The pharmacokinetics and pharmacodynamics of quinidine and 3-hydroxyquinidine

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1 The pharmacokinetics and pharmacodynamics of quinidine and 3-hydroxyquinidine based upon measurements of total and unbound serum concentrations were determined after a single dose (400 mg) and at steady state (200 mg every 6 h).

2 The oral clearance (7.6 ± 1.9 vs 4.8 ± 2.0 ml min⁻¹ kg⁻¹; $P < 0.05$) and renal clearance (1.2 ± 0.3 vs 0.63 ± 0.25 ml min⁻¹ kg⁻¹; $P < 0.005$) or quinidine were lower during steady state than after the single dose.

3 The area under the serum concentration vs time curve (AUC) of 3-hydroxyquinidine was greater at steady state than after the single dose (2.0 ± 0.7 vs 3.0 ± 0.6 mg l⁻¹ h; $P < 0.05$) and its renal clearance was less (3.0 ± 1.1 vs 1.54 ± 0.38 ml min⁻¹ kg⁻¹; $P < 0.05$).

4 The slope of the relationship between quinidine concentration and change in QTc interval was greater at steady state (40.1 ± 21.7 vs 72.2 ± 41.7 ms/(mg l⁻¹); $P < 0.05$).

Keywords quinidine 3-hydroxyquinidine metabolite pharmacokinetics pharmacodynamics

Introduction

Quinidine is used routinely in the management of life-threatening ventricular arrhythmias. Several reports indicate that the metabolites of quinidine, including the 3-hydroxy product, possess antiarrhythmic activity which is similar in potency to quinidine. (Drayer *et al.*, 1978; Holford *et al.*, 1981; Vozeh *et al.*, 1985). In addition, we have observed (Wooding-Scott *et al.*, 1987) that unbound serum concentrations of 3-hydroxyquinidine often exceed those of quinidine in patients receiving chronic quinidine therapy for suppression of arrhythmias.

The primary purpose of the present study was to evaluate the pharmacokinetics of total and unbound quinidine and 3-hydroxyquinidine in healthy volunteers after a single oral dose of quinidine sulphate and during dosage at steady state. The relationships between total and unbound concentrations and the duration of the QTc interval were also investigated.

Methods

Subjects

Six male, non-smoking, non-obese normal volunteers who ranged in age from 22 to 35 years and in weight from 61 to 84 kg, were studied. After obtaining informed consent, the volunteers underwent a physical examination including ECG, CBC with differential and serum chemistry profile. All six were free of identifiable medical disease and were receiving no drug therapy on a regular basis. After entering the study, each volunteer received a test dose of 200 mg quinidine sulphate orally to observe for any drug sensitivities. The protocol was approved by the Institutional Review Board and all subjects provided written informed consent prior to initiation of the study.

Single dose study

After an overnight fast, quinidine sulphate was given orally at approximately 08.00 h as two 200

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mg tablets (400 mg). Blood samples (10 ml) were drawn through an indwelling 20 gauge angiocatheter in a forearm vein. The samples were then transferred to unstoppered plain Vacutainer® tubes (Bectin-Dickinson). Collections were made immediately prior to and at approximately 0.5, 1.0, 1.5, 2.0, 3.0, 4.5, 5.0, 6.0, 8.0, 10.0, 24.0 and 36 h after drug administration. The volunteers were allowed food and coffee 2 h after drug administration. ECG recordings were made simultaneously with each blood sample collection. Urine was collected over the following intervals: 0–3 h, 3–6 h, 6–10 h and 10–36 h.

Steady state study

Seventy-two hours after the single dose study, each volunteer began a regimen of quinidine sulphate 200 mg every 6 h. At noon on the fourth day of this regimen, blood samples (10 ml) were collected during a dosing interval in the same manner as in the single dose study. Lunch was withheld for 2 h after administration of the quinidine dose. Timed collections were made immediately prior to the administration of the dose and at approximately 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0 and 6.0 h after the drug was taken. As in the single dose study, ECG recordings were obtained simultaneously with each blood sample collection. Urine was collected 0–2 h, 2–4 h and 4–6 h. On both study days, blood samples were allowed to clot, centrifuged and the serum was separated and stored at -4°C until analyzed.

