

MALARIA STUDIES

The Suppression of *Plasmodium falciparum* and
Plasmodium vivax Parasitemias by Mefloquine
(WR142490, a 4-quinolinemethanol)

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OBJECTIVES : To study the efficacy of the 4-quinolinemethanol, mefloquine (WR142490), in suppressing parasitemias in an area endemic for multidrug resistant *P. falciparum* and *P. vivax* malaria.

To compare the efficacy of mefloquine with that of the combination sulfadoxine-pyrimethamine.

BACKGROUND : Mefloquine (WR142490) is an a-(2-piperidyl)-4-quinolinemethanol which appeared to be longer acting than a previously studied parent compound, WR30090. Following evidence of the lack of toxicity in early studies, together with demonstration of the efficacy of Mefloquine as a chemotherapeutic and chemosuppressive agent, expanded studies, including the one reported here, were approved for conduct in Thai populations.

METHODS : The Bu Phram valley area, site of previous drug trials in Prachinburi Province, was again used. At the outset of the study, a census was taken and the villages were surveyed. The study protocol was explained to the villagers and those who wished to participate were asked to sign a consent form. The study population, numbering 1050, were randomly assigned to one of five major treatment groups and a smaller placebo group (Table 1). Under a double blind design, all participants received two tablets under observation each week. In the case of those on medication every other week or on one tablet each week placebo tablets were given. Younger participants in the study (weighing 22-35 kilograms) were given exactly $\frac{1}{2}$ the adult dose of Mefloquine. In the case of sulfadoxine-pyrimethamine no such reduction was deemed necessary. Study subjects were visited weekly by Laboratory technicians, who inquired about the villager's health, any illnesses or fevers during the past week, and whether the study subject had received any medications from an outside source. Every week a physician was available to see any ill study subject. A capillary blood was drawn for a thick-thin malaria slide, white blood cell count and micro-hematocrit. In the course of the trial, three venipunctures were done for determining biochemical parameters.

RESULTS : Nine hundred ninety study subjects began the 26 week field trial and 856 completed it (86.5%). There was no evidence of selection bias between the six treatment groups. Malaria transmission did occur during the field trial with calculated attack rates of greater than 1000/1000/yr for both *P. falciparum*

and *P. vivax*. Among 487 individuals receiving Mefloquine, there were only three instances of a falciparum parasitemia (Table 2). By contrast, nine villagers out of 333 receiving S-py. had a total of 12 episodes of falciparum parasitemia. Nineteen study subjects given placebo experienced a total of 40 episodes of parasitemia during the same time period. The duration of an asexual parasitemia in the S-Py and placebo groups was longer than the Mefloquine groups, although not statistically significantly so. Figure 1 shows the cumulative falciparum infection rates of the groups during the 26 week chemosuppressive phase and in the three month follow-up period. Malaria transmission was generally constant and there was no apparent loss of effectiveness during the study period in any of the drug treatment groups. After the chemosuppressive phase, the number of new falciparum infections in study subjects from the drug treatment groups increased. The three Mefloquine treatment groups had fewer study subjects contracting their first episode of falciparum malaria during the follow-up phase compared with the S-Py groups.

The number of vivax parasitemias among study subjects receiving Mefloquine during chemosuppression was small (4 cases) compared with the S-Py groups (28 cases) (Table 3). During the 26 week period of chemosuppression, there was a continuous accumulation of vivax parasitemias in the placebo group, reaching a proportion of 0.80 at 17 weeks (Figure 2). The rate of accumulation of parasitemias in the S-Py groups appeared to increase in the latter weeks of the study. This was followed by a marked increase in the proportion of individuals with vivax parasitemias occurring after termination of drug suppression in all groups.

Statistical evaluation comparing the various drug groups was undertaken using as the parameters the number of positive species-specific slides and the number of negative slides (Table 4). Evaluation between groups shows that Mefloquine, using the three Mefloquine groups combined, to be more efficacious than either of the S-Py regimens in suppressing a falciparum parasitemia ($p < 0.001$). The Fisher Exact Test fails to reveal any significant difference among the three Mefloquine groups themselves ($0.20 < P < 0.25$) for falciparum malaria. Analysis of the data based on the positive vivax slide readings showed the five treatment groups to be highly effective in suppressing vivax parasitemias ($p < 0.0001$). Evaluation of results showed Mefloquine to be more efficacious than the standard regimen (S-Py) in suppressing vivax parasitemias ($p < 0.0001$).

