

Quinine—Tetracycline and Quinine—Bactrim Treatment of Acute *Falciparum* Malaria in Thailand

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OBJECTIVE: Tetracycline and a combination of sulphamethoxazole and trimethoprim have been shown to be highly effective in terminating infections with chloroquine resistant strains of *Plasmodium falciparum*. Investigations by Rieckmann et al. (1971), Clyde et al. (1971) and Colwell et al. (1972) have demonstrated that tetracycline treatment alone was sufficient to produce radical cures of both experimentally and naturally acquired *P. falciparum* infections in subjects who exhibited low density parasitemias and mild degrees of illness. Benjapongs and associates (1970) reported that a combination of sulphamethoxazole—trimethoprim (SeptinR, Burroughs Wellcome and Co.), which was originally formulated for treatment of bacterial infections, effected radical cures of falciparum malaria in patients residing in an area highly endemic for chloroquine resistant strains.

However, the slow rate of these two alternative regimens, reflected by delayed clearances of patent parasitemia, does not permit their use for treatment of patients with moderate to severe degrees of illness. Subsequently, the efficacy of a combination of quinine and tetracycline was examined in acutely ill Thai patients residing in areas of chloroquine resistant falciparum malaria. A preliminary subcurative course of quinine was employed as an adjunctive agent for initial control of symptoms and parasitemia. These investigations showed that the quinine—tetracycline regimen was highly effective in controlling the symptoms and in producing a radical cure of the infection. A major disadvantage of this combination treatment was the prolonged course of drug administration (i.e., 13 days). The purpose of our investigations was to examine the efficacy of shorter courses of these alternative regimens in patients with acute falciparum malaria, with respect to onset of action, cure rate, cost and patient acceptability.

DESCRIPTION: The investigations were initiated in 1971 during the summer peak of malaria transmission at Phrabuddhabat, Saraburi Province in Central Thailand. When transmission subsided, the studies were relocated to Trat Province in Southeast Thailand. Both areas are highly endemic for chloroquine resistant strains of *P. falciparum*.

Subjects considered for admission to the study were acutely ill patients, aged 12 to 60 years, with single *P. falciparum* infections. Those with a history of antimalarial drug intake during the preceding four days and those with evidence of renal and cerebral complications were excluded. Selected subjects were assigned to one of two treatment groups and the drug combinations were concurrently initiated on the first day of observation. Subjects assigned to one group were given 540 mg of quinine base, orally, every eight hours for only one day and 250 mg of tetracycline, orally, every six hours for seven days. Subjects assigned to the other treatment group were administered a similar course of quinine and two tablets of sulphamethoxazole—trimethoprim (Bactrim, Roche Co.) every 12 hours for five days. Each tablet of Bactrim contains 400 mg of a long acting sulfonamide, sulphamethoxazole, and 80 mg of a folate antagonist, trimethoprim.

Blood smear examinations were obtained daily for the first seven days and at weekly intervals for the next three weeks. When patients were available, blood smears were also obtained two months after commencement of therapy. The method of Earle and Perez (1932) was employed for quantification of asexual and sexual forms of *P. falciparum*. A radical cure was presumed if asexual parasitemia cleared

during the first week and follow-up blood smear examinations remained negative for asexual parasites during the next three weeks.

More than 90% of the patients were hospitalized during the treatment period and they were examined daily during this period for clinical manifestations and dispensation of medications. The few non-hospitalized subjects were also examined daily during the treatment period, either at the outpatient department or at home visitation. There were no differences between the treatment groups which might lead to differences in re-exposure to malaria infections during the follow-up period.

PROGRESS: Forty-one subjects residing at both locations were chosen for the quinine-tetracycline (QT) regimen. Treatment and follow-up examination were successfully completed in 32. Thirty-nine subjects at both locations were chosen for the quinine-Bactrim (QB) regimen, and treatment and follow-up examinations were completed in 31.

Tables 1 and 2 show the age, sex and pretreatment levels of patent asexual parasitemia among patients of both groups in whom examinations were completed. There were 22 males and 10 females, ranging in age from 12 to 44 years (mean 24.1) in the QT group. The levels of asexual parasites in this group ranged from 1,200 to 192,700 per mm^3 with a geometric mean of 21,190 per mm^3 . In the QB group, there were 22 males and 9 females, ranging in age from 12 to 54 years (mean 26.2). The pretreatment levels of asexual parasites ranged from 1,100 to 414,480 per mm^3 with a geometric mean of 18,480 per mm^3 .

The clinical and asexual parasite responses among subjects in both treatment groups are summarized in Table 3. Presumptive radical cures were demonstrated in 84% of 32 subjects treated with QT and in 81% of 31 patients administered the QB regimen. These rates are not significantly different. The mean clearance times for fever in both groups were similar and almost as rapid as the fever clearance times for chloroquine and quinine treatment of susceptible strains of *P. falciparum*. However, the mean clearance of asexual parasitemia in the QT group was significantly longer in comparison with the mean clearance of patent parasitemia in the QB group. The latter clearance compares favorably with asexual parasite clearances observed with chloroquine and quinine treatment of susceptible strains. Blood smears were also obtained two months after commencement of therapy in 17 patients given QT and in 20 given QB. Only two of these patients, treated with QT, exhibited asexual parasites of *P. falciparum* at this time.

