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Research paper

Dose linearity of quinine in healthy human subjects

Chinedum P. Babalola [a,*], Oluseye O. Bolaji [a], Festus A. Ogunbona [a], Akintunde Sowunmi [b], Oladapo Walker [b]

[a] *Department of Pharmaceutical Chemistry, Obafemi Awolowo University, Ile-Ife, Nigeria*
[b] *Department of Pharmacology and Therapeutics, University of Ibadan, Ibadan, Nigeria*

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Abstract

The pharmacokinetics of quinine were assessed in seven healthy volunteers after administration of single oral doses of 250, 500, 750 and 1000 mg quinine in a randomized cross-over design. Serial blood samples were collected at predetermined times before and after the doses. Plasma quinine concentrations were assayed by a reversed-phase HPLC method with UV detection and the data were evaluated by non-compartmental methods to determine pharmacokinetic parameters. The mean elimination half-lives ($t_{1/2}$) of quinine, which did not vary with the dose, were 10.1 ± 4.3, 12.3 ± 1.6, 9.0 ± 2.8 and 13.4 ± 7.0 h, respectively after the four doses. The peak plasma levels (C_{max}) and area under the plasma level versus time curve (AUC) data showed dose-proportional response. The time to peak plasma concentration (t_{max}), oral clearance (CL/F) and apparent volume of distribution (V_d/F) were all similar regardless of the administered dose ($P > 0.05$). There were minor side effects which increased with increase in dose but the effects were all reversible. These findings suggest that quinine disposition is linear over the dose range studied. © 1997 Elsevier Science B.V.

Keywords: Quinine; Malaria; Dose-dependency; Pharmacokinetics; Toxicity

1. Introduction

Quinine is recommended as the drug of choice for the treatment of severe and/or cerebral malaria attacks as well as for chloroquine-resistant falciparum malaria [1]. It is also widely used for the prevention of night cramps. Despite its long use which spans over three centuries, uncertainty remains regarding its dose-dependent kinetics in human.

Berlin et al. (1975) reported that the elimination kinetics of quinine exhibited dose-dependency in both man and dogs [2]. The authors reported a doubling of the elimination half-life ($t_{1/2}$) and volume of distribution (V_d) values as the dose of quinine was increased from 100 to 650 mg although no significant change was observed in its plasma protein binding capacity. In this earlier study, quinine was assayed after a short sampling time using a fluorimetric method [3] which has since been found to be non-specific and relatively insensitive [4]. It has been demonstrated that a drug may exhibit apparently dose dependent kinetics if samples are collected over a short period of time or if the drug is assayed with non-specific and/or non-sensitive methods [5,6].

On the contrary, dose-independent kinetics of quinine was reported in rats after a relatively higher dose of 5–20 mg/kg in a study in which a high performance liquid chromatographic (HPLC) method of analysis was utilized [7]. The elimination half-life ($t_{1/2}$), clearance (CL) and volume of distribution (V_d) of

* Corresponding author. Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria. Tel./fax: +234 36 231733; e-mail: babalola@oauife.edu.ng

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quinine were reported to be constant over the dose range studied.

Quinine has a narrow therapeutic index and exhibits a number of side effects commonly known as cinchonism [8]. The side effects and the toxic reactions of quinine are also known to be concentration-dependent [9,10]. Non-linear pharmacokinetics of quinine may therefore cause difficulty in the accurate prediction of plasma drug concentrations which may lead to toxicity. This signifies the need to verify if quinine disposition is dose-dependent or not.

The aim of this study is thus to establish the relationship between the dose and the different kinetic parameters of quinine in healthy subjects using a sensitive and specific HPLC method as well as to establish the relationship, if any, between the dose and side effects of the drug.

2. Materials and methods

2.1. Subjects

Seven healthy male volunteers aged between 19 and 28 years and weighing between 50 and 68 kg participated in this study after giving written informed consent. They were judged healthy by physical, biochemical/hematological and electrocardiogram examinations. The protocol received approval of the Ethics Committee of the University College Hospital, Ibadan, Nigeria. All the subjects abstained from alcohol and other medications 1 week prior to and during the period of study. All subjects had an overnight fast until 4 h after the administration of each quinine dose following which food and drinks were allowed freely.

