The reproducibility of quinine bioavailability

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Plasma concentrations of quinine were measured in six healthy volunteers after a duplicate administration of 15 mg kg⁻¹ of quinine hydrochloride orally and the administration of 15 mg kg⁻¹ of quinine dihydrochloride as an infusion over 6 h. Quinine absorption rate devised by deconvolution was shown to be complete in less than 2 h. The mean ($\pm$ s.d.) fraction available (*F*) was 0.76 (0.11) after both oral doses and maximum plasma drug concentrations occurred at 1.90 (0.83) h and 2.00 (0.30) h, respectively. The reproducibility of absorption was high, with a within-subject coefficient of variation of less than 10% for *C*_{max}, AUC and *F*. Thus, quinine absorption is extensive, fast and reproducible in healthy volunteers.

Keywords intestinal absorption pharmacokinetics quinine

Introduction

Quinine is an essential drug in the management of chloroquine-resistant falciparum malaria (White, 1985). Despite its wide use, little information is available on the absolute bioavailability of oral quinine (Hall *et al.*, 1973; Salako *et al.*, 1992; Taggart *et al.*, 1948). Intraindividual variability in quinine kinetics after an oral dose was observed in subjects with malaria studied during the acute phase and in convalescence (Supanaranond *et al.*, 1991; White, 1985). In a previous study, an oral dose of quinine was given on two occasions to healthy volunteers (Garnham *et al.*, 1976), but the reproducibility of absorption was not studied formally, and a specific drug assay was not available. In the present study, performed in healthy subjects, the extent and rate of quinine absorption were assessed, together with their intraindividual variability.

Methods

Subjects

Six subjects, three males and three females, participated in the study. Their mean age (range) was 31 (21–40) years and their mean body weight was 72 (52–85) kg. All were found to be healthy by routine clinical examination and laboratory tests. They had taken no drugs for at least 1 week before the study. One female subject and two male subjects were smoking between 15 to 20 cigarettes per day.

Study design

The subjects were given two identical oral doses and an i.v. infusion dose of quinine on three separate occasions. The median (range) interval between the two oral doses was 11.5 (6–60) days and between the last oral dose and the i.v. infusion it was 23 (11–176) days. The oral dose was as close as possible to 15 mg kg⁻¹ and it was administered using 100 mg and 250 mg tablets of quinine hydrochloride dihydrate (KabiVitrum, Stockholm, Sweden). The i.v. dose was 15 mg kg⁻¹ and was administered as a constant rate infusion over 6 h. The infusion was prepared by dissolution of quinine dihydrochloride powder (Apoteksbolaget, Sweden) in isotonic NaCl to obtain a final concentration of 2.5 mg ml⁻¹, and the infusion fluid was assayed for quinine. Both quinine salts have a molecular weight of 397 and the intended dose was equivalent to 12.24 mg kg⁻¹ of quinine base. The actual mean ($\pm$ s.d.) oral dose was 12.06 (0.15) mg kg⁻¹ of quinine base. Five subjects received an i.v. dose of 11.97 (0.33) mg kg⁻¹ and one subject (subject 4) received 6.03 mg kg⁻¹ of quinine base over 3 h.

Study procedures

Informed consent was obtained from the subjects and the study was approved by the Ethics Committee of Huddinge University Hospital.

The subjects took the oral doses of quinine or the infusion was started at 08.00 h, after a light breakfast

had been taken at home. The other oral intakes were a coffee (from 0.33 to 2 h after the dose) and lunch (from 3 to 5 h after the dose), after which there were no dietary restrictions. The subjects were resting during the first 3 h after dosing.

Following the oral doses, blood samples (2 ml) were collected in heparinised tubes at the time of drug intake, every 20 min until 3 h, every hour from 3 to 12 h and at 24, 28 and 32 h. For the i.v. infusion dose, the blood samples were collected at the same intervals, except from 3 to 12 h, where blood samples were collected every 30 min. Plasma was separated within 1 h after collection by centrifugation for 7 min at 2000 g. The samples were stored at -20°C until assay.

Quinine assay

Quinine was measured by a reversed phase h.p.l.c. method with fluorescence detection. The excitation and emission wavelengths of the detector were set at 350 and 446 nm, respectively. Plasma samples (100 μl) were alkalized with sodium hydroxide, extracted with toluene and reextracted with phosphate buffer. The column was an Ultrasphere ODS 3 μm , 75×4.6 mm (Beckman). The eluent was prepared by mixing 480 ml phosphate buffer 0.1 mol l^{-1} , pH 1.9, 30 ml acetonitrile, 10 ml tetrahydrofuran and 8 ml triethylamine and adjusting pH to 3.5 with NaOH 5 mol l^{-1} . The flow rate was 1.0 ml min^{-1} . The within-assay coefficient of variation was 2–4%, and the day-to-day coefficient of variation was less than 4% during the study. The limit of determination was 2 nmol l^{-1} plasma.

Pharmacokinetic analysis

Adjustment to actual i.v. doses according to assay was made where appropriate. The maximum difference between intended and actual infusion dose was 6%.

