Br. J. clin. Pharmac. (1993), **35**, 265–271

A comparison of the pharmacokinetic and pharmacodynamic properties of quinine and quinidine in healthy Thai males

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1 Eight healthy Thai males, aged 19–27 years, received quinine or quinidine dihydrochloride 10 mg kg^{-1} body weight by intravenous infusion over 1 h. At least 1 week later, the alternative alkaloid was administered.

2 The terminal elimination half-time of quinidine was shorter than that of quinine (median [range]; 5.7 [5.0–10.0] *vs* 9.9 [8.8–15.1] h, $P < 0.01$), the volume of distribution at steady state (V_{ss}) for quinidine was larger than that for quinine (3.5 [2.5–5.6] *vs* 3.1 [1.8–4.1] 1 kg^{-1}; $P = 0.02$) and quinidine was less bound to plasma proteins (% free drug: 22.8 [15.4–47.2] *vs* 9.4 [7.3–15.0]%, $P < 0.01$). Total clearance was greater for quinidine (7.7 [3.9–11.4] *vs* 3.4 [1.8–4.6] ml min^{-1} kg^{-1}, $P < 0.01$) but not for clearance of unbound drug (32.2 [14.6–50.4] *vs* 29.9 [20.2–50.9] ml min^{-1} kg^{-1} respectively, $P > 0.2$).

3 Side-effects, including transient hypotension after quinidine in two cases, were mild.

4 Both drugs produced prolongation of the rate-corrected QT interval (QT_c), with similar rates of elimination from the cardiac conduction 'effect' compartment (k_{eo}; 4.14 [0.03–15.33] h^{-1} for quinine, 3.74 [1.63–13.14] h^{-1} for quinidine, $P > 0.19$). Using a linear concentration-response model, the intercept ('threshold') for quinidine effect was lower than that for quinine ($P = 0.004$) but the slopes (change in QT_c for a given change in free drug concentration) were similar ($P = 0.56$).

5 Quinine produced greater hearing loss across the range 0.5–8.0 kHz (mean loss 16 dB after quinine; 9 dB after quinidine; $P < 0.0001$), especially at frequencies > 4.0 kHz but pharmacodynamic analysis showed no significant differences between the drugs.

6 These data suggest that free plasma concentrations and prolongation of the QT_c are greater for quinidine than for the same dose of quinine. Nevertheless, quinidine appears a safe alternative to quinine in the treatment of chloroquine-resistant falciparum malaria.

Keywords quinine quinidine pharmacokinetics pharmacodynamics

Introduction

Although quinine is the treatment currently recommended for chloroquine-resistant falciparum malaria (Warrell *et al.*, 1990), there is evidence that its dextrorotatory diastereo-isomer quinidine has greater intrinsic antimalarial activity (Sabchareon *et al.*, 1988; Taggart *et al.*, 1948; White *et al.*, 1981) and, where quinine is unobtainable, quinidine has proved a satisfactory alternative for the treatment of severe malaria (Miller *et al.*, 1989). Indeed, parenteral quinine is no longer available in the U.S.A., leaving quinidine as the only drug available in that country for the treatment of severe chloroquine-resistant malaria. However, cardiovascular toxicity is a cause for concern when quinidine is used to treat acute malaria, as the therapeutic ratio is narrow and the dose is higher than that usually recommended for suppression of cardiac arrhythmias.

The systemic clearance and apparent volume of distribution (V_z) of quinidine are greater than those of quinine, consistent with lower plasma protein binding. As a consequence, blood concentrations of quinidine are lower (White, 1987). The only previously-reported within-subject pharmacokinetic comparison involved oral formulations and, although the lower plasma quinidine concentrations were attributed to reduced

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bioavailability (Jamaludin *et al.*, 1988), they could also be explained by a relatively large V_z. A comparison of the disposition and toxicity of intravenously-administered quinine and quinidine is needed as both drugs are in current use for the treatment of severe malaria. Since falciparum malaria *per se* is known to influence the disposition of antimalarial drugs (White *et al.*, 1982) and within-subject comparative studies in acute illness cannot be performed, we have investigated the relationship between the pharmacokinetic and pharmacodynamic properties of intravenous quinine and quinidine using a crossover design in healthy young adult male volunteers.

