

The Suppression of *Plasmodium falciparum* and *Plasmodium vivax*
Parasitemias by a Diformyl-dapsone—Pyrimethamine Combination

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OBJECTIVE: To study the effectiveness of the combination of diformyl-dapsone (DFD) 200 mg and pyrimethamine (Py) 12.5 mg in suppressing parasitemias in an area with known chloroquine resistant *falciparum* malaria.

BACKGROUND: The combination of dapsone (DDS) and pyrimethamine (Py) in the chemosuppression of chloroquine resistant *falciparum* malaria has been previously shown to be efficacious. The longer half life of the diformyl congener of dapsone should render this sulfone in combination with pyrimethamine a better chemosuppressive agent.

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

- a. DFD 200 mg and Py 12.5 mg
- b. DFD 400 mg
- c. DDS 100 mg and Py 12.5 mg
- d. Py 25 mg
- e. Placebo

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. Following the drug phase of the study four additional followup visits were made.

PROGRESS: Five hundred ninety-three study subjects (90%) completed the twenty-six week course of medication. Figure 1 shows that the weekly attack rates of new *falciparum* infections were lower during the medication phase of the trial in the sulfone groups (DFD—Py, DDS—Py, and DFD) compared to either the pyrimethamine or placebo group. It can be further seen that parasitemias were suppressed in the DFD—Py, DDS—Py, and DFD groups in the early phase of the study. An increased number of *falciparum* cases was seen in weeks 7—8 in both the DFD—Py and DFD groups, while a similar increase was seen in the DDS—Py group later (week 13).

Figure 2 shows the cumulative infection rates of individual study subjects in the course of the 26 week trial and the subsequent follow-ups. The data indicates a 4.6 fold reduction in the cumulative parasitemic rate for *P. falciparum* in the DFD—Py group and a 6.4 fold reduction in the DDS—Py group when compared to the placebo group.

The results of microscopy for *falciparum* parasitemias are given in Table 1.

Statistical evaluation comparing the various drug regimens was undertaken. Highly significant results were obtained which showed that DFD—Py, DDS—Py, and DFD alone were effective chemosuppressive agents against *P. falciparum* when compared with placebo alone ($0.0005 > p$). DFD—Py, as a combination, was more effective than its component parts: DFD ($0.0005 > p$) or Py ($0.0005 > p$) in suppressing a *falciparum* parasitemia. Significant differences, likewise, were seen when DDS—Py was compared with DFD alone ($0.0005 > p$), and Py alone ($0.0005 > p$); however, a direct comparison between DFD—Py and DDS—Py failed to reveal any significant difference in efficacy ($0.4875 > p > 0.475$). Table 2 summarizes these statistics.

Table 1. Results of Slide Microscopy* Drug Groups

Slide results	Pyrimethamine	DFD-Py	Placebo	DDS-Py	DFD
Negative slides	2139	2697	2015	2716	2528
Falciparum (P.f.t.) positive	433	27	449	28	58
Vivax (P.v.t.) positive	124	25	148	46	111
Mixed (P.f.t. + P.v.t.) positive	22	2	14	1	6
Total	2718	2751	2626	2791	2703

* Excluded are *P. falciparum* gametocytemia (P.f.g.) results and smears preceded the week before by absenteeism.

Table 2. Calculated Student-t-values for Falciparum Parasitemias (P value)

	DFD	Py	Placebo	DDS-Py
DFD-Py	3.7470* (0.0005 > p)	20.4216* (0.0005 > p)	21.0752* (0.0005 > p)	0.0553 (0.4875 > p > 0.475)
DDS-Py	3.8181° (0.0005 > p)	20.5830° (0.0005 > p)	21.2391° (0.0005 > p)	

* Values significant in favor of DFD-Py

° Values significant in favor of DDS-Py

While study subjects receiving the drugs: DDS-Py, DFD-Py or DFD alone were parasitemic less often (Table 3), no statistically significant difference ($X^2 = 2.1613$; $0.40 > p > 0.35$) in the density of falciparum parasites was seen (Table 4).