Peak plasma concentrations (C_{max}) and the time to reach peak concentrations (t_{max}) of quinine were noted. The terminal elimination rate constant (λ_z) was estimated by linear regression of the log linear portion of the terminal elimination phase. Areas under the plasma drug concentration-time curve (AUC) were calculated by the linear trapezoidal method with extrapolation to infinity. The mean percentage of the AUC extrapolated beyond the last data point was 13% for the oral doses and 16% for the infusion. Plasma clearance (CL), fraction of the dose absorbed (F), mean residence time (MRT) and volume of distribution at steady state (V_{ss}) were calculated after intravenous administration by standard equations (Gibaldi & Perrier, 1982).

The absorption of quinine from the oral dosage form was estimated by numerical deconvolution (Iga *et al.*, 1986) and the results were expressed as cumulative fraction absorbed with time. Because of the very rapid distribution phase plasma drug concentrations following infusion were described by a monoexponential function.

Statistical analysis

Within- and between-subject variation in the pharmacokinetic parameters was estimated using one-way analysis of variance based on two replicates for each of the six subjects. Coefficients of variation for within-subject variation (CV_W) and between-subject variation (CV_B) were calculated as

$$\text{CV}_W = \frac{\sqrt{\text{MS}_W}}{\bar{x}}$$

$$\text{CV}_B = \frac{\sqrt{(\text{MS}_B - \text{MS}_W)/n_0}}{\bar{x}}$$

where MS_W is the mean sum of squares within subjects, MS_B the mean sum of squares between subjects, $\bar{x}$ the overall mean for all observations and n_0 the number of replicates per subject, in our case two (Sjövall *et al.*, 1986).

The results are expressed as mean ($\pm$ s.d.), unless otherwise stated.

Results

All of the subjects experienced moderate side-effects. The most common were tinnitus, nausea, dizziness, dry mouth, shivering, and subjective hearing impairment. One subject reported a feeling of discomfort after 3 h of infusion. She was placed in the supine position and her condition improved rapidly. The arterial blood pressure was 110/60 mm Hg and her pulse was 120 min^{-1} . The infusion was stopped but the subject agreed to continue with the sampling procedure.

Following infusion, the mean AUC was 321 (71) $\mu\text{mol l}^{-1} \text{h}$ (normalised to a 6 h infusion for subject 4), $t_{1/2,z}$ was 11.3 (3.1) h, MRT i.v. was 14.9 (4.3) h, V_{ss} was 1.72 (0.38) l kg^{-1} and CL was 2.00 (0.50) $\text{ml min}^{-1} \text{kg}^{-1}$.

CV_W values of about 10% were found for C_{max} , AUC and F (Table 1). Absorption, calculated by deconvolution, was reproducible and eventually complete after 2 h (Figure 1).

Table 1 Pharmacokinetic parameters of quinine calculated from plasma concentrations after oral dosing

	First oral dose	Second oral dose	$\text{CV}_W(\%)$	$\text{CV}_B(\%)$
t_{max} (h)	1.84 (1.02–3.00)	2.01 (1.67–2.33)	27.4	13.9
C_{max} ($\mu\text{mol l}^{-1}$)	15.2 (2.8)	15.7 (1.7)	9.2	11.7
AUC ($\mu\text{mol h l}^{-1}$)	248 (62)	245 (65)	9.7	23.7
F	0.76 (0.11)	0.76 (0.11)	9.8	10.6
$t_{1/2,z}$ (h)	10.7 (2.88)	10.9 (3.70)	12.4	27.4

Values are expressed as mean ($\pm$ s.d.) except t_{max} : median (range).

Figure 1 Mean ($\pm$ s.d.) cumulative fraction of quinine absorbed with time in six healthy subjects after oral administration of 15 mg kg^{-1} on two occasions.

Discussion

Taggart *et al.* (1948) considered quinine to be almost completely absorbed, since less than 5% of the dose was recovered in the faeces. However, sugar coated

tablets were reported to give delayed and sometimes incomplete absorption (Garnham *et al.*, 1976). No significant difference were observed in the rate or extent of absorption of quinine using hydrochloride, sulphate and ethylcarbonate salts (Jamaludin *et al.*, 1988a). Our results show a somewhat lower extent of oral availability than that reported recently by Salako *et al.* (1992), who gave 600 mg doses of quinine hydrochloride to healthy adult Africans (76 compared with 88%).

Quinine absorption is presumed to be rapid since t_{max} values of 1 to 3 h have been reported (Garnham *et al.*, 1976; Jamaludin *et al.*, 1988a,b; Salako *et al.*, 1992; Taggart *et al.*, 1948; Wanwimolruk *et al.*, 1991). This is confirmed in the present study by deconvolution indicating complete absorption by 2 h after dosing (Figure 1). The disappearance of quinine after slow intravenous injection has been reported to be biexponential (White, 1985). However, the distribution phase is rapid with an initial half-life of 1.9 min and our assumptions of mono-exponential decay are presumed to have had little influence on the results of deconvolution. We conclude that the oral absorption of quinine is extensive, fast and reproducible in healthy subjects.

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