Methods

Subjects

Eight healthy adult Thai males aged 19–27 years were studied. No subject was taking regular medication. All gave informed consent to participation in the study which was approved by the Ethical Review Sub-Committee of the Research Committee, Ministry of Public Health, Bangkok, Thailand.

Methods

Each subject was studied on two occasions at least 1 week apart. On the first occasion, four subjects were randomised to receive quinine dihydrochloride and four to receive quinidine dihydrochloride (ACF Chemiefarma NV, Maarssen, Holland) dispensed from identical, coded ampoules. Subjects were unaware of the identity of the allocated drug. A sampling cannula was introduced into a forearm vein and baseline blood samples were taken for routine biochemistry, haematology and estimation of plasma quinine or quinidine concentrations. A 12-lead electrocardiogram was recorded, the standard lead with best definition of the QT interval was selected, and a long rhythm strip at 50 mm s^{-1} chart speed was taken. Baseline audiometry using a Kamplex AS7 portable audiometer was performed at frequencies between 0.25 and 8.0 kHz as described previously (Roche *et al.*, 1990). An infusion of 10 mg base kg body weight $^{-1}$ of allocated drug was then administered over 1 h by a motor-driven syringe pump. Blood was taken for assay of plasma drug concentrations at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18 and 24 h after the start of the infusion. Pulse rate, blood pressure and an ECG rhythm strip at 50 mm s^{-1} speed were recorded at 0.5, 1, 2, 4, 8, 12 and 24 h. Audiometry was performed and a symptom questionnaire was completed hourly for 4 h then at 8, 12 and 24 h. Adverse effects during the 24 h study period were recorded on a standard form. On the second occasion, the same protocol was followed but an infusion of the alternative alkaloid was administered.

Quinine and quinidine analysis

Plasma quinine and quinidine concentrations were assayed by h.p.l.c. as described previously (Karbwang *et al.*, 1989). The limit of quantitation for both compounds was 4 ng ml^{-1} plasma using a 0.25 ml sample. Calibration curves were linear (r = 1.0) in the range 0–7000 ng ml^{-1}. Interassay coefficients of variation for quinine were 6.8%, 0.3% and 1.2% at concentrations of 1.0, 16.0 and 32.0 mg l^{-1}, respectively, and for quinidine 1.8%, 2.7% and 3.7% at 1.0, 6.0 and 12.0 mg l^{-1}, respectively. Quinidine was used as the internal standard for quinine assay and quinine as the internal standard for quinidine assay; recoveries of quinine and quinidine were 76% and 81%, respectively (Karbwang *et al.*, 1989).

Plasma free concentrations of each drug were measured in 2 ml plasma samples after ultrafiltration at 33° C using an Amicon YMT system (Amicon Corporation, Massachussets, U.S.A.; Silamut *et al.*, 1985). Plasma samples were not buffered but were exposed to air for similar periods. The ultrafiltrates contained less than 0.1% w/v protein and loss of added [^{14}C]-labelled quinine from the system was negligible (Silamut *et al.*, 1991). Concentrations of quinine or quinidine were assayed in the filtrate using the methods described above after calibration with ultrafiltrate standards containing known amounts of added drug. The percentage free drug in each sample was calculated from free and total drug concentrations.

Pharmacokinetic and pharmacodynamic analyses

The plasma concentrations of quinine and quinidine were modelled using an iterative, unweighted, least squares curve fitting programme (PCNONLIN; Metzler & Weiner, 1984) and standard pharmacokinetic parameters were generated. Akaike's Information Criterion (AIC; Yamaoka *et al.*, 1978) was used to compare the goodness of fit of one and two-compartment open models with zero-order input. The volume of distribution at steady state in the two-compartment model (V_{ss}) was estimated as described previously (Riegelman *et al.*, 1968), while clearance and V_{ss} of unbound drug were calculated by dividing total clearance and V_{ss} respectively by the fraction of unbound drug.

