

The Suppression of *Plasmodium falciparum* and *Plasmodium vivax*
Parasitemias by a Sulfadoxine - Pyrimethamine Combination

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OBJECTIVE : To study the effectiveness of the combination of sulfadoxine (s) 500 mg and pyrimethamine (Py) 25 mg given in two dose regimens in suppressing parasitemias in an area with known chloroquine resistant falciparum malaria.

BACKGROUND : The combination of a sulfone or sulfonamide with pyrimethamine in the chemosuppression of chloroquine resistant falciparum malaria has been previously shown to be efficacious. The longer half life of a long acting sulfonamide, such as sulfadoxine ($t_{1/2} = 150-200$ hrs), should render this, in combination with a matched (in terms of $t_{1/2}$) dihydrofolic acid reductase, a better chemosuppressive agent.

DESCRIPTION : Seven hundred and fifty six semi-immune study subjects from four villages in Prachinburi Province, Northeast Thailand were assigned to one of five drug study groups. Subjects received, under a double blind design, one of the following medications :

- a. Sulfadoxine 1000 mg - pyrimethamine 50 mg biweekly
- b. Sulfadoxine 500 mg - pyrimethamine 25 mg biweekly
- c. Diformyldapsone 200 mg - pyrimethamine 12.5 mg weekly
- d. Diformyldapsone 400 mg - pyrimethamine 25 mg weekly
- e. Placebo weekly

Each study subject was visited weekly, at which time the medication was given and swallowed under supervision, a capillary blood drawn for a thick-thin malaria smear, and a history of illness since the prior visit noted. For those subjects receiving a biweekly medication regimen, placebo tablets were given on the alternate weeks; thus study subjects received two tablets weekly.

PROGRESS : Six hundred eighty-eight study subjects completed the 26 week trial (92%). Figure 1 shows that the weekly falciparum attack rates (based on a new asexual parasitemia) were lower during the medication phase of the trial in the four treatment groups compared with the placebo group. It can be further seen that an increased number of falciparum parasitemias were detected in the low dose DFD-Py group (weeks 7, 9 and 19); in the high dose DFD-Py group (week 10); and in the low dose S-Py group (week 10). Figure 2 shows the cumulative infection rates of individual study subjects in the course of the 26 week trial and in the subsequent follow-ups. The data indicate an 8-fold reduction in the cumulative parasitemic rate for *P. falciparum* in the high dose S-Py group, while a 4.4 fold reduction was noted in the high dose DFD-Py group when compared to the placebo group.

Statistical evaluation comparing the various drug regimens was undertaken. Highly significant results were obtained which showed that S (1000 mg)-Py (50 mg) given biweekly; S (500 mg)-Py (25 mg) given biweekly; DFD (400 mg)-Py (25 mg) given weekly; and DFD (200 mg)-Py (12.5 mg)

given weekly were effective chemosuppressive agents against *P. falciparum* when compared to placebo alone ($p < 0.0005$). Furthermore the higher dose S-Py regimen was more efficacious than the lower dose S-Py group, and more efficacious than either of the DFD-Py regimens in suppressing falciparum parasitemias. A direct comparison between the low dose S-Py group and the two DFD-Py groups failed to reveal any significant differences in efficacy. Table 1 summarizes these statistics.

We were able to identify one hundred seventy study subjects who participated in all three SMRL chemosuppressive studies. Of these 170, sixty seven individuals were known to have received DDS-Py in 1973; DFD-Py, DFD, or Dapsone-pyrimethamine (DDS-Py) in 1974; and to have received either S-Py or DFD-Py this year. Thus they received a sulfone preparation for a period of six months each year of the past two years, and subsequently received a sulfone or sulfonamide preparation for six months the next year. Analysis of this data was undertaken to discern any indication of increased susceptibility to a falciparum parasitemia among these individuals. When each of the current treatment groups was divided into two parts: those that received the prior sulfone drugs for two years and those that did not; it was found that there was no significant difference of chemosuppression between the groups. Further detailed analysis failed to discern any significant differences when the groups were compared as to which specific drug they received in the past (DDS-Py, DFD-Py, DFD) and which active medication this year.

Individuals (20) who received chloroquine in 1973, Py or Placebo in 1974, and DFD-Py or S-Py for the first time this year did not differ at all in suppression against falciparum parasitemias from those 67 study subjects described above.

