

THE TREATMENT OF *P. falciparum* MALARIA WITH A COMBINATION OF QUININE AND TETRACYCLINE

Principal Investigators : Ellen F. Boudreau, MAJ, MC
Lorrin W. Pang, CPT, MC
Kenneth, E. Dixon, LTC, MC
Tithipoom Ua-umnuay, 1st Lt., MC, RTA
Phung Phintuyothin, Gen, MC. RTA (RET)

Associate Investigators : Billy W. Sanford, SSC
Samrong Bamnetpandh
Withoon Thiemanum

OBJECTIVE : To determine the efficacy of the combination of quinine and tetracycline in various treatment regimens and to compare them to mefloquine for efficacy and severity of side effects.

BACKGROUND : With the rapid development of sulfadoxine-pyrimethamine resistance in Southeast Asia (1,2) especially in Thailand another effective treatment regimen for *P. falciparum* malaria must be defined. Increasing resistance to quinine treatment of *P. falciparum* malaria has been demonstrated in the last five years in Thailand. In a study conducted by Department of Medicine at AFRIMS at Phrabuddabat, Saraburi Province from September 1980 - January 1982, a 7 day course of quinine at doses of 650 mg administered 3 x/day resulted in 60% cure rate in 15 patients treated. Only a small improvement in cure rate to 69% was noted when the quinine course was extended to 10 days (3). Therefore, a combination of quinine and tetracycline was chosen for treatment of resistant cases.

At Mahidol University, a regimen using quinine 650 mg tid x 3 days together with 1 gm of tetracycline in divided doses x 7 days resulted in a 59% cure rate in a series of 21 patients originating from the Kampuchean Border area, of Eastern Thailand (4). These patients were hospitalized for a 42 day follow-up in Bangkok, thus excluding the possibility of reinfection.

In 1981, another study using quinine 600 mg tid for 3 days and 7 days of tetracycline at 500 mg bid was carried out by the Malaria Division of the Thai Ministry of Public Health which achieved a 100% cure rate in Kalasin Province, Northeastern, Thailand (5).

Since the vanguard of drug resistance in *P. falciparum* malaria originates along the Thai-Cambodian border, this study was designed to determine the efficacy of quinine and tetracycline regimens in patients contracting malaria in this difficult area.

METHODS : One hundred sixty two patients have been treated from August 1981 - April 15, 1983 at Sa Kaeo Malaria Research Center. Nine different quinine and tetracycline treatment regimens have been compared against mefloquine. The summary of treatment regimens are in Table 1.

The patients were selected from Royal Thai Army soldiers stationed along the Thai-Cambodian border in Prachinburi Province, and having :

1. *P. falciparum* parasitemia > 1000 and < 100,000.
2. No complications of malaria including : protracted vomiting, greatly decreased urine output, hypotension or CNS symptoms.
3. A willingness to volunteer for a 21 day hospital stay and to give informed consent.

The hospitalization of patients was in an area of no malaria transmission, so reinfection during follow-up was excluded. The patients had twice daily thick smears and CBC's during patency, then weekly for 28 days. Chemistries were monitored at days 0, 3 & 7. Daily physical exams were performed from day 0-21 and on day 28. Medications other than anti-pyretics or anti-emetic agents were withheld during the treatment period. Intravenous fluids were administered if necessary for rehydration. All treatment failures were treated with quinine 650 mg tid x 7 days and tetracycline 500 mg tid x 7 days. There were no recrudescences after retreatment.

In the most recent phase of the study, patients were assigned on randomized basis to one of four treatment groups on admission to the treatment facility : Quinine 650 mg tid x 6 days plus tetracycline 500 mg tid x 6 days (Q6 T6), quinine 650 mg tid x 3 day plus tetracycline 500 mg tid x 7 days (high dose Q3 T7), quinine initial loading of 650 mg quinine followed by 325 mg qid x 3 days plus tetracycline 250 mg qid x 7 days (low dose Q3 T7) or mefloquine 1500 mg single dose. All medications were administered orally. The study is still in progress. This data analysis pertains to the first 84 patients of a targeted 160 patient sample at completion.