The effects of quinine and quinidine on hearing and cardiac conduction tissue were compared using the pharmacokinetic-pharmacodynamic link model described by Sheiner *et al.* (1979) and Holford *et al.* (1981) and implemented using PCNONLIN. Standard electrocardiographic indices were measured. The rate-corrected electrocardiographic QT intervals ($QT_c = QT/\sqrt{RR}$) for each subject both during and after each infusion were subtracted from baseline pre-infusion values. The decibel (dB) hearing loss recorded at each of the nine frequencies after the start of the infusion was obtained by subtraction of hearing thresholds from their respective pre-infusion values. However, dB hearing loss was measured in conventional 5 dB increments and the maximal loss after infusion was, at most, only several orders of magnitude greater than this. To enable curve fitting from these discontinuous data, dB hearing loss data from all eight subjects were averaged for each drug, ear and frequency before analysis. Mean values for the pharmacokinetic constants C_1, C_2, λ_1 and λ_2 were also obtained and used to derive pharmacodynamic parameters for the group as a whole. To allow a direct comparison between

individuals, the maximal dB hearing loss at each frequency was also determined from the post infusion data for each subject.

The relationship between drug concentration in the effect compartment (C_e) and the magnitude of the response (E) was considered to be linear (Holford *et al.*, 1981), i.e. $E = m.C_e + b$, where m and b are the slope and intercept of the linear segment of the concentration-response continuum. This linear relationship makes no assumptions as to the magnitude of the maximal effect (E_{max}) and reduces the number of parameters to be derived from the three required for a conventional sigmoid-shaped 'E_{max}' model (Hill, 1910), to two (m and b). In all cases, AIC values for the 'E_{max}' model were greater than those for the linear concentration-response equation.

Statistical analysis

Since the data were not always normally or continuously distributed, nonparametric tests (Siegel & Castellan, 1988) were used for comparison of derived pharmacokinetic and pharmacodynamic parameters. Unless otherwise stated, data are reported as medians and absolute ranges. Analysis of post-infusion hearing loss data was by parametric multi-factor analysis of variance (Armitage & Berry, 1987).

Results

Subjective symptoms

All subjects developed nasal congestion after receiving quinidine (from 10 to 55 min after the start of the infusion) while only three subjects had this symptom after quinine (see Table 1; $P = 0.013$, Fisher exact test). Nasal congestion lasted a maximum of 2 h after onset and resolved without specific treatment in all cases. There was no significant difference between the two drugs in the incidence of other side-effects ($P > 0.2$ in each case; see Table 1). Two subjects felt light-headed, nauseated and then vomited after receiving quinidine; these subjects did not have the highest free plasma quinidine concentrations in the post infusion period.

Cardiovascular effects

There were no consistent changes in pulse rate or blood pressure. The maximum rise in heart rate was 40 beats min^{-1} one subject 1.5 h after the start of a quinidine infusion but there was no concomitant change in blood pressure. The average increase in heart rate was 17 beats min^{-1} after quinidine and 18 beats min^{-1} after quinine. The systolic blood pressure did not change by more than 15 mm Hg in six of the subjects during either study. In one subject there was a reduction of 26 mm Hg after quinidine and in another subject a 20 mm Hg reduction occurred after quinine. In both these subjects, normal blood pressure was restored after elevation of the legs.

There was minimal prolongation of the mean duration of the QRS complex at the end of the one-hour infusion period relative to the baseline (0 h) value for both quinine (0.093 ± 0.015 *vs* 0.099 ± 0.012 s) and quinidine (0.095 ± 0.007 *vs* 0.103 ± 0.014 s). The PR interval did not change during the infusion of either drug. Both quinine and quinidine produced prolongation of the QT_c to a maximum value at either 1.5 h (three cases after quinine, four after quinidine) or 2.0 h (five cases after quinine, four cases after quinidine). The maximum change in QT_c after quinine (from 0.417 ± 0.014 to 0.499 ± 0.031 s) was approximately half that after quinidine (from 0.407 ± 0.020 to 0.557 ± 0.070 s).