Analytical procedures

Serum, ultrafiltrate and urine samples were assayed for quinidine and 3-hydroxyquinidine using a modification of the h.p.l.c. procedure of LeRoy *et al.* (1982). The principal modification of this procedure was the addition of an extraction procedure in the analysis of serum and urine samples. After the addition of a saturated solution of sodium chloride, the samples were alkalinized with 3 N NaOH. After vigorous vortexing, chloroform (2.5 ml), was added and the solution vortexed and centrifuged. The organic layer (1.8 ml) was removed and evaporated to dryness under a gentle nitrogen stream at 55°C . The sample was reconstituted with mobile phase and injected onto the column. The rest of the assay and that used for the analysis of ultrafiltrate samples was as previously described (LeRoy *et al.*, 1982). The intraday coefficients of variation (CV) for the analysis of quinidine were 1.9%, 0.9% and 4.2% for measurements in serum,

urine and ultrafiltrate, respectively. The interday CVs were 4.2%, 3.1% and 2.4%, respectively. The intraday CVs for the analysis of 3-hydroxyquinidine were 1.5%, 2.7% and 2.9% and the interday CVs were 4.0%, 1.5% and 5.8%, respectively.

Protein binding was measured by ultrafiltration using the Amicon micropartition system (MW cutoff 12000–14000). Serum (500 μl) adjusted to $\text{pH } 7.4 \pm 0.05$ was introduced into the system and centrifuged at 1250 g for 15 min at 25°C . Serum concentrations of α_1 -acid glycoprotein were measured by a radial immunodiffusion assay (Mancini *et al.*, 1965) in each volunteer on both study days.

Analysis of the data

Quinidine and 3-hydroxyquinidine serum concentration vs time curves following single dose administration were subjected to log-linear regression analysis to estimate the terminal slopes. The area under the serum concentration vs time curve (AUC) for both quinidine and 3-hydroxyquinidine was determined using the trapezoidal rule and extrapolated to infinity by dividing the last measured time point by the terminal slope estimate and adding this value to the calculated AUC. The urinary recovery of drug and metabolite were also extrapolated to infinity using the terminal slope estimates. From these values oral clearance ($\text{CL}_\text{O} = \text{Dose}/\text{AUC}$) and renal clearance ($\text{CL}_\text{R} = \text{Ae}(\infty)/\text{AUC}$) were determined after the single dose. The administration sulphate dose was converted to the equivalent dose of quinidine base. At steady state, clearance values were calculated from the AUC and $\text{Ae}(\infty)$ determined over the dosing interval (Gibaldi & Perrier, 1982). The free fraction of drug in serum (f_u) was calculated by dividing the unbound concentration by the total drug/metabolite concentration.

The rate-corrected QT interval (QTC) was determined from the ECG recording by a cardiologist who was blind to the quinidine and 3-hydroxyquinidine concentrations. Effect was assessed as the change in the QTC interval from the baseline value. The relationship between serum concentrations (total and unbound) of quinidine and 3-hydroxyquinidine and ECG effect was described using a simple model describing effect as a linear function of concentration (Holford *et al.*, 1981).

The potential contribution of the metabolite, 3-hydroxyquinidine, to effect was assessed by adding this concentration to the quinidine concentration assuming different relative potencies (*viz.* 0.0, 0.25, 0.50, 0.75, and 1.0).

All data are presented as the mean $\pm$ s.d. A paired *t*-test was used to compare parameters between single dose and steady state. Linear regression analysis was used to evaluate the concentration effect relationships.

Results

Single dose study

After the single dose, the maximum concentration of quinidine averaged 1.35 mg l^{-1} (range: $0.92\text{--}2.13 \text{ mg l}^{-1}$) and for 3-hydroxyquinidine it was 0.32 mg l^{-1} (range: $0.2\text{--}0.54 \text{ mg l}^{-1}$). The oral clearance averaged $7.6 \pm 1.9 \text{ ml min}^{-1} \text{ kg}^{-1}$ and the mean renal clearance was $1.2 \pm 0.3 \text{ ml min}^{-1} \text{ kg}^{-1}$. Other pharmacokinetic parameters are shown in Table 1. Serum concentration vs time profiles in a representative subject are shown in Figure 1.

The mean AUC of 3-hydroxyquinidine was $2.0 \pm 0.7 \text{ mg l}^{-1} \text{ h}$, which was substantially lower than the AUC for total quinidine. The renal clearance of 3-hydroxyquinidine was $3.0 \pm 1.1 \text{ ml min}^{-1} \text{ kg}^{-1}$ and terminal half-life was $9.0 \pm 3.4 \text{ h}$ (see Table 1).

The free fraction of quinidine averaged 0.14 ± 0.02 ($n = 24$) and was constant over the concentration range studied. Thus, unbound concentrations of quinidine were determined by multiplying total serum concentrations by the free fraction measured in each volunteer. The free fraction of 3-hydroxyquinidine averaged 0.45 ± 0.098 ($n = 38$) but decreased as total concentration increased according to the relationship: $f_u = -0.26 \times \text{concentration} + 0.52$; $r = 0.598$, $P < 0.001$. Therefore, unbound concentrations of 3-hydroxyquinidine, in instances where they were not measured, were estimated from the free fraction obtained from the regression line.