Table 1. Statistical Evaluation Significance of Difference Between Two Sample Proportions (p value) for *P. falciparum* Suppression

	S - Py (1)	DFD - Py (h)	DFD - Py (1)	Placebo
S - Py (h)	2.9445 ($p < 0.002$)	3.7240 ($p < 0.0002$)	3.8595 ($p < 0.00015$)	18.2165 ($p < 0.0001$)
S - Py (1)	—	0.6038 ($0.25 < p < 0.30$)	1.1713 ($0.10 < p < 0.15$)	15.9411 ($p < 0.0001$)

(h) high dose

(1) low dose

With the cessation of chemosuppression the following number of new falciparum parasitemias were seen in the course of the two follow-up visits (weeks 29 and 40): 6 (at week 40) in the high dose S-Py group, 6 in the low dose S-Py group, 18 in the high dose DFD-Py group, 12 in low dose DFD-Py group, and 15 in the placebo group. Of these post-suppression falciparum parasitemias most (37 or 59) occurred at week 40. This would correspond to May, 1975 and the start of a new malaria transmission season.

This year we again had a large number of *P. vivax* parasitemias as shown in Table 2. The placebo group had a 55% cumulative vivax infection rate while the high dose S-Py and high dose DFD-Py had 19%. Both low dose groups were approximately equal with respect to numbers of study subjects

infected. Statistical evaluation showed that all four major treatment groups were efficacious *vis a vis* placebo. However, the high dose S-Py and DFD-Py were both equally effective in preventing vivax parasitemias, and were superior to the lower dose S-Py and DFD-Py regimens. There was no difference in efficacy between the lower dose regimens. Table 3 summarizes this information.

Following completion of the chemosuppressive phase of the study there was an increase in the number of primary vivax parasitemias. These numbered as follows: S-Py (high dose) group-27; S-Py (low dose) group-19; DFD-Py (high dose) group-34; DFD-Py (low dose) group-18; and placebo group-none. Thus the increase in the cumulative values for vivax parasitemias are for the S-Py (high dose) group from 0.19 to 0.36; for the S-Py (low dose) group from 0.26 to 0.38; for the DFD-Py (high dose) group from 0.19 to 0.40; for the DFD-Py (low dose) group from 0.29 to 0.41; and there was no change in the placebo group.

There were no reported episodes of drug related disease from the 747 study participants who started the study. All study subjects who finished the study were also seen during the follow-up period. Those with parasitemias were treated. Study subjects with a falciparum parasitemia were given a therapeutic dose of sulfadoxine-pyrimethamine, while those with a vivax parasitemia were treated with the standard regimen using chloroquine. Primaquine was given only to those study subjects known to be G-6-PD normal.

Hematocrits were monitored biweekly for evidence of hemolysis secondary to a G-6-PD deficiency. Of major concern were the two DFD-Py groups. There were 26 instances where individuals experienced falling hematocrits. These episodes were evenly distributed among the five treatment groups. In most instances repeat hematocrits a week later pointed to a probable laboratory error. Paired information using hematocrits at week 0 and week 26 were statistically analyzed. The study subjects as a whole in each of the four major treatment groups showed a significant increase in the

Table 2. *P. vivax* Parasitemia Experienced by Study Subjects During Chemosuppression

Group	No. Subjects	No. (prop.) Infected
S (1000 mg.)-Py (50 mg.)	155	29 (0.19)
S (500 mg.)-Py (25 mg.)	156	41 (0.26)
DFD (400 mg.)-Py (25 mg.)	162	31 (0.19)
DFD (200 mg.)-Py (12.5 mg.)	153	45 (0.29)
Placebo	62	34 (0.55)

value of their hematocrit over the twenty-six week trial period. For the DFD-Py high and low dose groups the rises (0.7% and 1.0%) were significant at the 5% level, while for the S-Py high and low dose groups the rises (1.46% and 2.98%) were significant at the 1% level. The result for the placebo group showed a slight increase in the average hematocrit value (0.52%), which was not significant. Evaluation of hematocrits of males with G-6-PD deficiency in the high dose DFD-Py regimen (18 out of 133 males) showed that they too experienced an increase in their hematocrits (2.2%) which was significant at the 2% level.

Table 3. Statistical Evaluation Significance of Difference Between Two Sample Proportions (p value) for *P. vivax* Suppression

	S-Py (1)	DFD-Py (h)	DFD-Py (1)	Placebo
S-Py (h)	2.9445 (0.0016 < p < .002)	0.4763 (0.30 < p < 0.35)	4.6588 (p < 0.0005)	13.1462 (p < 0.0005)
S-Py (1)	—	2.5383* (0.005 < p < 0.01)	1.5935 (0.05 < p < 0.10)	10.3316 (p < 0.0005)

* In favor of DFD-Py (h).

(h) high dose

(1) low dose

Likewise all study subjects were monitored for leucopenia. At the start and during the trial there were 240 instances of a leucopenia (defined as <4000 cells/ml). These episodes of leucopenia were distributed evenly among all five treatment groups, and there was no bias detected ($X^2_4 = 3.5103$; $0.40 < p < 0.50$). Statistical evaluation was undertaken to detect any significant differences in WBC determinations following a six month ingestion of sulfonamides or sulfones using paired data from weeks 0 and 26. While all groups experienced a decrease in WBC counts, only the S-Py (high dose) group showed a significant decrease (see Figure 3). This amounted to an average decrease of from 7645 WBC/ml at the start to 6850 WBC/ml at the end of the trial ($p < 0.05$).