Pharmacokinetics

The AIC values for a two compartment model were significantly lower than those for a one compartment model for both drugs (median [range] AIC for quinine 11.9 [3.1–29.1] *vs* 22.9 [7.1–34.4]; for quinidine −0.7 [−21.1–19.2] *vs* 14.8 [−13.7–24.5] Wilcoxon, $P < 0.02$ in each case). Plasma quinine and quinidine concentrations are shown in Figures 1 and 2, and derived pharmacokinetic parameters are shown in Table 2. The terminal elimination half-lives of quinidine were significantly shorter than those of quinine ($P < 0.01$) and the volumes of distribution at steady state (V_{ss}) were significantly larger ($P = 0.0195$). The systemic clearance of quinine was significantly less than that of quinidine ($P < 0.001$). Plasma free quinine concentrations 1 h after the end of the infusion were significantly lower than those of

Table 1 Numbers of subjects experiencing side-effects during or after quinine and quinidine infusions

Symptom	*Quinine*	*Quinidine*
Nasal congestion*	3	8
Dizziness	1	2
Vomiting	0	2
Subjective hearing loss	1	1
Nausea	0	1
Flushing	1	0
Blurred vision	1	0
No symptoms	2	0

*$P = 0.013$.

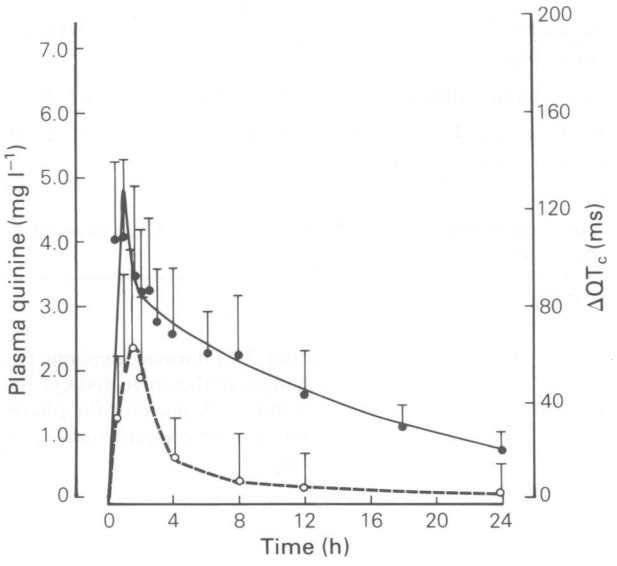

Figure 1 Mean (+ s.d.) total plasma quinine concentrations (●) and mean (+ s.d.) change in the rate-corrected QT interval (ΔQT_c) from the pre-infusion baseline (○) during the 24 h of the study.

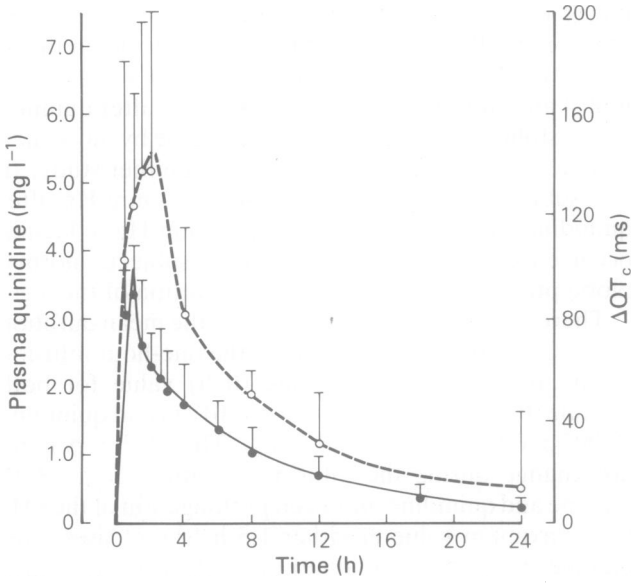

Figure 2 Mean (+ s.d.) total plasma quinidine concentrations (●) and mean (+ s.d.) change in the rate-corrected QT interval (ΔQT_c) from the pre-infusion baseline (○) during the 24 h of the study.