One hundred seventy one study subjects who received the S-Py preparation this year and received a sulfone/sulfonamide preparation in one or more past field trials were compared with 23 individuals who received S-Py for the first time this year. Of these twenty-three individuals in the first time S-Py group, one developed a falciparum parasitemia. Sixteen of the 171 individuals experienced a malaria parasitemia: 11 individuals had a vivax parasitemia, four had a falciparum parasitemia, and one individual had both. Mathematical evaluation using the Fisher Exact Test for a 2 x 2 table showed no significant differences between a group that had repeated exposure to a sulfonamide or sulfone preparation and a group that did not ($p = 0.2670$).

There was no clinical evidence of drug-related adverse effects from the 990 study participants who started the study. There were 30 instances of

individuals had an apparent decrease in hematocrit during the study. These individuals were evenly distributed among the six treatment groups. In most instances, repeat hematocrits a week later were normal and thus suggested a possible laboratory error or very transient condition. Paired information using hematocrits at week 0 and week 24 were analyzed within the treatment groups. Study subjects on the weekly S-Py regimen, the Mefloquine 180 mg weekly, and Mefloquine 360 mg biweekly experienced significant increases in their hematocrits ($p < 0.01$). The results from the other treatment groups were not significant.

There were 631 instances of leucopenia (defined as < 4000 cells/ml). These episodes of leucopenia were distributed among all treatment groups. Statistical evaluation showed a significant difference ($\chi^2 = 18.4313$; $p < 0.01$) among the groups with the differences appearing in the fortnightly S-Py group and in the placebo group. Further evaluation was undertaken to detect any significant differences in WBC determination following a six month ingestion of medication using paired data from weeks 0 and 26. While most treatment groups experienced a decrease in WBC's, the S-Py fortnightly group experienced the most significant decrease ($p < 0.003$).

There were no significant changes in the measured biochemical parameters.

All study subjects who finished the study were also seen during the follow-up period. Those with parasitemias were treated. Those study subjects with a falciparum parasitemia were given a therapeutic dose of sulfadoxine (1500 mg)-pyrimethamine (75 mg), while those with a vivax or malariae parasitemia were treated with the standard regimen using chloroquine (1500 mg over a 3 day period). Primaquine was given for 14 days to those study subjects known to be G-6-PD normal.

Table 1. Treatment groups and dose schedule for study subjects during chemosuppression for 26 weeks

No. subjects starting study	Dosage schedule
190	S(1000mg)-Py(50 mg) every two weeks
192	S(500mg)-Py(25 mg) every week
189	M(180mg) every week, children 22-35 kgs 1/2 dose
191	M(360mg) every week, children 22-35 kgs 1/2 dose
184	M(360mg) every two weeks, children 22-35 kgs 1/2 dose
44	PLACEBO

Table 2. *P. falciparum* Parasitemias Experienced by Study Subjects During Chemosuppression for 26 Weeks

Group	No. subjects completing study	No. (prop.) infected	No. episodes	Average duration (weeks) of episode
S(1000mg)-Py(50mg) fortnightly	162	5(0.03)	8	2
S(500mg)-Py(25mg) weekly	171	4(0.02)	4	3
Mefloquine(180mg) weekly	160	1(0.01)	1	1
Mefloquine(360mg) fortnightly	169	0(0.00)	0	-
Mefloquine(360mg) weekly	158	2(0.01)	2	1
Placebo	36	19(0.53)	40	2

Table 3. *P. vivax* Parasitemias Experienced by Study Subjects During Chemosuppression for 26 Weeks

Group	No. subjects completing study	No. (prop.) infected	No. episodes	Average duration (weeks) of episode
S(1000mg)-Py(50mg) fortnightly	162	15(0.09)	16	2
S(500mg)-Py(25mg) weekly	171	13(0.07)	14	2
Mefloquine(180mg) weekly	160	3(0.01)	4	1
Mefloquine(360mg) fortnightly	169	0(0.00)	0	-
Mefloquine(360mg) weekly	158	1(0.01)	2	2
Placebo	36	29(0.80)	51	2

Table 4. Results of Slide Microscopy* (chemosuppressive phase) drug groups

Slide results	S(1000)- Py(50) fortnightly	S(500)- Py(25) weekly	M(180) weekly	M(360) fortnightly	M(360) weekly	Placebo
Negative	3468	3779	3605	3708	3415	559
Falciparum (P.f.t.) positive	17	10	1	0	2	66
Vivax (P.v.t.) positive	26	29	4	0	4	82
Malariae (P.m.t.) positive	0	0	0	0	0	26
Mixed (P.f.t. + P.v.t.) positive	0	2	0	0	0	5

* Excluded are P.f.g. results and smears preceded the period before by absenteeism.