Table 3. *P. falciparum* Asexual Parasitemias Experienced by Study Subjects During Chemosuppression

Group	Number subjects	Number (prop.) infected	Total (average) number of episodes	Average duration (weeks) of episode
DDS-Py	123	12 (0.10)	17 (1.42)	1.42
DFD-Py	118	16 (0.14)	19 (1.19)	1.42
Diformyldapsone	117	26 (0.22)	42 (1.62)	1.43
Pyrimethamine	118	64 (0.54)	207 (3.23)	1.89
Placebo	117	73 (0.62)	234 (3.21)	1.98

Table 4. Densities of *P. falciparum* Asexual Parasitemias Experienced by Study Subjects During Chemosuppression

Group	Number (proportion) parasitemias*	
	≤20	> 20
DDS—Py	16 (0.94)	1 (0.06)
DFD—Py	16 (0.84)	3 (0.16)
Diformyldapsonsone	39 (0.93)	3 (0.07)
Pyrimethamine	180 (0.87)	27 (0.13)
Placebo	208 (0.89)	26 (0.11)

* In parasites per 100 white blood cells.

With cessation of chemosuppression the following new falciparum infections were seen in the five groups: thirteen in the DFD—Py group; eleven in the DFD group; fifteen in the DDS—Py group; one in the pyrimethamine group; and two in the placebo group. Of these post-treatment falciparum parasitemias, 24 of 42 occurred four months later. This would correspond to June, 1974, and the start of a new malaria transmission season.

A large number of vivax infections were seen in this study as shown in Table 5.

Table 5. *P. vivax* Parasitemia Experienced by Study Subjects During Chemosuppression

Group	Number of subjects	Number (prop.) infected
DDS—Py	123	17 (0.14)
DFD—Py	118	16 (0.14)
DFD	117	28 (0.24)
Py	117	52 (0.44)
Placebo	117	51 (0.44)

The Py and placebo groups each had a 44% cumulative vivax infection rate while the DFD—Py group had 14%, the DDS—Py group 14%, and the DFD group 24%. Statistical evaluation (Table 4) showed that the three sulfone groups suppressed vivax parasitemias better than pyrimethamine when compared with the control group. Py alone was totally ineffective. DFD—Py was not only more effective than its component parts: DFD (0.0005 > p) and Py (0.0005 < p), but DFD—Py was also more efficacious than DDS—Py (0.01 > p > 0.005) in the weekly chemosuppression of vivax malaria. DDS—Py likewise was more effective than DFD alone (0.0005 > p) and Py alone (0.0005 > p) in the weekly suppression of *P. vivax* parasitemias. Table 6 summarizes this information.

Table 6. Calculated Student-t-values for Vivax Parasitemias (p value)

	DFD	Py	Placebo	DDS-Py
DFD-Py	7.7092* (0.0005 > p)	9.2758* (0.0005 > p)	9.2758* (0.0005 > p)	2.2793*
DDS-Py	5.7599° (0.0005 > p)	7.4425° (0.0005 > p)	8.5668° (0.0005 > p)	—

* Values significant in favor of DFD-Py

° Values significant in favor of DDS-Py

Following completion of the chemosuppressive phase of the study there was an increase seen in new cases of vivax malaria in the DFD-Py group, 15; DDS-Py, 16; DFD, 11; Py, 4; and placebo, 5. The increase in the cumulative values for vivax infections are for the DFD-Py group from 0.14 to 0.29; for the DDS-Py group from 0.14 to 0.27; for the DFD group from 0.24 to 0.33; for the Py group 0.44 to 0.48 and for the placebo group from 0.44 to 0.49.

SUMMARY: The combination DFD-Py given weekly was shown to be an effective chemosuppressive against both falciparum and vivax parasitemias, causing a four fold plus reduction in falciparum parasitemias, and an approximately three fold reduction in vivax parasitemias; however, this combination was not more efficacious than DDS-Py for the chemosuppression of falciparum malaria. DFD was only moderately effective, while there was no difference in chemosuppression between pyrimethamine and placebo.