Table 2 Pharmacokinetic parameters of quinine and quinidine derived from two-compartment fit of plasma concentrations in healthy volunteers. Data are medians and (ranges)

Variables	*Quinine*	*Quinidine*
Peak plasma drug concentration (mg l^{-1})	4.0 (2.1–5.8)	3.3 (2.1–4.8)*
Elimination half-life initial (min)	3 (2–8)	3 (2–107)
Terminal elimination half-life (h)	9.9 (8.8–15.1)	5.7 (5.0–10.0)*
Volume of the central compartment (l kg^{-1})	0.3 (0.2–0.9)	0.5 (0.3–3.7)
Volume of distribution (V_z) (l kg^{-1})	3.2 (1.8–4.3)	4.5 (2.7–6.5)*
Volume of distribution at steady state (l kg^{-1})	3.1 (1.8–4.1)	3.5 (2.5–5.6)*
Total clearance (ml min^{-1} kg^{-1})	3.4 (1.8–4.6)	7.7 (3.9–11.4)*
Plasma unbound drug (%)	9.4 (7.3–15.0)	22.8 (15.4–47.2)*
Unbound volume of distribution at steady state (l kg^{-1})	27.7 (20.4–42.7)	15.9 (7.3–24.6)*
Unbound clearance (ml min^{-1} kg^{-1})	29.9 (20.2–50.9)	32.2 (14.6–50.4)

*$P < 0.02$.

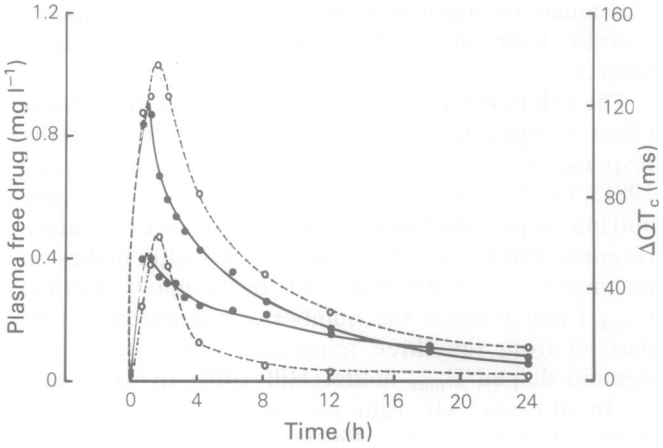

Figure 3 Mean plasma free quinidine (upper solid line) and quinine (lower solid line) concentrations (●) and mean changes in the rate-corrected QT interval (ΔQT_c) for both quinidine (upper interrupted line) and quinine (lower interrupted line) (○) during the 24 h of the study.

quinidine (median [range] 0.34 [0.18–0.42] *vs* 0.50 [0.35–1.00] mg l^{-1}) in all cases ($P < 0.01$). Mean free plasma quinine and quinidine concentrations are shown in Figure 3 and free percentages are summarised in Table 2. The volume of distribution for unbound drug at steady state was significantly greater for quinine than quinidine ($P < 0.004$) but clearance of unbound drug was similar (see Table 2).

Pharmacodynamics

i) Prolongation of the corrected QT interval Mean (+ s.d.) changes in the electrocardiographic QT_c interval during and after the 1 h quinine and quinidine infusions are shown in Figures 1 and 2, and together with free drug concentrations, in Figure 3. The medians and ranges of the derived parameters k_{eo}, m and b are shown in Table 3. There was no significant difference between the k_{eo} values for the two drugs (Wilcoxon, $P > 0.19$). The median half-time for elimination ($t_{½,z}$) of quinine from the effect compartment was 0.17 h (10 min) and that for quinidine was 0.19 h (11 min). Consistent with the assumption that the effect compartment is distinct from the peripheral compartment of the pharmacokinetic model, k_{eo} values were significantly greater than those for k_{21} for both quinine ($P = 0.004$) and quinidine ($P = 0.027$; see Table 3).

There was no statistically significant difference between the slope m of the linear concentration-response relationship of the two alkaloids whether expressed as a function of total ($P = 0.14$) or free ($P = 0.56$) drug

Table 3 Pharmacodynamic parameters derived from analysis of changes in the corrected QT interval after infusion of quinine and quinidine. Values for the pharmacokinetic rate constant k_{21} are included for comparison with those of k_{eo}. Data are medians and (ranges)

k_{eo} (h^{-1})	4.14 (0.03–15.33)*	3.74 (1.63–13.14)*
m (ms 1 mg total $drug^{-1}$)	119 (33–370)	213 (2–582)
m (ms 1 mg free $drug^{-1}$)	853 (344–3,000)	613 (9–3,779)
b (ms)**	−22.6 (−52.8–−6.6)	12.3 (−10.4–34.6)
k_{21} (h^{-1})	1.93 (1.27–4.59)	1.82 (0.18–2.42)

*$P \leq 0.027$ *vs* k_{21}.
**$P = 0.004$.