2.2. Drug administration and sample collection

The study was conducted in a randomized cross-over design with all subjects receiving quinine sulphate tablets (Lot 82, Labarez Laboratories, Ambares, France) equivalent to 250, 500, 750 and 1000 mg of quinine base, at each part of the study, respectively. All drug administrations were separated by a period of 2 weeks to allow for complete drug washout. On each study day, the drug was administered with a glass (about 200 ml) of water. Venous blood (5 ml) was taken from the forearm by venipuncture prior to (0 h) and at 0.5, 1, 2, 3, 4, 8, 12, 24, 36 and 48 h after each drug intake. The blood samples were drawn into 10 ml lithium heparin tubes and stored at -20°C until analysis.

Throughout the study, the subjects were questioned and examined for the presence of adverse drug reactions.

2.3. Sample and data analysis

All samples were analyzed for quinine by an ion-pair HPLC method developed in our laboratory [11]. A reversed-phase C18 column was used with an UV detector at a wavelength of 254 nm. Primaquine was used as the internal standard. The mobile phase was a mixture of 0.02 M potassium dihydrogenphosphate, methanol and acetonitrile (75:15:10 v/v) containing 74 mM perchloric acid as the counter ion. Blank plasma collected prior to quinine administration showed no endogenous sources of interference with the assay. The limit of detection was 10 ng/ml. The between-day precision for this method averaged between 1.4 and 6% over the concentration range of 0.4–10 μg/ml while the recovery ranged between 91 and 98%.

Plasma quinine concentration versus time data were evaluated by non-compartmental methods to obtain the pharmacokinetic parameters [12]. The elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda z$, where λz is the elimination rate constant which is the absolute value of the slope of the least-squares regression line for n terminal data points ($n > 3$). The area under the plasma drug concentration versus time curves (AUCs) were estimated by the trapezoidal methods extrapolated to infinity by $C_t/\lambda z$, where C_t is the last determined plasma drug concentration. The clearance was calculated as 'oral clearance' (CL/F) = Dose/AUC while the apparent volume of distribution (V_d/F) was estimated as 'OralClearance'/λz relative to the bioavailability (F) of quinine. The highest observed plasma concentration for the drug, C_{max}, and the time to reach it, t_{max}, were obtained directly from the plasma concentration time curve.

Statistical evaluations were performed using ANOVA analysis to compare mean values between groups while the Student Newman Keuls (SNK) procedure was used to compare mean parameter values with respect to dose differences (significance of $P < 0.05$). Linear regression procedures were utilized to determine whether C_{max} and AUC values were proportional to the administered dose (250–1000 mg). All results are recorded as mean $\pm$ S.D.

3. Results

The mean plasma concentration-time profiles after administration of the four different doses of quinine to the seven volunteers are shown in Fig. 1. The profiles showed exponential decline and followed a similar pattern for all four doses. The key pharmacokinetic parameters are summarized in Table 1. There were considerable intra- and inter-individual variations in the observed pharmacokinetic parameters. The t_{max} varied between 2.7 and 4.4 h after the respective doses and the

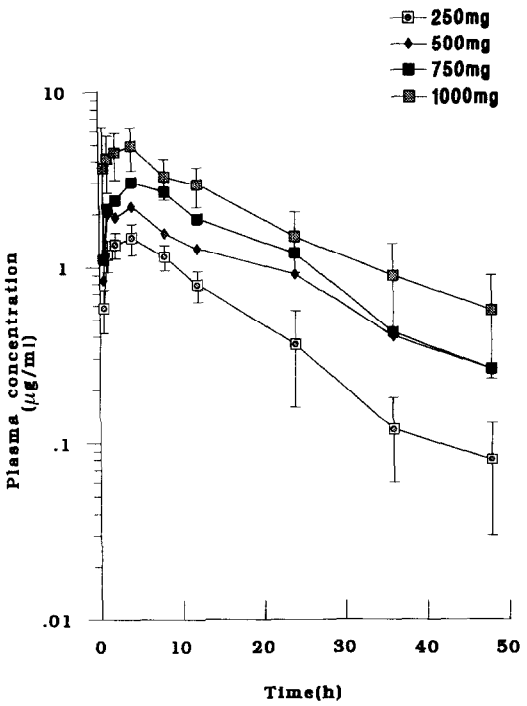

Fig. 1. Mean concentration-time profiles of quinine in plasma after administration of 250, 500, 750 and 1000 mg as single oral doses to seven volunteers.