Follow-up visits to the local health center revealed only four study subjects who received antimalarial therapy (3 received sulfadoxine-pyrimethamine, one received oxytetracycline) from other sources. Weekly smears taken from these four study subjects while under outside therapy were not included in the results.

From the point of view of drug tolerance there seemed to be no instances of untoward reactions, and this agrees with the experience of others. There was no evidence of marked leucopenia except for a lowering of the WBC in the high dose S-Py group. Values for hematocrits in all major treatment groups were increased possibly due to supplementary hematinics given ($FeSO_4$, vitamins) to all study subjects at the time of tablet ingestion and blood smearing.

SUMMARY : Sulfadoxine (1000 mg)-pyrimethamine (50 mg) given biweekly was shown to be an effective chemosuppressive against both falciparum and vivax parasitemias, causing an eight fold reduction in falciparum parasitemias, and an approximately three fold reduction in vivax parasitemias. While the low dose S-Py group and the two DFD-Py groups were less effective than the high dose S-Py group in suppressing falciparum parasitemias, the high dose DFD-Py combination was as effective as the high dose S-Py combination in suppressing vivax parasitemias.

FIGURE I
WEEKLY ATTACK RATE OF SUBJECTS INFECTED WITH *P. FALCIPARUM*
BY STUDY GROUP

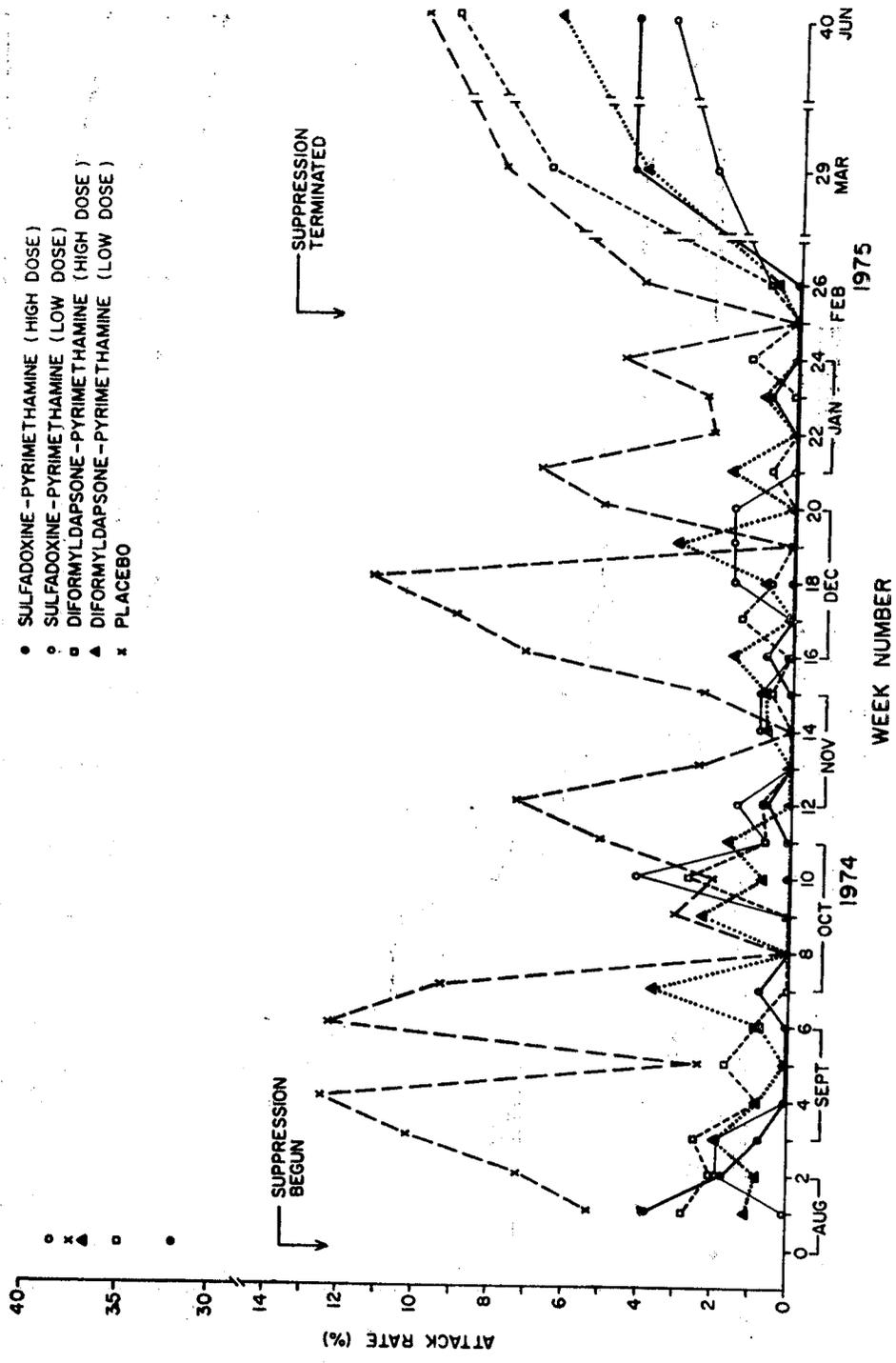


FIGURE 2.
 CUMULATIVE PROPORTION OF SUBJECTS INFECTED WITH *P. FALCIPARUM*
 BY STUDY GROUP

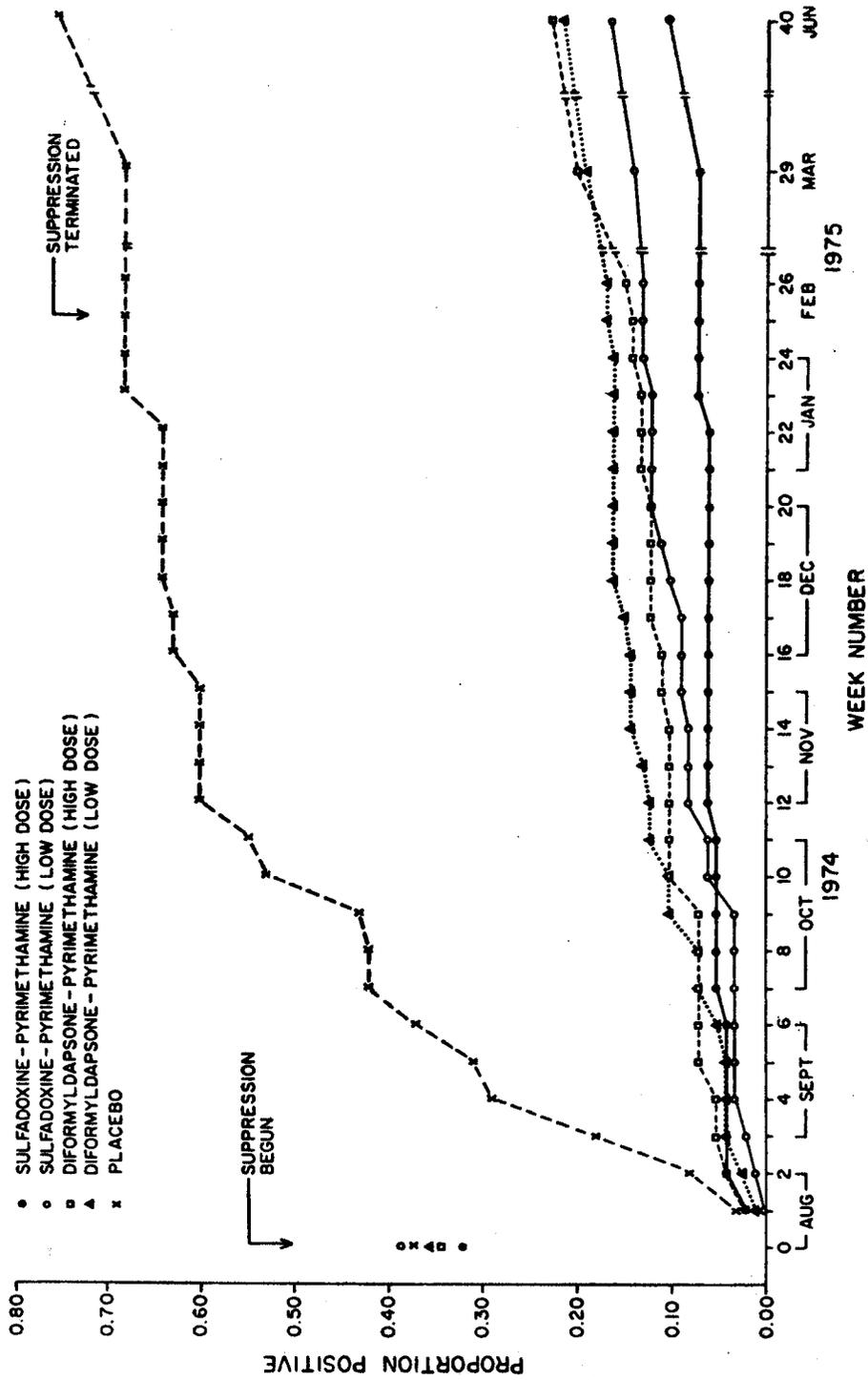


FIGURE 3
EFFECT OF TREATMENT ON WHITE BLOOD CELL COUNTS