Table 4 Pharmacokinetic data derived from analysis of averaged pharmacokinetic parameters and post-infusion hearing loss values. Data are medians and (ranges) for the nine frequencies tested

	Quinine		*Quinidine*	
	Left ear	*Right ear*	*Left ear*	*Right ear*
k_{eo} (h^{-1})	2.5 (1.8–13.4)	2.6 (1.9–3.4)	2.5 (0.4–2.6)	4.8 (2.0–29.7)
m (dB 1 mg total $drug^{-1}$)	10.2 (6.3–43.4)	8.4 (3.8–12.9)	9.1 (1.2–79.5)	10.1 (7.5–42.8)
m (dB 1 mg free $drug^{-1}$)	101.0 (62.4–429.7)	83.2 (37.6–127.7)	38.3 (5.1–335.4)	42.6 (31.6–180.6)
b (dB)	−3.7 (−5.3–−2.1)	1.4 (−1.8–4.5)	−2.7 (−6.8–0.2)	0.1 (−5.2–1.9)

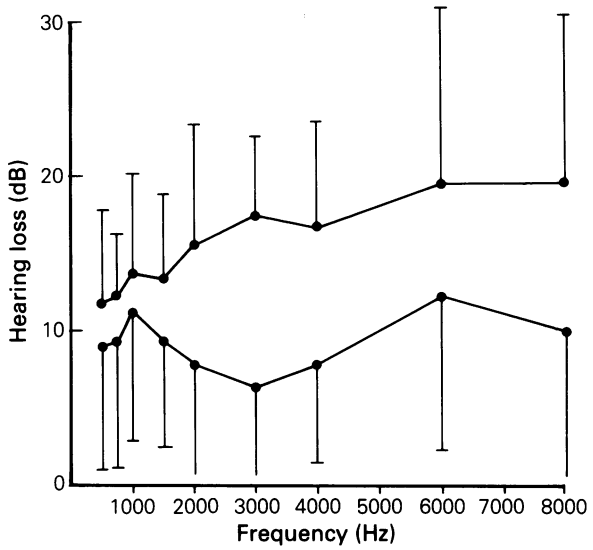

Figure 4 Mean (+ s.d. or − s.d.) maximum hearing loss after both quinine (upper line) and quinidine (lower line) across the frequency range 500–8,000 Hz.

concentration (see Table 3). However, the intercept b was significantly greater for quinidine than for quinine in all eight subjects ($P = 0.004$; see Table 3).

ii) Hearing loss Absolute post-infusion hearing loss data are shown in Figure 4. There was a significant difference in the hearing loss induced by the two drugs ($F_{(1,56)} = 80.75$, $P < 0.01$), with quinine causing greater loss than quinidine ($P < 0.0001$). The average hearing loss across the frequency range 500–8,000 Hz was 16 dB after quinine and 9 dB after quinidine. There was also a significant difference between frequencies ($F_{(8,56)} = 2.82$, $P < 0.05$), and *post-hoc* multiple range testing revealed that quinine-induced hearing loss was greater at higher than lower frequencies (6.0 and 8.0 kHz *vs* 0.5, 0.75, 1.0 and 2.0 kHz; 4.0 kHz *vs* 0.5 and 0.75 kHz; $P < 0.05$ in each case). The same trend was also evident in quinidine-induced hearing loss (see Figure 4), but the overall effect was much smaller and no statistically significant differences were found.

