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THE EVALUATION OF QUININE ALONE OR IN COMBINATION WITH TETRACYCLINE AND PYRIMETHAMINE AGAINST FALCIPARUM MALARIA IN THAILAND

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INTRODUCTION

The standard radical treatment against falciparum malaria used by the National Malaria Eradication Project (NMEP) of Thailand since October 1971 is a single dose of sulphormethoxine combined with pyrimethamine plus 5 daily doses of primaquine. Since studies to date by Harinasuta *et al.*, (1967), Chin *et al.*, (1973), and Chin and Rattanarithikul (1973), indicated that the use of sulphormethoxine-pyrimethamine against Thai strains of *Plasmodium falciparum* can result in a failure rate of up to 10%, an alternative regimen for these cases of treatment failure is required.

Of the limited antimalarials presently available for consideration as an alternative regimen, quinine remains the drug of choice. Data on the sensitivity of Thai strains of *P. falciparum* to quinine are limited and conflicting. Studies on at least two Thai strains of falciparum malaria performed in the United States, utilizing infections induced in nonimmune prisoner volunteers, indicated that a 100% cure rate can result from 5 days of quinine treatment with a dosage of 10 gr 3 times per day (WHO, 1967). Conversely, Harinasuta *et al.*, (1965) reported that of 6 Thai falciparum patients given 4 or 5 days of quinine treatment, none were cured and that 7

days of quinine treatment were required for consistent cures in 8 additional falciparum cases. A regimen of quinine treatment requiring 7 days has obvious disadvantages of prolonged duration and accompanying side reactions. Such limitations render impractical its field use by a malaria operational program.

Recently, Colwell *et al.*, (1972) reported that tetracycline, given for 10 days to asymptomatic Thai falciparum patients, resulted in a cure rate of 100% in 12 cases. In 4 additional cases, tetracycline was discontinued after 72 hours and standard antimalarials substituted when the subjects developed increasing symptoms. While the side reactions to tetracycline are minimal, the requirement of 10 days' treatment as well as its slow action also limits its usefulness for administration in the field.

It is not known whether the addition of tetracycline to quinine would produce synergistic effect enabling reduction in total duration of treatment. A potentiation effect between quinine and pyrimethamine against Vietnam strains of falciparum malaria has been reported (Sheehy *et al.*, 1967), but it is unknown whether these two drugs would have the same effect against Thai strains.

This study was undertaken to assess the quinine sensitivity and the effectiveness of quinine combinations against Thai strains of falciparum malaria in order that an alterna-

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tive regimen might be developed for use by the NMEP against those falciparum infections not cured by sulphormethoxine-pyrimethamine.

MATERIALS AND METHODS

Subjects of this study were chosen from male and female falciparum patients ages 15 years or older seeking treatment at the Prapokklao Hospital in Chantaburi, a city in Southeast Thailand some 350 km from Bangkok. The selection of subjects for inclusion in the study was based on two criteria : (1) that they be free of malarial complications, such as cerebral malaria and (2) that they be able to return to the hospital following discharge for 4 weekly visits for examination of their blood smears. The subjects were then hospitalized and given, on an alternating basis, one of the following treatment:

- Treatment I :** Quinine 10 gr 3 times per day \times 7 days
- II :** Quinine 10 gr 3 times per day \times 5 days
- III :** Quinine 10 gr 3 times per day \times 4 days
- IV :** Quinine 10 gr and tetracycline 250 mg given together 3 times per day \times 3 days
- V :** Same as IV plus pyrimethamine 50 mg given with the first dose of quinine-tetracycline.

Thick-thin blood smears were examined and leucocyte count determined once daily (for the purpose of calculating parasite density/c.mm blood) while the patient was hospitalized. Patients were discharged following completion of treatment and requested to return once weekly for 4 weeks.

The infection was deemed cured if the 4 weekly follow-up blood smears were negative

for asexual forms of falciparum malaria. Treatment failure was indicated when any of the 4 weekly follow-up smears was positive for asexual forms of falciparum malaria. In the event of treatment failure, the standard NMEP treatment for falciparum malaria (sulphormethoxine 1 gm + pyrimethamine 50 mg + primaquine 15 mg daily for 5 days) was administered.

In those cases of mixed infection in which vivax malaria was detected during one of the weekly follow-up visits, radical treatment with chloroquine-primaquine was given and further follow-up of the subject was discontinued.

RESULTS

Of the 59 patients included in the study, 26 were females and 33 males. The pre-treatment observations of the subjects are summarized in Table 1. As indicated the average weight of the patients in the respective treatment groups ranged from 45.8 kg to 49.8 kg and the average pre-treatment parasite counts ranged from 7,066/c.mm to 19,790/c.mm blood.

The initial response to treatment with the respective regimens as noted in Table 2 was satisfactory and well within normal limits in that clearance of patent asexual parasitemia and fever was observed in all 59 subjects within 4 days. The average number of days required for clearance of patent parasitemia and fever for each of the treatment group ranged from 1.6-2.6 days and 2.2-3.0 days respectively.

Toxic side reactions (cinchonism) were reported by virtually every patient. In fact, it was so severe in five of the 59 patients whose weights ranged from 35 kg - 44 kg that the daily quinine dosage, beginning on the second day of treatment, was reduced from 30 gr to 20 gr. On the other hand, while the toxic

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Table 1

Pre-treatment observations of study subjects.