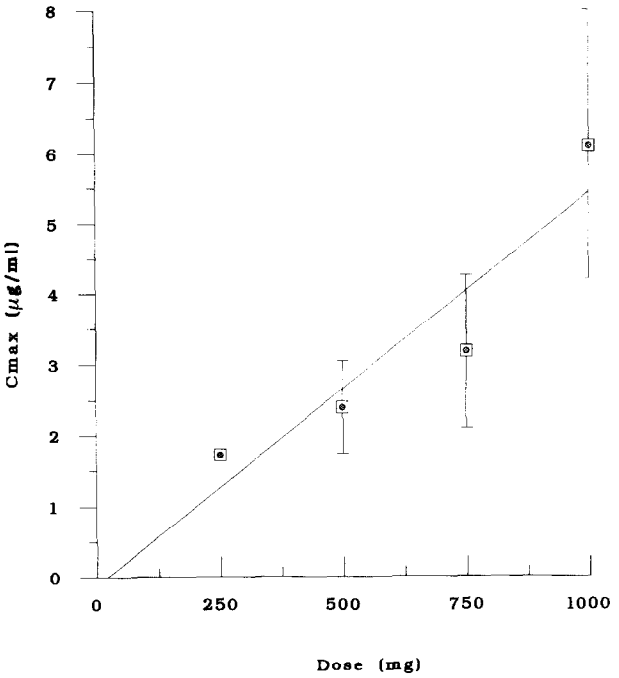

Fig. 2. Mean C_{max} versus dose of quinine after four single oral doses to volunteers. (C_{max} for y-axis and dose for x-axis). Linear regression equation: $y = -0.048 + 0.005x$; $r^2 = 0.927$.

variation was independent of dose. The levels of quinine declined with elimination half-life of 10.1 ± 4.3, 12.3 ± 1.6, 9.0 ± 2.8 and 13.4 ± 7.0 h following doses of 250, 500, 750 and 1000 mg of the drug, respectively. The mean oral clearance ranged between 3.3 and 4.48 ml/min/kg while the mean volume of distribution ranged between 2.46 and 3.78 L/kg after the four doses. No significant differences as a function of administered doses were observed in the ANOVA of the t_{max}, $t_{1/2}$, CL/F and V_d/F of the drug at the different doses ($P > 0.05$). The C_{max} and AUC parameters increased linearly ($r^2 = 0.93$, $P < 0.02$) with increase in dose (Figs. 2 and 3). Observed C_{max} values were 1.7 ± 0.65, 2.4 ± 1.1, 3.2 ± 1.8 and 6.1 ± 4.1 μg/ml while the AUC values were 28.1 ± 13.8, 52.2 ± 37.8, 63.0 ± 51.0 and 110.8 ± 85.1 μg·h/ml after the 250, 500, 750 and 1000 mg doses, respectively.

Table 2 represents the various side effects reported by the volunteers. At doses 250 mg and 500 mg, no serious side effects were reported by any of the volunteers. However after 750 mg and 1000 mg doses, some of the subjects complained of abdominal pain, dizziness, tinnitus, nausea and loss of appetite. Two subjects whose respective C_{max} values were 9.2 and 11.6 μg/ml after the 1000 mg dose complained of tinnitus, nausea and dizziness. One of these two also suffered from loss of appetite which lasted for 24 h. All the side effects were however reversible.

4. Discussion

This study reveals that quinine is almost completely cleared from the body within 48 h even when the dose is increased up to 1000 mg. The pharmacokinetic parameters such as t_{max}, $t_{1/2}$, CL/F and V_d/F obtained in this study as well as the observed wide intra- and inter-individual variations in the data are in general agreement with previous reports [13,14]. These four parameters remained significantly unchanged from the 250 mg to 1000 mg dose which is an indication of

Table 1
Mean (± S.D.) pharmacokinetic parameters of quinine following administration of four single oral doses to seven volunteers

Dose (mg)	t_{max} (h)	C_{max} (μg/ml)	AUC (μg·h/ml)	$t_{1/2}$ (h)	CL/F (ml/min per kg)	V_d/F (l/kg)
250	2.67 (1.48)	1.73 (0.65)	28.05 (13.83)	10.06 (4.28)	3.36 (2.81)	2.46 (1.46)
500	2.36 (1.58)	2.39 (1.08)	52.15 (37.75)	12.34 (1.61)	3.56 (1.56)	3.63 (1.00)
750	4.40 (2.15)	3.18 (1.84)	62.97 (51.04)	9.03 (2.82)	4.48 (1.87)	3.32 (1.65)
1000	2.90 (1.56)	6.09 (4.11)	110.79 (85.14)	13.36 (7.04)	4.16 (2.95)	3.78 (2.59)

