THE EVALUATION OF THE PRESUMPTIVE AND RADICAL TREATMENTS AGAINST FALCIPARUM MALARIA IN THAILAND

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INTRODUCTION

Presumptive treatment is used in malaria eradication programs, during both the late attack and consolidation phases, to treat suspected cases of malaria prior to confirmation of diagnosis by the examination of a blood smear for malaria parasites. This treatment, commonly given as a single dose, consists of a schizontocide, usually a 4-aminoquinoline, and a gametocytocidal or sporontocidal drug such as primaquine or pyrimethamine, respectively. The purpose of such a treatment is two-fold: First, the schizontocide will afford symptomatic relief to people infected with malaria while, at the same time, the antigametocyte drug will prevent or minimize further transmission of malaria until their blood smear is confirmed as positive and radical treatment is given. In Thailand, beginning in 1958, pyrimethamine (50 mg) in combination with chloroquine (600 mg base) is the standard presumptive treatment used by the National Malaria Eradication Project (NMEP). In a small operational area in Central Thailand (Zone Pakchong) pyrimethamine was replaced by primaquine in 1965.

The radical treatment for all blood smear confirmed malarias since 1963 consists of chloroquine 1.5 gm (base) given over 3 days and 5 doses, 15 mg daily, of primaquine.

The ease with which resistance is developed by malaria parasites to pyrimethamine is well known. That this resistance extends to the gametocytes was reported by Burgess and Young (1959). Furthermore, in at least three strains of chloroquine-resistant falciparum malaria originating from Thailand and studied in prisoner-volunteers in the United States, resistance by the asexual forms to pyrimethamine has been well documented (WHO, 1967). On the other hand, to date, there has been no reported evidence of resistance developing against primaquine.

Chloroquine-resistant falciparum malaria was first reported from Thailand by Harinasuta *et al.*, (1962). Since that time, investigations performed in Thailand by Harinasuta (1965, 1967) and by personnel from the SEATO Medical Research Laboratory (Bourke *et al.*, 1966), and the Thailand Malaria Operational Research Unit (Chin, 1970), have shown rates ranging from 50-100%. Because of the problem of chloroquine resistance, coupled with the fact that the Thai strains of falciparum malaria were found to be sensitive to sulphormethoxine (Fanasil^{R}, Roche)-pyrimethamine (Chin *et al.*, 1966; Harinasuta *et al.*, 1967; Chin *et al.*, 1973), this combination was adopted by the NMEP in October, 1971, as the new standard radical treatment for falciparum malaria. Since the sporontocidal property of this combination against falciparum malaria was not well known, the NMEP also decided to to continue the use of 5 daily doses of primaquine as part of this new radical treatment.

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In view of the findings cited, it was deemed necessary to assess the antimalarial properties of the chloroquine-pyrimethamine presumptive treatment and the recently adopted sulphormethoxine-pyrimethamine portion of the radical treatment as well as gametocytocidal property of primaquine against falciparum malaria in Thailand under field operational conditions.

MATERIALS AND METHODS

This study was carried out at the NMEP Zone Office in Siracha, a town some 70 km southeast of Bangkok. The subjects chosen were adult males and females, 15 years of age or older, infected with falciparum malaria parasites and seeking treatment at the Passive Case Detection (PCD) post located at the Zone Office. The purpose and method of the study were explained to the patients and those willing to participate were assigned to one of two treatment groups:

Rx I: Subjects who were only mildly symptomatic and whose parasite density with few exceptions was less than 5,000/c.mm were *given* presumptive treatment consisting of single dose of chloroquine 600 mg (base) and pyrimethamine 50 mg.

Rx II: Subjects who were fully symptomatic regardless of parasite density were given the schizontocidal component of the radical treatment which comprised of a single dose of sulphormethoxine 1 gm and pyrimethamine 50 mg.