Characteristics of the patient population : Prior malaria experience was low in all treatment groups, with 73% - 84% having less than two prior illnesses diagnosed as malaria. The bulk of the patient population could be classified as non-immune (Figure 1). Malaria in Thailand could be described as a disease limited to the densely forested area and foothills where the vectors *Anopheles dirus*, *minimus* and *maculatus* having their ecological niche. A soldier's presence in these areas between dusk and dawn define his malaria risk. Figure 2 is a map of locations where malaria was contracted by this patient group.

RESULTS : Cure rates on these four treatment regimens ranged from 87% in the high dose Q3 T7 group to 100% in the Q6 T6 group. The mefloquine regimen 1500 mg single dose was 95% curative (18/19) with one RI recrudescence at day 21. This patient was retreated with quinine 650 mg tid x 7 days and tetracycline 500 mg tid x 7 days and was negative for malaria parasites on day 30 follow-up. The high dose, Q3 T7 regimen had an 87% cure rate (14/16) with 2 RI recrudescences (at day 25 and 28).

The low dose Q3 T7 had a 90% cure rate (9/10) with 1 RI recrudescence at day 28. The largest patient group treated was Q6 T6 where all 36 patients were sensitive to therapy. *P. vivax*, not present on thick smear at the time of admission relapsed in 12-20% of the quinine-tetracycline treatment groups during the 28 day follow-up. No such relapse pattern was noted in the mefloquine treatment group (see Table 2).

The parameters of malaria treatment, parasite clearance time (PCT) and fever clearance time (FCT), were much lower for mefloquine than for the quinine-tetracycline regimens. The mean PCT for mefloquine was 68 hr, while the comparable values for high dose Q3 T7, low dose Q3 T7, and Q6 T6 were 93 hr, 109 hr, and 85 hr respectively.

The mean FCT for mefloquine was 35 hr while the same value for high dose Q3 T7 low dose Q3 T7 and Q6 T6 was 66 hr, 63 hr and 60 hr, respectively.

The side-effects seen with both mefloquine and the quinine and tetracycline regimens. With mefloquine (n = 19), the incidence of gastrointestinal side effects was : diarrhea (58%) vomiting (20%), nausea (68%) and abdominal pain in (6%). With the three quinine and tetracycline regimens, diarrhea was less of a problem than with mefloquine. However, the incidence of vomiting and tinnitus increased as the duration of quinine therapy was prolonged (Table 3).

The median initial parasite counts per mm³ are comparable for mefloquine, Q6 T6 and low dose Q3 T7 at (levels of 12,800, 12,000 and 11,340 respectively). The median initial parasite count for the high dose Q3 T7 treatment group was twice as high at 25,200/mm³.

Serum samples on admission were analyzed for quinine and sulfa levels. Only 2/36 patients on Q6 T6 had quinine detected at levels of (1.5 and 7.4 mg/l). These patients are on chloroquine and Fansidar prophylaxis (1 tablet of chloroquine weekly and 2 tablets of Fansidar every 2 weeks). The mean blood sulfa level for this treatment group was less than 4 mg%.

In the high dose Q3 T7, low dose Q3 T7 and mefloquine treatment groups, quinine levels were found in 2/17 patients (1.7, 3.2), 0/11 patients and 1/19 patients (15.2 mg/l) respectively. Mean sulfa levels were less than 4 mg% in both high and low dose quinine - tetracycline regimens. For the mefloquine treatment group the mean sulfa level was 6.6 mg%. The biochemical parameters monitored in this study (Bilirubin, SGOT & BUN) reverted to normal by day 7 post admission. They were highest prior to drug therapy and were attributed to the disease process.

CONCLUSIONS : In our study to date, high dose Q3 T7 approximates the cure rate of mefloquine and Q6 T6 but with fewer side effects.

Table 1.

	Drug regimens	No. of Patients	S	R	Incomplete follow-up	% cure	PCT	FCT	IPC mean
Phase I	Q7 T7	7	4	0	3	100	-	-	-
	Q6 T6	10	4	2	4	67	-	-	-
	Q5 T5	3	1	2	0	33	76.5	62.7	11,580
Phase II	Q5 T6	11	9	2	0	82	91	70	30,354
	Q4 T6	10	5	4	1	56	96	63	16,206
	Q3 T6	10	9	0	1	100	94	76	24,455
Phase III	Q2 T6	5	3	2	0	60	95	78	20,487
	Q3 T6	24	16	5	3	76	94	83	22,484
	Q6 T6	24	24	0	0	100	90	70	22,932
	Mefloquine	8	8	0	0	100	62	33	13,031
Phase IV	Q6 T6*	36	36	0	0	100	85	60	20,925
	Q3 T7 high dose	17	16	1	0	94	93	66	26,260
	Q3 T7 low dose	10	9	1	0	90	109	63	17,754
	Mefloquine	19	18	1	0	95	68	35	21,316

* Patient No. in Phase IV includes the number in the same drug regimen in Phase III and is continuation of a successful drug regimen. Therefore, the Q6 T6 regimen began 13 months before the Q3 T7 high and low dose regimens, and the mefloquine regimen began 8 months before initiation of the Q3 T7 series.