Hearing loss relative to that before drug administration was usually maximal at the end of the infusion regardless of ear and frequency. For example, at 8.0 kHz the average hearing loss was 15 dB at 1 h, falling to 12, 8, 6 and 3 dB at 4, 8, 12 and 24 h respectively. The results of pharmacodynamic analysis of averaged hearing loss data are shown in Table 4. There were no significant differences between k_{eo} values at the nine frequencies tested when considered by both drug and ear (Friedman test, $F_r = -3.83$, $k = 4$, $P > 0.3$). This was also the case for the slope of the dose-response line expressed in terms of total ($P = 0.5$) and free ($P = 0.32$) drug concentration, although the median of values of m across the frequencies as a function of free quinine concentration were approximately twice those of quinidine (see Table 4). There was a significant difference between the intercept of the dose-response line ($P = 0.0002$) but multiple comparison testing indicated that this was due to a difference between the two ears ($P < 0.05$) and not between drugs ($P > 0.05$). One-way nonparametric analysis of variance by frequency revealed no significant differences between the drugs for k_{eo}, slope (expressed in terms of total and free drug) and intercept values ($P = 0.91, 0.91, 0.94$ and 0.85, respectively).

Discussion

The cinchona alkaloids quinine and quinidine have been used in medicine for over 350 years, first as treatments for fever (specifically 'ague') and , more recently, in the treatment of cardiac arrhythmias (quinidine), night cramps (quinine) and chloroquine-resistant falciparum malaria (both drugs). The therapeutic ratios of these alkaloids are narrow, and quinidine has been recognised as relatively more dangerous because of its greater action on the cardiovascular system. This may have caused some clinicians to hesitate in using quinidine for the treatment of falciparum malaria despite the fact that it appears to be intrinsically more active than quinine against *Plasmodium falciparum in vitro* (Sabchareon *et al.*, 1988; Taggart *et al.*, 1948; White *et al.*, 1981). Our results provide an objective means of assessing the risks of toxicity associated with intravenous administration of the two diastereo-isomers based on their pharmacokinetic properties and measurable biological effects.

The disposition of both quinine and quinidine could be described by a two compartment open model as found previously (Davis *et al.*, 1988; Guentert *et al.*, 1979). Consistent with earlier reports (Jamaludin *et al.*, 1988; Phillips *et al.*, 1985; White, 1987), the plasma concentrations of quinine were higher than those of quinidine for the same dose, suggesting a more rapid systemic clearance and larger total apparent volume of

distribution for quinidine (White, 1987). The values of V_z for quinine found in the present study tended to be larger than those reported previously in seven healthy volunteers (1.9 [1.4–2.4] 1 kg^{-1}; White *et al.*, 1983) but were comparable to estimates of V_z in patients convalescing from uncomplicated malaria (mean ± s.d. 2.74 ± 0.47 l kg^{-1}; White *et al.*, 1982). The values of V_z for quinidine in the present study were higher than estimates determined using a h.p.l.c. assay in older Caucasian patients with coronary artery disease (3.0 [1.6–4.9] 1 kg^{-1}; Conrad *et al.*, 1977). Such comparisons are, however, complicated by differences in assay methods. For example, measurement of quinine and quinidine by the extraction-fluorescence method (Cramer & Isaksson, 1963) includes some fluorescent metabolites as well as the parent drug (Edstein *et al.*, 1983), leading to overestimation of plasma drug concentrations and thus to underestimation of V_z.

The pharmacokinetic differences between the two diastereo-isomers based on total plasma drug concentrations are accounted for, in part, by their different binding to plasma proteins. The principal binding protein for these two basic drugs is α_1-acid glycoprotein (Silamut *et al.*, 1991). The proportion of unbound quinidine was, on average, approximately twice that of quinine in our series of subjects, a result which is in broad agreement with the findings of a variety of other studies (Mihaly *et al.*, 1987; Ochs *et al.*, 1980; Silamut *et al.*, 1985, 1991). This finding is consistent with the larger volume of distribution and shorter $t_{½,z}$ of quinidine, but both drugs have a large V_{ss} implying extensive tissue binding. Clearance data also paralleled plasma protein binding, with total intrinsic clearance of quinidine approximately double that of quinine in the presence of comparable values for clearance of unbound drug.

