

THE PHARMACOKINETICS OF INTRAVENOUS QUININE IN PATIENTS  
WITH NATURALLY ACQUIRED FALCIPARUM MALARIA

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OBJECTIVE : A phase IV study to determine the pharmacokinetics of intravenous quinine in patients with falciparum malaria using specific analytical assay methodology and to identify factors (protein binding, volume of distribution and metabolite formation) responsible for variability of quinine plasma levels.

BACKGROUND : Quinine has been used in western medicine for over three centuries and is still an important agent in the treatment of malaria (1). Further, the drug is also useful in the occasional patient who is acutely ill with blood forms of malaria, and cannot tolerate oral medication. Quinine is currently the only parenteral antimalarial which is readily available in most parts of the world.

The success of quinine treatment in malaria depends in large measure on achieving adequate blood drug concentrations. Significantly greater cure rates of recrudescing infections of falciparum malaria among United States troops in Vietnam were achieved when quinine was given as an infusion than when given as Tablets (2). The difference in efficacy was probably related to a difference in blood concentrations of quinine. Quinine resistance appears to be a relative resistance, and even resistant strains of falciparum malaria are susceptible to higher quinine blood levels. Thus, an understanding of quinine pharmacokinetics has important practical and clinical relevance.

Previous bioavailable and pharmacokinetic studies have not used analytical methods specific for quinine (3-5). One study of quinine drug interactions used a TLC method which was specific for quinine, but the assay sensitivity and reproductibility are not reported (6). Fluorometric procedures are the most commonly employed methods, using various types of sample preparation procedures, including : protein precipitation (7); single extraction (8); and double extraction (9). These analytical methods are probably not specific for quinine. Lack of specificity has been demonstrated repeatedly for quinidine, the stereoisomer of quinine, and its metabolites (10-12). This lack of specificity can result in misleading determination of pharmacokinetic parameters and inappropriate dosing regimens. Using methods which are not specific for quinine are likely to overestimate bioavailability and peak plasma levels and under-

estimate clearance and dosage regimens. Reliable pharmacokinetic parameter estimates for quinine are unknown.

There are large interindividual variations in plasma quinine levels following oral or intravenous therapy (3, 4). Variability may have important clinical ramifications if inadequate drug levels are produced using conventional dosing regimens and this problem deserves more careful study. Metabolism is the major route of drug elimination, with less than 20% of a quinine dose eliminated unchanged in urine. The liver extraction ratio is about 20-25%, making the liver an important metabolizing organ for quinine. Variability in plasma levels would therefore be caused by: (I) variation in liver blood flow; (II) variability in plasma protein-binding; (III) variation in the intrinsic metabolic capacity.

Plasma protein binding for quinine varies between 67 and 76% in normal subjects (6). The protein binding of quinine in patients with malaria has not been reported. Various disease can influence drug binding to plasma proteins (13). Variation in protein binding can lead to substantial variation in the liver extraction ratio. Quinine protein-binding, liver blood flow and intrinsic metabolic capacity are important determinants of drug clearance. This investigation expected to elucidate pharmacokinetic parameters such as quinine clearance, volume of distribution and protein binding and to identify major factor accounting for variability in quinine disposition in patients undergoing therapy.

The ultimate goal of this studies was to improve antimalarial drug therapy with quinine by identifying factors affecting quinine disposition and to improve the predictability of drug blood levels.

**METHODS:** The patients were chosen from both sexes between 21-50 yrs. of age with acute falciparum malaria. They were ill patients presenting to the malaria clinic in Phrabuddabat for diagnosis and treatment. Other patient selection criteria were an initial parasitemia between 10,000-100,000/mm<sup>3</sup>, body weight within 15% of ideal body weight and no concurrent illness. The patients were admitted to the study after informed consent was obtained.

Prior to admission to the study each patient received a complete physical examination, a complete blood count thick and thin malaria smear with asexual and sexual parasites qualified per mm<sup>3</sup>, serum protein electrophoresis, liver function tests including SGOT, SGPT, serum bilirubin and renal function tests consisting of urinalysis and BUN.

During hospitalization: A detailed record of signs and symptoms were recorded by one of the physicians twice daily and parasite counts were taken twice daily during parasitemia and once daily thereafter, until discharge. If the patient's parasitemia markedly increased or the patient's clinical condition worsened, the patient was dropped from the study and appropriate conventional therapy was given. Liver and renal function studies were repeated on the second day of the study. Routine IV fluids and adjunct medication (antidiarrheal, antiemetics and antipyretics) were administered as clinically indicated and the dosages and times of administration were recorded.