All the subjects were requested to return on the following Wednesday and weekly thereafter for at least 4 weeks for follow-up smear examination and possible feeding of mosquitoes if their smears showed gametocytes. *Anopheles balabacensis balabacensis* adult females, caged in pint size containers with screen covering on the two open ends, were transported from the TMORU insectary in Bangkok to Siracha where they were fed on the patients showing highest gametocytemia following treatments with the presumptive (chloroquine-pyrimethamine) or radical (sulphormethoxine-pyrimethamine) regimens. Mosquitoes were allowed to feed on any particular subject only once. Following feeding of the mosquitoes the subjects were treated with 30 mg of primaquine, and the mosquitoes were returned to the insectary where they were maintained at a maximal temperature and a relative humidity of 80°F and 80% respectively.

On day 7 following feeding, gut dissection of the mosquitoes was undertaken to detect oocysts. Both gut and gland dissections were undertaken on additional mosquitoes on day 14 and day 21 following blood meal.

An attempt was made to complete the follow-up on each patient given either *Rx* I or *Rx* II by requesting them to return for blood smear examination on the following Wednesday and weekly thereafter up to at least day 28 (day of treatment is designated as day 0). Those cases given *Rx* I whose smear became positive for asexual forms during any of the follow-up visits of more than 7 days after treatment were then given *Rx* II (sulphormethoxine-pyrimethamine). Those cases whose infections were not cured by *Rx* II were given quinine 650 mg, 3 times per day for 5 days.

RESULTS

The effect on the asexual stage of falciparum malaria following presumptive and radical treatments is summarized in Table 1. As indicated, there was a marked contrast in schizontocidal effect resulting from the two treatments. Cure rates of 23.3% and 91.2% were observed following treatment with the presumptive and radical regimens respectively. The onset of recrudescence of asexual parasitemia in those cases not cured

Table 1

The effect of presumptive and radical treatments against asexual form of falciparum malaria in Siracha, Thailand.

Type of *Rx*		No. Cases*	Parasite count on day of *Rx*: Range (average)/c.mm	Cures** No.	Cures** %
Presumptive	(chloroquine 600 mg base) (pyrimethamine 50 mg)	43	100-21,400 (2,949)	10	23.3
Radical	(sulphormethoxine 1,000 mg) (pyrimethamine 50 mg) Given alone	31	200-48,900 (13,345)	28	90.3
	Given following presumptive *Rx* failure	26	300-23,100 (2,665)	24	92.3
	Total	57		52	91.2

* Includes only these cases with complete weekly follow-up to day 28.
** 4 weekly negative blood smears for asexual forms.

by the respective regimens is summarized in Table 2. As may be observed, of the 33 subjects not cured by presumptive treatment, 28 were still positive by day 7 or had recrudescence of patent infection by day 14. This represented a rate of 28/43 (65%) of subjects treated with the presumptive regimen. In general, these subjects experienced little or no symptomatic relief from chloroquine.

The course of gametocytemia following presumptive (chloroquine-pyrimethamine) or radical (sulphormethoxine-pyrimethamine) treatment is summarized in Table 3. As noted, only 13.9% - 23.1% of the subjects in the respective treatment groups did not develop patent gametocytemia while 38.7%-51.2% of the cases were positive for gametocytes on the day of treatment. The development of patent gametocytemia following treatment was noted in 34.6% - 38.7% of the subjects in each treatment group with the average time of onset ranging from 7.6 - 10.9 days after receiving treatment.

Table 2

Onset of recrudescence of asexual parasitemia of *P. falciparum* in presumptive and radical treatment failures.

Follow-up days	Presumptive *Rx* failures No.	Radical *Rx* failures No.
7	17	1
14	11	2
21	3	1
28	2	1
Total	33	5

The feeding of *A. b. balabacensis* was accomplished in 12 subjects after administration of presumptive treatment (chloroquine-pyrimethamine) and in 15 subjects following radical treatment (sulphormethoxine-pyrimethamine). The results of mosquito

Table 3

The occurrence of gametocytemia before and following presumptive (chloroquine-pyrimethamine) and radical (sulphormethozine-pyrimethamine) treatment against falciparum malaria.