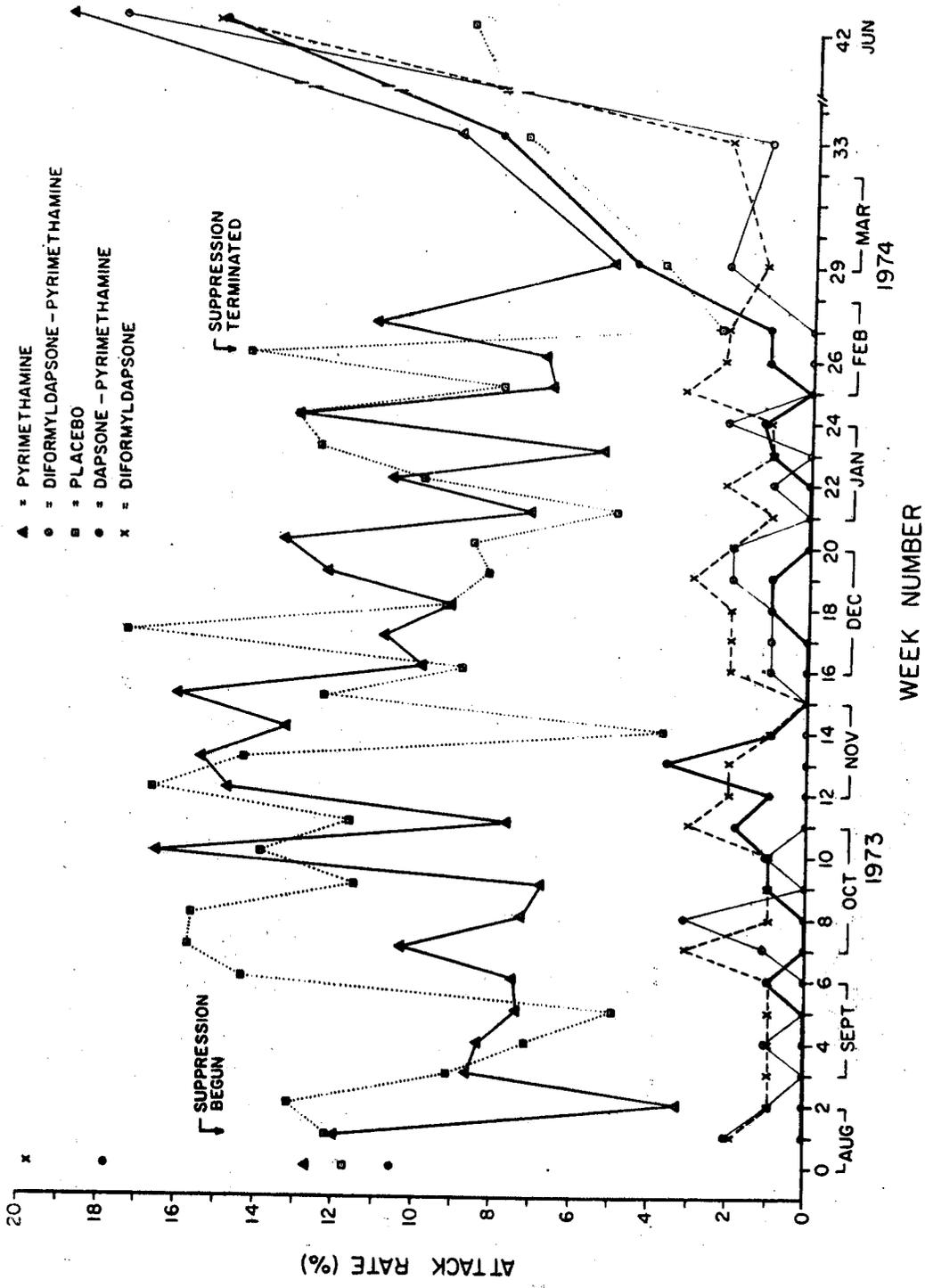


FIGURE 1. WEEKLY ATTACK RATE OF SUBJECTS INFECTED WITH *P. falciparum* BY STUDY GROUP

