

A Comparative Evaluation of Sulfalene—Trimethoprim and
Fanasil—Pyrimethamine Against Falciparum Malaria in Thailand

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OBJECTIVE: Chloroquine resistant falciparum malaria was first reported from Thailand in 1962. Subsequent surveys performed in this country have indicated a rate ranging from 50—100%.

Because of the problem of drug resistance and because the administration of quinine to large numbers of patients in the field is operationally impractical, the need in Thailand for a simple and effective regimen against falciparum malaria is most urgent. Presently, 2 sulfonamide combinations have the potential for meeting this critical need. These are:

1. Sulfalene—trimethoprim and
2. Fanasil—pyrimethamine.

The purpose of this study was to assess these 2 combinations against falciparum malaria in adult Thai males, with respect to rapidity of action, cure rate, and possible side effects, especially side effects in individuals deficient in erythrocytic glucose—6—phosphate dehydrogenase (G—6—PD) activity.

DESCRIPTION: Subjects for this evaluation were chosen from acutely ill individuals seeking treatment at the Trad Provincial Hospital located in Southeast Thailand. Selected were adult males, 15 years of age or older, with a positive blood smear for falciparum malaria who, by history and physical examination, were found to be free of obvious evidence of renal, cerebral, or hepatic complications.

Initial laboratory determinations consisted of hematocrit and leukocyte count. A venous blood sample was obtained for the assessment of possible G6PD deficiency by the Hyland G—6—PD spot test. Subjects were then alternately assigned to one of 2 treatment groups listed below.

Treatment I: S—T (Sulfalene 1 gm and trimethoprim 0.5 gm).

Treatment II: F—P (Fanasil 1 gm and pyrimethamine 0.050 gm).

Following treatment, patients were admitted to the medical ward where they were observed initially for vomiting and, when required, given supportive care.

As patients became asymptomatic they were discharged after at least 3 consecutive days of negative blood smears.

Hematocrits, leukocyte counts, and thick—thin blood smears were taken at least daily during the patients' hospitalization and weekly thereafter on days 7, 14, 21 and 28 following discharge. (The day of treatment was designated day 0). The smears were treated with Giemsa stain. Parasites per cmm were calculated by multiplying the number of parasites per 100 WBC by the factor obtained from each patients' white blood (WBC) count taken on the same day. (Factor=WBC/cmm of blood ÷ 100). If 5 minutes of examination failed to disclose parasites, a smear was considered negative.

In this study, cure was defined as the clearance of patent asexual parasitemia by day 7 with no recrudescence during the remaining weekly follow—up examinations to day 28. Failure was the lack of clearance of patent parasitemia by day 7 or reappearance of patent asexual forms during any of the weekly follow—up examinations after initial clearance.

PROGRESS: Eighty-eight patients were selected for inclusion in the study. Adequate history from 75 of the patients indicated that 73% took some antimalarials prior to their hospital admission. The medication most frequently utilized was chloroquine, although occasionally intramuscular quinine had been administered.

More than 90% of the subjects had been ill for an average of 6 days prior to hospital admission. Fewer than 10% stated that they had come to the hospital on the first day of illness or that they had been ill for greater than one month. Approximately 60% of the patients had a history of one or more malaria infections.

The subjects were divided on an alternating basis into 2 groups. S-T was given to 45 cases and F-P given to the other 43. The pre-treatment observations of the 2 groups were quite comparable with respect to age, weight and initial parasite density (Table 1).

The results of the immediate response to treatment are summarized in Table 2. The results observed in the 2 groups were again comparable. There was one case in each of the treatment groups in which patent parasitemia was not cleared within 7 days.

Follow-up for one month was possible in 65 of the 88 cases. The results of these 65 cases are summarized in Table 3. Although the F-P regimen produced a better cure rate than that of S-T, the difference was not significant, the Chi square value for the observed differences being only 0.261. In the cases of delayed treatment failure, patent parasitemia was cleared initially within 2-4 days in 4 S-T treated individuals and within 6-7 days in 2 cases given F-P.

The WBC count and hematocrit values of all subjects were within the usual range found in patients with malaria. The lowest WBC count, 1,320/cmm, was recorded on day 21 from one case given F-P treatment. This individual's WBC count rose to 7,700/cmm on day 28.

G-6-PD deficiency was found in 11 (12.5%) of the 88 subjects. Comparison of the post-treatment hematocrit values of these 11 individuals with the other subjects disclosed no detectable differences.

The effect of treatment of gametocytemia in 63 of the cases observed for 28 days is shown in Table 4. In both treatment groups, gametocytes usually developed approximately 6 days after treatment. In general, gametocyte densities were found to be less than 1,000/cmm. In one exceptional case, a maximal density of 18,778/cmm was observed 7 days after treatment with F-P.

Two patients given S-T vomited soon after treatment. The other subjects in both groups tolerated the medications well; and no adverse side reactions were observed.

SUMMARY: In areas of the world where chloroquine resistant falciparum malaria is a significant problem, long-acting sulfonamide combinations have a definite place as an alternative treatment in proven drug resistant cases. Experience in Thailand indicates that the rational field use of such combinations should be guided by the following considerations:

1. The recurrence of patent infection with asexual forms of falciparum malaria within one month following treatment with a presumptive dose of chloroquine (600 mg base) is sufficient indication of chloroquine failure, suggesting the intervention of long-acting sulfonamide combinations as the next treatment.
2. Until more information is available regarding the possible sporontocidal property of long-acting sulfonamide combinations, the additional use of primaquine as a gametocide is recommended.
3. Prior to contemplated mass use, an evaluation should be undertaken to determine susceptibility of local strains to the long-acting sulfonamide combinations.
4. Following failures to cure with such combinations, treatment with quinine should be instituted.

It is apparent that sulfonamide combinations, because of their known limitations, are not the final solution to the problem of drug resistant falciparum malaria. Until a better treatment is developed, such combinations can, if used judiciously, fill existing needs.

Table 1.
Pre-treatment observations of study subjects

Rx	No. cases	Age in yrs. Range (average)	Wt. in kg Range (average)	Parasite count/cmm Range (geometric mean)
Sulfalene-trimethoprim	45	15-50 (26.1)	25-90 (50.9)	59-120,054 (6,473)
Fanasil-pyrimethamine	43	15-51 (25.5)	31-63 (48.6)	271-125,400 (7,010)

Table 2.
Immediate response to treatment

Rx	No. Cases	Clearance of patent parasitemia by day 7 No. (%)	Average No. days to clear parasitemia	Average No. days to clear fever (100°F)
Sulfalene-trimethoprim	45	44 (97.8%)	2.2	2.4
Fanasil-pyrimethamine	43	42 (97.6%)	2.6	2.5

Table 3.
Treatment results in patients followed one month

Rx	No. cases*	No. cured (%)	Day of recrudescence in delayed failures
Sulfalene—trimethoprim	31	26 (83.9%)	14, 28, 21, 28
Fanasil—pyrimethamine	34	31 (91.2%)	28, 28

* Also includes the 2 immediate treatment failures noted in Table 2.

Table 4
The effect of S—T and F—P treatment on gametocytemia in cases followed for one month.

Rx	Total cases	Gametocytes present on initial smear No. (%)	Gametocytes not observed during 28 days No. (%)	Gametocytes developing after treatment No. (%)
Sulfalene—trimethoprim	30	3 (10%)	7 (23.3%)	20 (66.6%) range = 1—14 days average = 5.9 days
Fanasil—pyrimethamine	33	1 (3%)	4 (12.1%)	28 (84.8%) range = 1—23 days average = 6.2 days