Treatment	Gametocytes present on day of *Rx*		Gametocytes not observed following *Rx*		Gametocytes developing after *Rx*	
	No.	%	No.	%	No.	%
Presumptive	22	51.2	6	13.9	15	34.9
					Days*	
					Range	**Average**
					7-21	(10.7)
Radical alone	12	38.7	7	22.6	12	38.7
					7-14	(7.6)
Radical following Presumptive	11	42.3	6	23.1	9	34.6
					7-21	(10.9)

* First day of treatment is day 0.

Table 4

Results of feeding *A. b. balabacensis* on subjects infected with *P. falciparum* and exhibiting gametocytemia following treatment with presumptive (chloroquine-pyrimethamine) or radical (sulphormethoxine-pyrimethamine) regimens.

	Treatment	
	Presumptive	Radical
Total No. feedings	12	15
No. feedings resulting in no oocysts and sporozoites	3	5
No. feedings resulting in only oocysts	2	3
No. feedings resulting in both oocysts and sporozoites	7* (58.3%)	7** (46.6%)

* All 7 cases resulted in treatment failure.

** Only one case of the 7 was treatment failure with recrudescence of patent parasitemia on day 21.

dissections are summarized in Table 4. As noted, infections in *A. b. balabacensis*, with development up to the sporozoite stage, were observed in 58.3% and 46.6% of the lots of mosquitoes following feeding on subjects given respective treatments with the presumptive and radical regimens.

Of the 7 lots of infected mosquitoes (to the sporozoite stage) fed on patients following presumptive treatment, 3 lots were fed 7-9 days post-treatment while 4 lots were fed between 14-22 days post-treatment. Of the sporozoite positive mosquitoes from the radical treatment group, 5 lots were fed on patients 7-9 days following treatment and 2 lots were fed 13-14 days after treatment. In those mosquitoes found to be gland positive, in excess of 90% were heavily infected with normal appearing sporozoites. Follow-up results of the patients whose gametocytes were infective to mosquitoes showed that 7/7 and 1/7 resulted in failures following respective presumptive and radical treatments.

Smears from subjects treated with a single dose of 30 mg primaquine following feeding of mosquitoes showed consistent clearance of patent gametocytemia within 7 days.

DISCUSSION

Presumptive treatment

The results indicate that the chloroquine-pyrimethamine presumptive treatment is no longer efficacious against falciparum malaria in areas of Thailand where drug resistance is a significant problem. The majority of the subjects given this treatment experienced little or no symptomatic relief and more than half of the mosquitoes fed on subjects who developed patent gametocytemia after they received presumptive treatment became infected.

The World Health Organization (1959) reported that a single 25 mg dose of pyrimethamine has sporontocidal effect against some falciparum strains for approximately 3 weeks. Nevertheless, it is conceivable that the occurrence of infected mosquitoes fed particularly on those cases where 50 mg of pyrimethamine was given some three weeks earlier may be due to insufficient concentration of the drug. It should be emphasized also that, under normal operational conditions of most malaria programs, the lag time between presumptive and radical treatment is usually 2-4 weeks. The question therefore of whether the mosquitoes were infected because of low level of pyrimethamine or, as we believe more likely, because pyrimethamine no longer possesses sporontocidal effect becomes, from an operational viewpoint, one of academic interest only. A more important consideration is that the presumptive treatment regimen of chloroquine-pyrimethamine devised some years ago should no longer be relied upon without qualification to produce the intended effect in areas where drug-resistant falciparum malaria is a problem.

There is at present no suitable substitute for the 4-aminoquinoline component of the presumptive treatment. This, coupled with the fact that currently other species of malaria besides falciparum are still sensitive to 4-aminoquinolines, indicates that readjustments in administration of available drugs is necessary. The results of this study suggest first of all that pyrimethamine be replaced by primaquine, a drug which has not shown any decrease in its gametocytocidal property. Secondly, that every effort be made to decrease the lag time between administration of the presumptive and radical treatments.

