reflect the contribution of immunity in adult subjects.

Table 1. Results of treatment of *P. vivax* with pyrimethamine 50 mg. and sulfadoxine 1 gm.

Patient No.	Initial Asexual Count	Fever Clearance Time (hours)	Asexual Parasite Clearance Time (hours)	Serum Sulfonamide Level		Comment
				24 Hours After Drug Administration	7-Day Follow-up	
11-0348	34,390	42	53	13 mg/100 ml	3 mg/100 ml**	
11-0353	6,300	80	No clearance by Day 7*	"	6 "	
11-0355	4,452	30	64	-	6 "	**
11-0366	13,800	80	No clearance by Day 7*	"	6 "	
11-0367	8,310	No fever	52	"	9 "	
11-0376	3,080	72	No clearance by Day 7*	"	6 "	
11-0388	5,796	120	102	"	8 "	Relapse Day 21*
11-0399	1,160	28	20	"	11 "	
11-0400	1,700	96	140	"	8 "	Relapse Day 28*
11-0401	5,360	72	No clearance by Day 7*	"	6 "	

* Patients were retreated with Chroloquine-Primaquine

** Day 14

Since there have been no verified reports of vivax resistance to chloroquine, it should be emphasized that whenever species diagnosis of malaria is possible, chloroquine is the drug of choice for termination of the acute vivax attack, particularly in areas where pyrimethamine resistance is suspected or documented. Primaquine, of course, is necessary for the prevention of relapse. Dosage of primaquine depends upon the local prevalence of G-6-PD deficiency and must be adjusted accordingly.

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