Q subscript, T subscript - The subscript indicates the days of drug therapy. Quinine was administered as 650 mg every 8 hr in Q6 T6 and in high dose in Q3 T7. In low dose Q3 T7 quinine was given as 650 mg first dose then 325 every 6 hr and Tetracycline was administered as 500 mg q 8 hr except in low dose Q3 T7 where tetracycline 250 mg q 6 hr was given.

Table 2. Incidence of *P. vivax* relapse following treatment for *P. falciparum*.

Treatment groups			
Low dose Q3 T7	20%	(2/10)	(day 27, 28)
High dose Q3 T7	12%	(2/17)	(day 28, 38)
Mefloquine	0%		

Table 3.

Treatment drug	Diarrhea	Vomiting	Nausea	Tinnitus
Mefloquine (n = 19) 1500 mg single dose	58%	20%	68%	-
Quinine 650 mg loading dose then 325 mg qid x 10 days (n = 11)	36%	27%	27%	36%
Tetracycline 250 mg qid x 7 day				
Quinine 650 mg tid x 3 days (n = 17)	12%	36%	36%	65%
Tetracycline 500 mg tid x 7 days				
Quinine 650 mg tid x 6 days (n = 36)	9%	37%	50%	90%
Tetracycline 500 mg tid x 6 days				

