

Sporontocidal Effect of Antimalarials in

P. vivax Malaria

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OBJECTIVE : To determine the effect of several therapeutic regimens upon the sexual and sporogonic cycles of *Plasmodium vivax*.

BACKGROUND : In the therapy of malaria, three effects are hoped for. First, the antimalarial should terminate the parasitemia and symptomatology of the acute attack. Secondly, the exoerythrocytic phase of relapsing infections should be eliminated in order to obviate the possibility of relapse. Thirdly, transmission of the infection by a vector mosquito from the patient under therapy to an uninfected individual should be prevented; i.e., gametocytes should be eliminated or rendered non-infectious. The first effect has been studied and reported upon elsewhere in this Annual Report. The second effect has not been examined at this facility. The third effect is the subject of the current report.

Treatment of falciparum malaria with Fansidar, and other sulfonamides, has been seen to result in an increase in gametocyte-positive individuals as well as an increase in the intensity of gametocytemia. Fansidar has been used in great quantities recently in Thailand for the therapy of malaria, both falciparum and vivax. Whether gametocyte stimulation occurs with *P. vivax* has not previously been investigated.

Mefloquine hydrochloride, a new antimalarial developed by the U.S. Army's Drug Development Program, has not been studied in the field in vivax infections. Its effect upon gametocytemia and infectivity of gametocytes has not been evaluated previously.

METHODS : The study was initiated at the Phrabuddhabat Hospital, Saraburi Province and continues at the Phraya Paholpolpayahasena Hospital in Kanchanaburi Province. The usual conditions for admission of patients to AFRIMS therapeutic trials were observed. Patients were assigned to therapy groups using one of the following treatment regimens : Mefloquine hydrochloride, Fansidar in either a two-tablet or a three-tablet dose, chloroquine, chloroquine plus a short course of primaquine, and pyrimethamine alone.

Before the initiation of therapy, and on Days 1, 7, 14 and 21 after therapy, 60 laboratory reared *Anopheles balabacensis* and 60 *Anopheles maculatus* (IMR strain) were allowed to feed on patients. Two species of vector mosquitoes were

used for comparison of susceptibility. Ten mosquitoes from each species were withheld for determination for longevity (subject of a separate report). Mosquitoes were also fed on uninfected volunteers for simultaneous control. Mosquitoes were dissected 7 and 14 days after feeding. Guts and glands were examined for oocysts and sporozoites, and oocyst indices and sporozoite densities were determined.

RESULTS : The groups were similar in the rate of positivity of mosquito feeds, both in oocysts and sporozoites, prior to initiation of therapy (Table 1). In general, *Anopheles balabacensis* was more likely to become infected than *Anopheles maculatus* fed upon the same patient. The group treated with two tablets of Fansidar were less likely to infect mosquitoes fed before treatment, however. There is no obvious reason for this finding.

After therapy, on day 1, patients treated with Fansidar or with pyrimethamine alone were more likely to give rise to mosquito infections than patients treated with mefloquine, chloroquine, or chloroquine plus primaquine. Patients who had been treated with primaquine in addition to chloroquine infected no mosquitoes, even after only a single dose of primaquine (15 mg.). The three tablet dose of Fansidar has an apparent association with increased mosquito positivity.

As expected, gametocytes disappeared quickly after therapy, along with the asexual forms. Except for patients in the two-tablet Fansidar group who were positive on day 7 and patients who relapsed there were no gametocyte-positive patients available for mosquito feeding after day 1.

When patients were examined in terms of producing at least one positive mosquito infection (Table 2) groups were once again similar prior to therapy, with the note again that the group who later received two tablets of Fansidar produced a generally lower infectivity rate. After therapy fewer patients from the chloroquine and chloroquine-primaquine groups infected mosquitoes. In fact, the single dose of primaquine was associated with only one mosquito infection.

Data are still being collected from this study and a similar examination of *P. falciparum* is underway.

Table 1. *P. vivax* development in vector mosquitoes before and after anti-malarial therapy

Therapy	<i>An. balabacensis</i> Percent Positive		<i>An. maculatus</i> Percent Positive	
	Oocysts	Sporozoites	Oocysts	Sporozoites
a. Before Treatment (Day 0)				
Mefloquine	33	27	23	23
Fansidar (2 tablets)	13	13	6	6
Fansidar (3 tablets)	26	13	16	17
Chloroquine	29	29	19	15
Chloroquine + Primaquine	26	19	22	13
Pyrimethamine	32	29	37	32
b. After Treatment (Day 1)				
Mefloquine	41	13	16	8
Fansidar (2 tablets)	23	20	17	11
Fansidar (3 tablets)	43	56	62	40
Chloroquine	7	5	3	3
Chloroquine + Primaquine	0	0	0	0
Pyrimethamine	39	40	26	31

Table 2. Percent of patients giving rise to at least one positive mosquito feed

Therapy	Before Therapy (Day 0)	After Therapy (Day 1)
Mefloquine	47%	41%
Fansidar (2 tablets)	25%	50%
Fansidar (3 tablets)	64%	67%
Chloroquine	48%	22%
Chloroquine	56%	4%
Pyrimethamine	60%	40%