Circulating gametocytes were never observed in 16 of 52 patients who demonstrated presumptive radical cures. In addition, gametocytemias were low in density and transient in duration (i.e., less than 8 days) in 27 of the remaining 36 patients. These observations could reflect an inhibition or reduction of gametocyte production by early institution of the QT and QB treatments. The latter phenomenon has also been reported with the early administration (i.e., within first week of patent asexual parasitemia) of chloroquine and quinine for susceptible strains of *P. falciparum*. High levels of circulating gametocytes which persisted for longer than 2 weeks were observed in 9 successfully treated patients of whom 5 and 4 were given the QT and QB regimens, respectively.

With regard to cost and patient acceptability, the QT regimen appears to be superior to the QB regimen. The cost of the latter treatment was thrice that of the QT treatment. Although no serious toxic reactions were observed with either regimen, nausea and vomiting were observed more frequently during the treatment period among patients given the QB combination regimen.

SUMMARY: Two antimalarial treatments were assessed for onset of action, cure rate, cost and patient acceptability. Thirty-two subjects were given a quinine-tetracycline (QT) combination consisting of 540 mg of quinine base every eight hours for only one day and, concurrently, 250 mg of tetracycline, four times daily for 7 days. Thirty-one patients were given a quinine-Bactrim (QB) combination consisting of a similar course of quinine and, concurrently, 2 tablets of Bactrim every 12 hours for 5 days. Each tablet of Bactrim contains 400 mg of sulphamethoxazole and 80 mg of trimethoprim.

Presumptive radical cures were demonstrated in 84% treated with QT and in 81% given the QB regimen. All patients exhibited initial clearance of fever and asexual parasites. The mean fever clearance times in both groups were similar and almost as rapid as that observed with chloroquine and quinine treatment of susceptible P. falciparum strains. However, the mean clearance of asexual parasitemia in the QT group was significantly delayed (4.0 vs. 3.0 days) in comparison with the mean clearance of the QB group. Neither treatment appeared to exert a gametocytocidal effect.

With regard to cost and patient acceptability, the QT regimen was superior to the QB regimen. The latter costs thrice as much as the QT regimen. Although no serious toxic side effects were observed, nausea and vomiting were more frequently observed in the QB group.

Table 1.
 Pretreatment observations in subjects administered quinine-tetracycline*

Age (years)	Sex	Asexual parasite count (per mm ³)
12	Female	192,720
36	Male	191,400
38	Female	189,000
26	Male	159,250
25	Female	101,400
19	Male	81,900
14	Female	79,170
36	Male	69,960
16	Female	61,160
25	Male	51,320
15	Male	50,600
14	Male	47,860
31	Female	37,100
15	Female	28,620
17	Male	24,000
16	Male	21,800
23	Male	20,520
25	Male	19,800
18	Male	17,180
20	Male	14,760
18	Female	13,560
42	Male	13,200
14	Male	11,200
43	Male	8,820
27	Male	8,820
20	Male	6,600
17	Male	4,640
14	Male	2,540
18	Female	2,460
38	Male	2,440
44	Female	1,410
34	Male	1,200

* Simultaneous initiation of quinine (540 mg every 8 hours for 1 day) and tetracycline (250 mg every 6 hours for 7 days).

Table 2.
 Pretreatment observations in subjects administered quinine—Bactrim^{R*}

Age (years)	Sex	Asexual parasite count (per mm ³)
12	Male	414,480
45	Male	251,700
12	Male	127,600
15	Female	80,100
16	Male	67,160
52	Female	52,860
41	Male	51,280
12	Female	50,600
14	Female	47,160
19	Female	33,360
50	Male	31,040
14	Male	28,440
49	Male	22,720
15	Female	21,600
17	Male	21,040
16	Male	20,350
14	Male	16,360
23	Male	12,360
45	Male	11,860
54	Male	10,860
24	Male	10,640
19	Male	10,590
32	Male	9,720
27	Male	7,120
23	Male	6,880
18	Male	5,300
19	Female	4,320
18	Female	3,300
27	Male	2,920
33	Male	1,940
34	Female	1,100

* Simultaneous initiation of quinine (540 mg every 8 hours for 1 day) and Bactrim^R (2 tablets every 12 hours for 5 days).

Table 3.
 Clinical and asexual parasite response to quinine-tetracycline or quinine-Bactrim^R
 treatment of acute falciparum malaria

Treatment	No. treated	Radical cure		Mean clearance time (Range) days	
		No.	%	Fever	Asexual parasites
Quinine-tetracycline	32	27	84.3	2.4 (1-6)	4.0 (1-7)
Quinine-Bactrim*	31	25	80.6	2.7 (1-6)	3.0 (1-5)

* Bactrim (Roche Co.) is a combination tablet containing sulphamethoxazole (400 mg) and trimethoprim (80 mg).