

THE COMPARATIVE BIOAVAILABILITY AND RENAL CLEARANCE OF
THE COMBINATION OF QUININE AND TETRACYCLINE GIVEN
SIMULTANEOUSLY OR SEQUENTIALLY

Principal Investigators : Ellen F. Boudreau, MAJ, MC
Lorrin W. Pang, CPT, MC
Lawrence Fleckenstein, Pharm, D.
Kenneth E. Dixon, LTC, MC
Phung Phintuyothin, MG, RTA (RET)

Associate Investigators : Suphat Noeypatimanond, M.D.
Danai Duriyananda, M.D.

OBJECTIVE :

1. To evaluate the bioavailability of tetracycline by comparing the steady state levels of the drug in sequential versus simultaneous administration with quinine.
2. To evaluate the renal clearance of tetracycline on and off quinine.
3. To evaluate quinine levels when used alone or in combination with tetracycline in patients with falciparum malaria.
4. To evaluate the protein binding of quinine and tetracycline changing over a course of treatment.
5. To evaluate the clinical course and drug side effects in patients receiving quinine and tetracycline in combination or sequentially.

BACKGROUND : The combination of quinine and tetracycline for the treatment of chloroquine resistant *P. falciparum* malaria was initially tested in Thailand in 1972 (1) and with the emergence of Fansidar resistance in the last five years, (2,3,4) has become the mainstay of therapy in many sections of Southeast Asia. The rationale for this drug combination is to overcome the four day tetracycline lagtime before significant reduction in parasitemia occurs, by the rapid blood schizonticidal action of quinine. Although quinine provides a rapid clearance of parasitemia, the tetracycline portion of the drug combination produces a radical cure (5).

Although pharmacokinetic studies have been performed on quinine levels in malaria, this study will be the first reporting blood levels of both drugs in malaria using the quinine-tetracycline combination given together or separately. Also previous studies used benzene extraction and spectro photofluorimetric analysis for quinine levels (6-10) and the current study plans to utilize High Performance Liquid Chromatography for more precise determination of quinine and tetracycline bioavailability (11-12).

METHODS : Twenty-five adult males with acute *P. falciparum* malaria were diagnosed on presentation to the malaria control clinic in Phrabuddabat and were admitted to the study if they met the following criteria: (1) were between 21-50 years of age (2) were within 15% of ideal body weight (3) had no history of chronic illness (4) with parasitemias 100,000 (5) without CNS involvement, renal insufficiency, gastrointestinal bleeding or protracted vomiting and (6) were willing to give informed consent to have numerous blood drawings performed and to remain in the hospital for a 7 to 10 days treatment period. Patients were randomly assigned to the two treatment regimens, Group I received quinine sulfate 650 mg q 8 hr po x 3 days followed by tetracycline HCl 250 mg - 250 mg-500 mg q 8 hr po on day 4 and the course continued for 7 days finishing on day 10. Group II received quinine sulfate 650 mg q 8 hr po x 3 days together with tetracycline HCl 250 mg-250 mg-500 mg q 8 hr for 7 days. In both groups tetracycline was administered on an empty stomach. Patients were monitored by an admission physical examination and daily physicals until discharge, complete blood counts daily, malaria parasite counts twice daily, and by serum protein electrophoresis, serum glycoprotein electrophoresis, SGOT, SGPT, Bilirubin & BUN on days 0, 3 and 7.

In both groups, 10 cc of blood was drawn before every other drug administration for either quinine or tetracycline drug levels. The plasma was separated from the heparinized specimen and frozen at -20°C . All patient urine was collected in 24 hr increments, total volume was measured, and a 20 cc aliquot was saved from each daily collection and frozen at -20°C . From each aliquot of urine, a quinine and tetracycline drug level was assayed and on days 1, 3 and 7 a urine creatinine was also performed. The plasma and urine specimens were air shipped frozen on dry ice to WRAIR. The drug level analysis on plasma and urine was done at the Division of Experimental Therapeutics, WRAIR, as was the pharmacokinetic analysis of the drug concentration over time curves. Both analyses have not been completed to date.

RESULTS : From 15 June 1982 - 25 April 1983 twenty-five patients were treated under this protocol. Twelve subjects received sequential treatment (Group I) and 13 subjects received simultaneous therapy (Group II) with the quinine and tetracycline combination.

Mean parasite clearance time (PCT), mean fever clearance time (FCT) and mean initial parasite counts (IPC) were not significantly different between Group I and Group II (Table 1).

The mean age of both groups was 28 years old and the mean weight was 53 kg in Group I and 57 kg in Group II.

Side effects on the quinine and tetracycline regimens were essentially the same as outlined in Table II.

Changes in serum protein and glycoprotein patterns in acute malaria have been a topic of interest over the last 15 years. Predictable patterns of α_1 , α_2 and γ glycoprotein fluctuations were forecast by Klainer (13) in induced malaria.

Such reliable patterns of increase α_1 & γ glycoproteins and decreased α_2 glycoprotein were not found in our study (Table III). But these patients were only monitored at day 0, 3 & 7, not at day 28 post infection and they were compared to glycoprotein levels in American controls (14) not Thais. There was no correlation with high initial parasite count, or length of illness prior to admission with these abnormal values of serum glycoprotein. Serum protein electrophoresis patterns were within normal limits. Further work needs to be done to assess the role of acute phase reactants in malaria.

Twenty-eight day follow-up was instituted in the last five patients in this study and all were sensitive. Prior to this time, the patients were not asked to return weekly as monitoring of quinine-tetracycline efficacy was not a goal of this study. There were no RII or RIII drug resistance patterns found in this patient population.

The major pharmacokinetic results of this study will be reported at a later date.

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Table 1.

	Mean PCT	Mean FCT	Range of parasitemia (per mm3)	Mean IPC (per mm3)	Median IPC (per mm3)
Quinine 650 mg x 3 days followed by Tetracycline 1 gm per day x 7 days (Group I) (n = 12)	92 hr	66 hr	(2,080 - 54,984)	21,780	8,640
Quinine 650 mg x 3 days together with Tetracycline 1 gm per day x 7 days (Group II) (n = 13)	88 hr	59 hr	(420 - 73,602)	18,864	7,780

Table 2.

	Side Effects					
	Diarrhea	Nausea	Vomiting	Abd. Pain	Blurred Vision	Tinnitus
Q-T Sequential (n = 12)	0	7	3	0	2	12
Q-T Simultaneous (n = 13)	0	8	3	1	1	13

Table 3.

	<u>Elevation</u>	<u>Decrease</u>
	(S.D. from mean)	(S.D. from mean)
α_1 glycoprotein (n = 20)	12/20 (range 21.7-30.4%) 7/12 beginning Day 0 5/12 beginning Day 3 10/12 normalized by Day 7	0
α_2 glycoprotein (n = 20)	6/20 (range 41.7-58.8%) 4/6 beginning Day 0 2/6 normalized by Day 7	2/20 (range 16.9-19.5%)
γ glycoprotein (n = 20)	2/20 (range 38.8-49.5%)	4/20 (range 10.2-14.2%)
Ablumin glycoprotein	0	17/20 (range 0-1.8%)