Drug Administration: A 490 mg dose of quinine base was administered as an intravenous infusion in 500 ml of normal saline over 2 hours. The drug was quinine dihydrochloride injection, NF manufactured by the Vitarine Co, Inc. Lot #11338A. It was stored in an air conditioned room at Phrabuddabat Provincial Hospital during the study. 10 ml blood samples were collected before the infusion at the end of the infusion and at 5, 10, 15, 20 minutes and 1, 2, 3, 5, 7, 10, 24 and 26 hours after termination of the infusion. The 10 ml aliquots of blood were anticoagulated in 200 u of heparin and collected in glass tubes provided by WRAIR. The plasma was removed and frozen at  $-20^{\circ}\text{C}$ . The samples were shipped frozen on drug ice to WRAIR. No other antimalarial medications were administered during the first 26 hours following the single quinine infusion. After that time period the patients were treated with standard therapy for this locally by the attending physician.

Evaluation of the Data: The determination of quinine and its major metabolite 2-hydroxyquinine are being performed by high pressure liquid chromatography using the method of Guentert and associates. The quinine serum-concentration over time data will be fit to a 2 compartment model for pharmacokinetic analysis. Estimates of central and tissue volumes of distribution of quinine, intercompartmental rate constants, hydroxylation clearance, renal clearance, clearance by metabolite formulation, plasma volume of distribution of quinine and volume of distribution of 2-hydroxyquinine will be made by non linear least square iteration.

RESULTS: Between 6 January 1982 and 2 July 1983, 19 patients (4 females and 15 males) were treated in this study.

Only the clinical parameters are discussed in this section. A later report will contain the results of the pharmacokinetic analysis.

The mean initial parasite count of the group was 31,284 per  $\text{mm}^3$  with a range of 11,049 - 89,260 per  $\text{mm}^3$ .

All patients were clinically ill on admission (from 2 days - 20 days) and febrile during their course.

The history of prior malaria in this group was: 4/19 had no prior infections, 12/19 had only 1 previous infection, 2/19 had 2 or 3 previous malaras and only 1/19 had been treated several times before for malaria.

The age range of the patients was 21-42 yrs. of age.

Clinical lab studies revealed no significant abnormalities in SGOT, SGPT, bilirubin or BUN. By the 2nd determination the admission abnormalities had resolved.

Admission hematology values were very close to normal for the Thai populations. The mean hematocrit was 37%, and mean white blood cell count was 6,548 per  $\text{mm}^3$ . Only the mean platelet count was low at 136,000 per  $\text{mm}^3$ . In the initial differential counts lymphopenia  $< 1,000$  per  $\text{mm}^3$  was seen in only 5/19 patients. Eosinophilin a was seen in 2/19 patients.

According to the attending physicians' clinical judgement, the patients following their single IV quinine infusion were treated in one of five ways. Twelve patients received quinine 650 mg q 8 hr x 3 days and tetracycline 500 mg q 8 hr x 7 days (group 1), 2 patients received treatment 2 quinine 650 mg q 8 hr x 3 days with tetracycline 1 gm per day x 7 days (250 mg qid 1 pt, 250-250-500 mg q 8 hr 1 pt)(group 2), 3 patients received quinine 650 mg q 8 hr x 7 days then primaquine 15 mg qd x 5 days (group 3), patient received quinine 650 mg q 8 hr x 5 days with tetracycline 500 mg q 8 hr x 7 days (group 4) and 1 final patient received treatment with quinine 650 mg q 8 hr x 10 days and primaquine 15 mg qd x 5 days (group 5). Each patient who left with rare parasites on his smear on day 4. The range of days hospitalized is 5-8 days. For those patients discharged prior to 7 days their treatment was completed as an outpatient. Therefore cure rate of these patients is unknown but there was only 1 RII patient who required at 7 day course of quinine and tetracycline. Mean weight for the male patients in the study was 60.1 kg (n = 14) range (48 - 68.9) and for the female patients was 45.6 kg (n = 4) range (37 - 55).

The synthesis of a pharmacokinetic curve awaits completion of high pressure liquid chromatography analysis of serum and urine quinine levels.

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Table 1.

	Parasite Clearance Time (hr)	Fever Clearance Time (hr)
Treatment I n = 1	105	92
Treatment II n = 2 1 pt	73	Fever nonclearance in 92
Treatment III n = 3	96	73
Treatment IV n = 1	91	8 days
Treatment V n = 1	69	35

Figure 1. Pharmacokinetic model summarizing the know disposition characteristics of quinine and 2 hydroxyquinine