Radical Treatment

The use of a single oral dose of a long-acting sulfonamide such as sulphormethoxine in combination with pyrimethamine against

falciparum malaria is of recent origin. Using a single dose of sulphormethoxine (1 gm) and pyrimethamine (50 mg), Chin *et al.*, (1966) reported cures in all of 6 volunteers infected with a multi-resistant strain of *P. falciparum* which originated from Thailand. Harinasuta *et al.*, (1967) using the same dosage, reported radical cures in 17 of 19 (89.5%) Thai patients infected with chloroquine-resistant falciparum malaria. More recently Chin *et al.*, (1973) reported a cure rate of 31 of 34 (91.2%) similarly treated falciparum patients from the Province of Trad, Thailand.

The results of the sulphormethoxine-pyrimethamine radical treatment reported not only confirmed the above findings of high cure rates but also provide additional baseline data on the effectiveness of the combination in another malarious area of Thailand, Siracha.

The infection rate of 46.6% in *A. b. balabacensis* following feeding on patients showing gametocytemia after treatment with sulphormethoxine-pyrimethamine indicates that this combination, when used in areas of high prevalence of drug-resistant falciparum malaria, possessed little or no sporontocidal effect. Since the use of primaquine proved effective in eliminating gametocytes its inclusion as part of the radical treatment for falciparum malaria is recommended.

The major limitation to the use of sulphormethoxine-pyrimethamine as an antimalarial is its potential for development of resistance. Verdrager *et al.*, (1968) reported that probable cross resistance to sulphormethoxine-pyrimethamine was observed in falciparum when the combination was given subsequent to treatment failure with Dapsone. Chin *et al.*, (1970) confirmed this latter finding when they reported that, following exposure to a single, non-curative dose of a mixture of cycloguanil pamoate and 4, 4[1]-diacetyl-aminodiphenyl sulfone, only one out of 5 chloroquine-resistant falciparum infections was cured with sulphormethoxine-pyrimethamine compared to a 100% cure rate in 6 cases infected with the same strains prior to exposure of the parasite to the cycloguanil pamoate-sulfone mixture. Resistance has yet to be reported following prior use of sulphormethoxine-pyrimethamine combination. In an attempt to detect possible emergence of resistance to the combination by falciparum strains, the NMEP has instituted a system of semi-annual monitoring of the cure rate of this combination against falciparum malaria in Pakchong.

While the sulphormethoxine-pyrimethamine combination has obvious advantages of ease of administration and high efficacy as a radical treatment regimen in areas with high rate of chloroquine-resistant falciparum malaria, its possible use as a suppressive regimen cannot be recommended. It is recognized that unusual situations involving organized human activities in highly malarious areas may require the use of sulphormethoxine-pyrimethamine for chemosuppression. Should this be the case, serious consideration must be given in weighing the long-term risk of development of resistance in falciparum malaria and pathogenic bacteria against possible short-term gains of alleviation of a temporary problem. In the last analysis, operational use of sulphormethoxine-pyrimethamine should be looked upon as a temporary measure to fill exigent needs until more suitable antimalarials become available.

SUMMARY

The antimalarial properties of the present standard presumptive treatment (chloroquine-pyrimethamine) and radical treatment (sulphormethoxine-pyrimethamine) used by the National Malaria Eradication Project of Thailand against falciparum malaria were assessed.

The results showed that the effectiveness of the presumptive treatment has been reduced. Blood smears from 28 of 43 subjects given this treatment were either still positive at day 7 or the infections experienced recrudescence of asexual forms of falciparum malaria by day 14. Seven of 12 (58.3%) of the mosquito lots fed 7-22 days after presumptive treatment on patients exhibiting gametocytemia resulted in infections to the sporozoite stage.

Radical treatment with sulphormethoxine-pyrimethamine resulted in a cure rate of 52 of 57 (91.2%) cases treated. Mosquitoes fed on subjects with gametocytemia who had received radical treatment 7-14 days earlier resulted in infection to sporozoite stage in 7 of 15 (46.6%) of the lots. Single dose treatment with 30 mg primaquine resulted in consistent clearance of patent gametocytemia by day 7.

The major limitation of sulphormethoxine-pyrimethamine as an antimalarial is discussed.

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