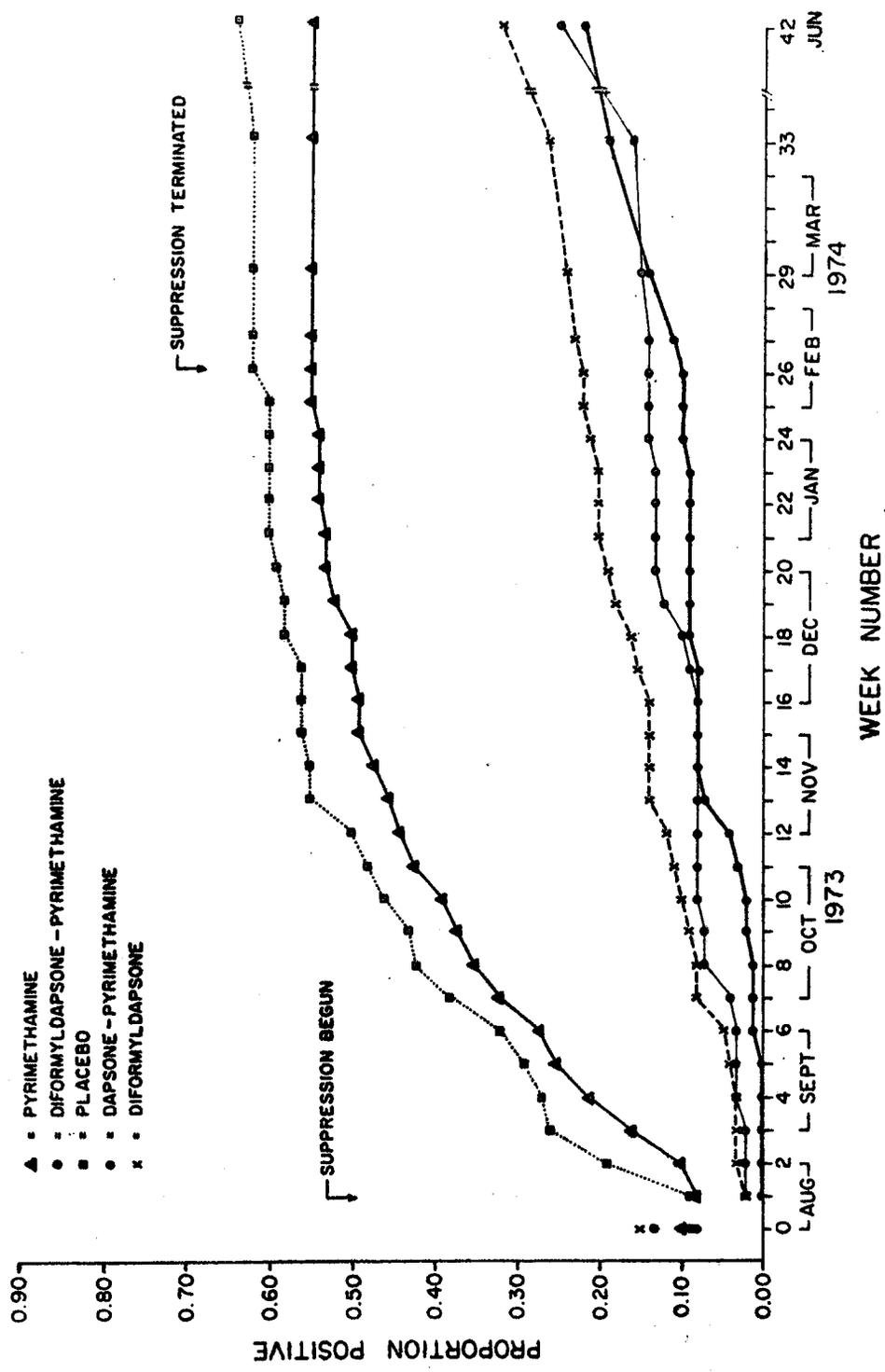


FIGURE 2. CUMULATIVE PROPORTION OF SUBJECTS INFECTED WITH *P. FALCIPARUM* BY STUDY GROUP