Treatment group	Total No. cases	Age in years		Weight in kg		Initial parasitemia/c.mm	
		Range	Average	Range	Average	Range	Average
I	10	16-49	28.6	40-70	49.8	2442-63,504	19,790
II	13	16-49	26.7	37-53	47.6	667-59,608	17,482
III	11	18-56	26.7	35-57	47.5	1000-34,506	11,954
IV	12	17-49	28.5	37-64	48.8	383-19,600	7,066
V	13	16-52	26.5	39-54	45.8	1392-25,248	9,936

Table 2

Immediate response to treatment.

Treatment groups	Average No. days to clear parasitemia	Average No. days to clear fever (100°F)
I	2.1	3.0
II	2.6	2.2
III	2.4	2.5
IV	2.4	2.2
V	1.6	2.8

reactions were significant, none of the subjects requested discontinuation of the treatment because of it.

One month follow-up of the subjects was completed in 39 of the 59 cases (66%). Three of the completed cases were patients who had received the reduced quinine dosage. Of these three cases, two were cured following modified treatment regimens III or IV and recrudescence of patent infection was observed in the third patient 28 days after initiation of modified treatment II. The cure rates based on the cases with one month follow-up, excluding the three cases given reduced quinine treatment regimens, are noted in Table 3. As shown, none of the treatment regimens resulted in an acceptable high cure rate. In general, treatments I, IV, and V resulted in higher cure rates (66.7 - 75.0%) than treatments II and III (33.3 - 42.9%).

Table 3

Treatment results in patients followed one month.

Treatment groups	No. cases	No. cured (%)	Day of recrudescence
I	8	6 (75.0)	21 22
II	7	3 (42.9)	21 21 26 28
III	6	2 (33.3)	19 21 28 28
IV	6	4 (66.7)	15 22
V	9	6 (66.7)	22 27 27

DISCUSSION

The results reported in this study indicate that none of the proposed alternative treatments evaluated produced cure rates which are acceptable for field use against falciparum malaria.

The seven-day treatment with quinine yielded the highest cure rate of 75.0%. This is a significant reduction in cure rates reported from studies of Thai strains of *P. falciparum* from the United States (WHO, 1967) and from Harinasuta (1965).

Whether there has been an actual decrease in sensitivity of the Thai strains of *P. falciparum* to quinine during the past few years is open to speculation. The fact that recurrence of patent parasitemia in the two subjects whose infections were not cured by 7 days of quinine did not occur until follow-up days 21 and 22 respectively renders impossible the exclusion of reinfection following discharge from the hospital. The nature of undoubtedly high and perhaps even daily exposure to infection by most of the study subjects further compounds the accurate assessment of results. Given the fact that quinine has little or no effect on the exoerythrocytic forms of malaria, it follows that the occurrence of patent parasitemia in 2 subjects some 3 weeks after treatment with 7 days of quinine may be due either to infection acquired prior to or following hospitalization or to drug failure. Further studies of such strains in human volunteers with controlled exposure and in the absence of reinfection will be required to determine whether in fact strains of falciparum malaria exist in Thailand which are resistant to 7 days' treatment with quinine.

The finding that the 5 days and 4 days of quinine treatment resulted in cures, albeit at low rates (42.9% and 33.3% respectively) suggests that the spectrum of response to

quinine by the falciparum strains in the study area is wide.

The combination of quinine-tetracycline given for 3 days yielded a cure rate close to that observed following 7 days treatment with quinine and better than the 5 and 4 days of quinine given alone. This would suggest that the combination gave rise to at least an additive effect. However, given the small number of cases treated in each category, such a conclusion would be tenuous at best. The addition of 50 mg of pyrimethamine to the 3 days of quinine-tetracycline, disappointingly, produced no enhancement in cure rate.

In the final analysis, none of the 5 treatment regimens evaluated can be recommended for field use as an alternative treatment for strains of falciparum malaria "resistant" to sulphormethoxine-pyrimethamine. The possibility exists that adjustment of the quinine-tetracycline regimen perhaps to 4 days rather than 3 days may give rise to cure rates acceptable by malaria programs. Further studies along such lines are obviously needed. Equally obvious is the fact that because of the side effects, even 4 days of quinine-tetracycline treatment may not receive wide acceptance by the patients when such treatment is administered unsupervised in the patient's home. The need therefore for the development of new drugs feasible for operational use by malaria programs to counter the problem of multi-resistant strains of falciparum malaria is of utmost urgency.

SUMMARY

The sensitivity of Thai strains of falciparum malaria against quinine alone or in combination with tetracycline and pyrimethamine was assessed. Fifty-nine adult male and female subjects were treated on an alternating basis with 5 respective treatment regimens. Completion of follow-up for one month in patients receiving a full course of one of 5

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treatment regimens was accomplished in 36 subjects. In general the highest cure rates, 66.7% - 75.0%, were observed following treatment with 7 days of quinine and 3 days of quinine-tetracycline or quinine-tetracycline pyrimethamine combinations.

The results are sufficiently suggestive of a possible additive effect between quinine-tetracycline that this finding be followed up with additional studies along similar lines.

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