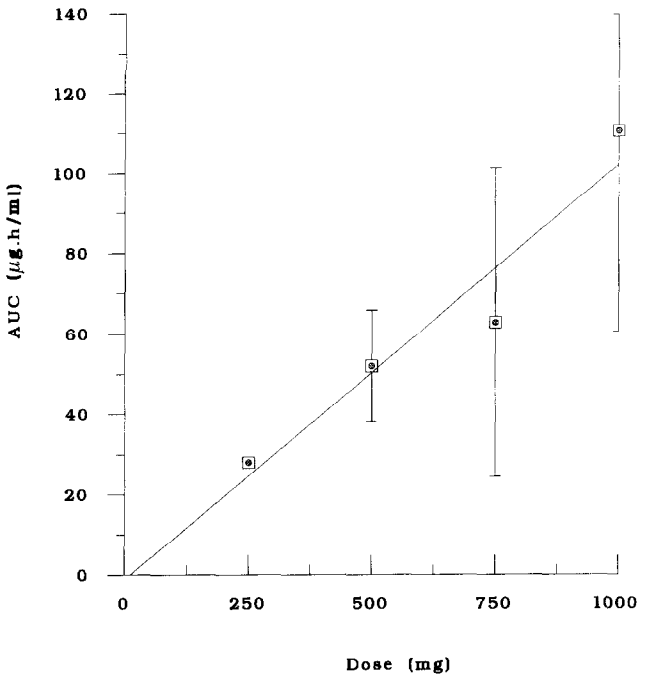

Fig. 3. Mean AUC versus dose of quinine after four single oral doses to volunteers. (AUC for y-axis and dose for x-axis). Linear regression equation: $y = -0.508 + 0.100x$; $r^2 = 0.932$.

dose-independent kinetics over this dose range. This however contrasts with a previous report of dose dependent increases in V_d and $t_{1/2}$ of the drug in man and dog [2]. The relatively lower dose range (100–650 mg) and the short sampling time might have contributed to the deduction of this earlier report. Moreover, the non-specific fluorimetric assay method employed in that study, is known to quantitate both parent drug and metabolites [3,4] while the HPLC method used in this present study is quite specific and sensitive and could differentiate between the drug and its major metabolites [11]. However, our finding is comparable to that reported in rats following administration of a similar dose range (5–20 mg/kg) in which quinine disposition was observed to be dose-independent [7].

The proportional increase in C_{max} and AUC with dose also suggests that quinine kinetics may be linear in man over the dose range (250–1000 mg) employed in this study. There was an approximately four-fold increase in the mean C_{max} and AUC values as the dose was increased from 250 to 1000 mg (Table 1). In the earlier studies in the dog and rat [2,7], the dose dependent kinetics of quinine were based on the relationship between dose and disposition parameters (such as $t_{1/2}$, V_d and CL) only with no reference to the relationship between dose and plasma quinine levels as was investigated in our study.

The occurrence of side effects was related to dose and plasma quinine concentrations indicating a relationship between dose and toxicity in the dose-independent kinetics of the drug. Symptoms of cinchonism as observed in the present study are known to occur when plasma concentrations exceed 5 μg/ml [10,15]. Recent studies have also shown that there is a relationship between plasma quinine concentrations and its effect on auditory acuity [9,16]. However, the incidence of hearing loss observable during therapy with quinine is reversible as was previously demonstrated and also observed in this study.

In summary, it can be stated that quinine exhibits linear kinetics in man at doses between 250 and 1000 mg, however, caution should be exercised in the use of quinine due to its narrow therapeutic index, the correlation between side effects and concentration as well as the wide variations in its kinetics. Quinine may be a candidate for therapeutic monitoring although more information on its benefit on quinine therapy is required before this can be strongly recommended.

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Table 2
Side-effects of quinine following single oral doses of 250, 500, 750 and 1000 mg of the drug to volunteers

Subject no.	Dose (mg)	Side-effect	Time of onset of side-effect after drug administration	Duration of side-effect (min)	Plasma conc. during period of side-effect (μg/ml)	C_{max} (μg/ml)	t_{max} (h)
2	500	Abdominal pain	60	10	1.03	2.20	4.0
1	750	Dizziness	90	10	2.30	2.46	4.0
4	1000	Nausea	30	720	4.14–9.17	9.17	4.0
6	1000	Dizziness	75	35	6.05–6.50	11.55	0.5
		Tinnitus	30	720	5.01–11.55	11.55	0.5
		Poor appetite	—	1440 (24 h)	3.44–11.55	11.55	0.5

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