FIGURE I

PRIOR MALARIA EXPERIENCE

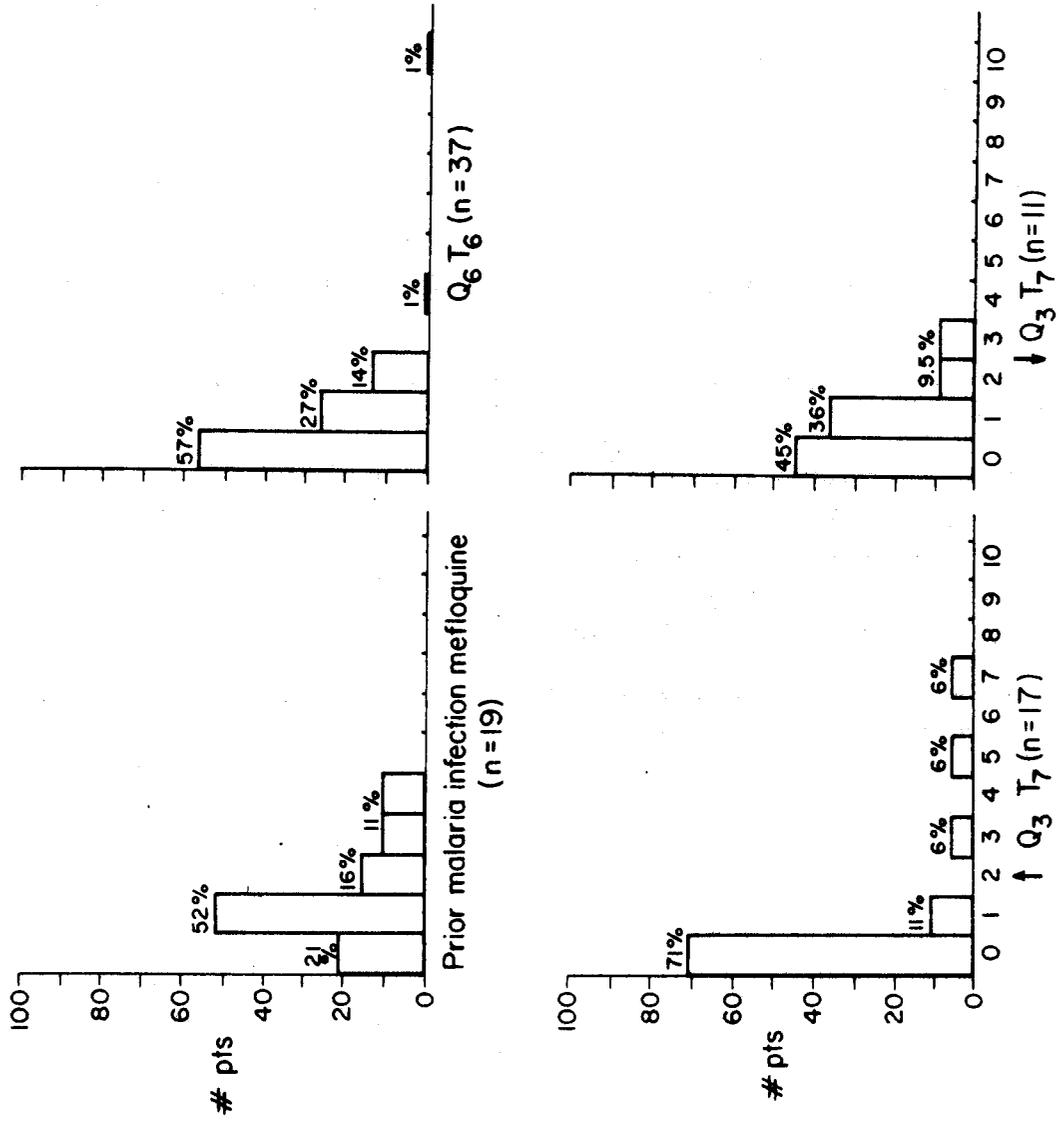
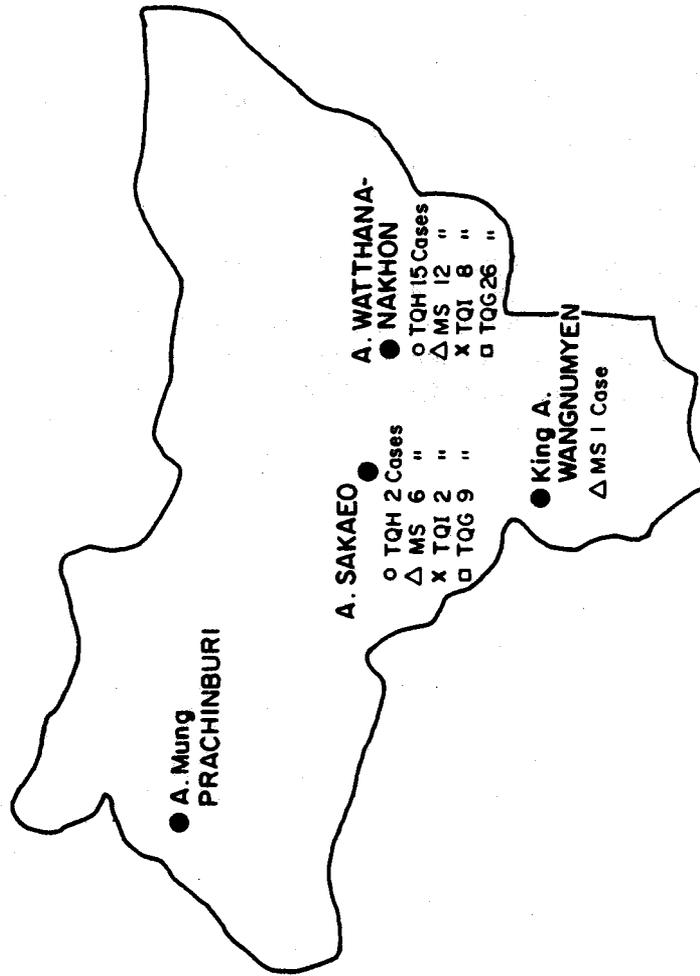


FIGURE 2

LOCATIONS WHERE MALARIA WAS CONTRACTED
PRACHINBURI PROVINCE



- Quinine 650 mg. 28 hr. x 3 days plus Tetracycline 500 mg. 28 hr. x 7 days.
- △ Mefloquine 150 mg. single dose
- x Quinine 325 mg. 26 hr. x 3 days plus Tetracycline 250 mg. 26 hr. x 7 days.
- Quinine 650 mg. 28 hr. x 6 days plus Tetracycline 500 mg. 28 hr. x 6 days.

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