Pharmacodynamic analysis of changes in the electrocardiographic QT_c interval revealed that the cardiac conduction effect compartment is distinct from the peripheral compartment of the pharmacokinetic model. The rate of transfer of drug from the effect compartment (k_{eo}) was much more rapid than from the peripheral compartment (k_{21}), but k_{eo} values for quinine and quinidine were similar and consistent with those found previously in a study of normal Caucasian subjects who received a much lower intravenous dose of quinidine (Holford *et al.*, 1981). There was also no significant difference between the two diastereo-isomers for values of the slope of the linear concentration-response relationship expressed as a function of both total and free drug concentration. By contrast, values for the intercept b were consistently lower for quinine. For a given change in cardiac conduction tissue concentration above the different 'thresholds' for each drug, the resulting change in QT_c is similar, a situation best illustrated by the essentially parallel curves for change in QT_c shown in Figure 4.

Because of its discontinuous measurement scale and the subjective component of audiometric testing, formal pharmacodynamic analysis of hearing loss proved more difficult. Simple analysis of post-infusion hearing loss in individual subjects revealed that both drugs cause hearing loss, especially at frequencies above 4.0 kHz, but that quinine had a larger effect than quinidine. The reversible effect of quinine on hearing loss at frequencies greater than 1.5 kHz has been reported previously (Roche *et al.*, 1990).

There were no significant differences between the pharmacodynamic constants k_{eo}, m nd b derived for each frequency from averaged hearing data for the two alkaloids. However, the median value for m expressed in terms of free drug concentration was consistently higher for quinine than quinidine (see Table 4). This suggests that quinine might have a proportionately greater effect than quinidine on hearing loss for the same effect compartment concentration, with both drugs having similar effect 'thresholds'. Values for k_{eo} were intermediate between estimates of k_{eo} for cardiac conduction tissue, and of k_{21} from the pharmacokinetic analysis. This finding is consistent with the proposition that the auditory effect compartment is distinct from these two other model-dependent compartments and that within this compartment the two diastereo-isomers have intrinsically different dynamic activities.

Although several reports have shown the safety of oral quinidine in the treatment of falciparum malaria (Bunnag *et al.*, 1987; White *et al.*, 1981) and of its parenteral administration in general (Swerdlow *et al.*, 1983), intravenous quinidine may cause hypotension when infused rapidly. In the present study, neither quinidine nor quinine produced any serious cardiovascular side-effects although two subjects developed transient hypotension after quinidine. Phillips *et al.* (1985) studied the pharmacokinetics and toxicity of intravenous quinidine gluconate in 13 patients with severe falciparum malaria (15 mg base kg^{-1} followed by 7.5 mg base kg^{-1} 8 hourly). Two patients became hypotensive during the initial infusion but there was no other clinical evidence of cardiovascular toxicity. Although periods of hypotension may be mild and short-lived, regular assessment of the haemodynamic state of the patient should be carried out when parenteral quinidine is given.

A 1 h intravenous infusion of 10 mg base kg^{-1} body weight of alkaloid proved safe in our healthy subjects, but recommendations for treatment of patients with acute falciparum malaria should not be based on pharmacokinetic and pharmacodynamic data derived from normal subjects. Patients with malaria have increased plasma concentrations of the acute phase protein α_1-acid glycoprotein (Mihaly *et al.*, 1987; Silamut *et al.*, 1985) with contracted volumes of distribution and longer terminal elimination half-lives for both drugs relative to values in healthy controls (White, 1987). Therefore, total plasma concentrations will be much higher in patients with malaria receiving the same doses. However, free drug concentrations are not necessarily increased in patients with malaria. Indeed, serious cardiotoxicity following intravenous quinine administration in falciparum malaria is most unusual, even in cases in which total plasma concentrations exceed 15 mg l^{-1} (Davis *et al.*, 1990; White, 1987).

The pharmacokinetic and pharmacodynamic differences between quinine and quinidine provide evidence for stereoselectivity in protein binding, cellular transport and biological effect. The two drugs act differently on both cardiac conduction tissue and the auditory apparatus for the same free plasma concentrations, but the magnitude of these effects and the haemodynamic responses during and after intravenous administration provide

further evidence that quinidine is a safe and valuable alternative to quinine in the treatment of severe falciparum malaria.

We are grateful to the nursing staff of the Hospital for Tropical Diseases, Bangkok for their co-operation and help during the study. This study was part of the Wellcome-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

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(Received 8 May 1992, accepted 3 September 1992)