Figure 1 Serum quinidine (circles) and 3-hydroxyquinidine (squares) concentration vs time profile following a single 400 mg quinidine sulphate dose in a representative subject. Closed symbols represent total drug/metabolite concentrations and open symbols unbound concentrations. Quinidine concentrations obtained at 24 and 36 h were below the detection limits of the assay, and those obtained for 3-hydroxyquinidine were undetectable in this subject at 10, 24 and 36 h.

The serum concentration vs time profiles of unbound drug and metabolite in a representative subject are also shown in Figure 1. Because of the difference in protein binding, the unbound concentrations of 3-hydroxyquinidine were similar to those of quinidine. The $C_{\max}$ for unbound 3-hydroxyquinidine averaged $0.13 \pm 0.02 \text{ mg l}^{-1}$ which was similar to the $C_{\max}$ for unbound quinidine, $0.17 \pm 0.04 \text{ mg l}^{-1}$.

Steady state study

Steady state conditions were reached in all subjects with 6 h postdose quinidine concentrations ($1.12 \pm 0.41 \text{ mg l}^{-1}$) being similar to predose concentrations ($1.15 \pm 0.35 \text{ mg l}^{-1}$).

Table 1 Pharmacokinetic parameters for quinidine and 3-hydroxyquinidine after single dose administration and after dosing to steady state

	Single dose	Steady state	P value
<i>Quinidine</i>			
AUC ($\text{mg l}^{-1} \text{ h}$)	10.3 ± 3.0	9.1 ± 4.6	NS
CL_O ($\text{ml min}^{-1} \text{ kg}^{-1}$)	7.6 ± 1.9	4.8 ± 2.0	< 0.05
CL_R ($\text{ml min}^{-1} \text{ kg}^{-1}$)	1.2 ± 0.3	0.63 ± 0.25	< 0.005
f_u	0.14 ± 0.02	0.13 ± 0.02	NS
<i>3-hydroxyquinidine</i>			
AUC ($\text{mg l}^{-1} \text{ h}$)	2.0 ± 0.7	3.0 ± 0.6	< 0.05
CL_R ($\text{ml min}^{-1} \text{ kg}^{-1}$)	3.0 ± 1.1	1.5 ± 0.38	< 0.05
f_u	0.45 ± 0.098	0.40 ± 0.094	NS

Figure 2 Serum quinidine (circles) and 3-hydroxyquinidine (squares) concentration vs time profile at steady state (quinidine sulphate 200 mg 6 h) in a representative subject. Closed symbols represent total drug/metabolite concentrations and open symbols represent unbound concentrations.

The concentration vs time profile in a representative subject is shown in Figure 2. $C_{\max}$ values exceeded those observed after a single dose (1.91 ± 0.56 vs 1.35 ± 0.47 mg l⁻¹; $P < 0.02$). Both the oral and renal clearances of quinidine were lower at steady state. However, the fraction excreted unchanged in the urine (f_e), was unchanged. The free fraction of quinidine remained unchanged (see Table 1), as did the concentration of the binding proteins albumin (4.9 ± 0.4 vs 4.7

± 0.2 g dl⁻¹) and α_1 -acid glycoprotein (63 ± 15 vs 75 ± 26 mg dl⁻¹).

The $C_{\max}$ of 3-hydroxyquinidine, 0.66 ± 0.15 mg l⁻¹, at steady state was significantly higher than that observed after single dose administration ($P < 0.005$). The AUC of 3-hydroxyquinidine was increased and its renal clearance was decreased at steady state. The free fraction of 3-hydroxyquinidine was unchanged at steady state (Table 1).

Figure 2 shows the concentration vs time profile for unbound concentrations at steady state in a representative subject. The unbound $C_{\max}$ of 3-hydroxyquinidine was almost twice that observed after the single dose, 0.23 ± 0.05 vs 0.13 ± 0.02 mg l⁻¹ and was similar to the $C_{\max}$ of unbound quinidine $C_{\max}$, 0.26 ± 0.06 mg l⁻¹.

Pharmacodynamics

The change in the QTC interval correlated with total and unbound quinidine concentrations in all subjects after both single dose and continuous administration with the exception of subject 5 at steady state (Table 2). In this subject variability in the measurement of the QTC interval obscured any correlation between this parameter and drug/metabolite concentrations. The slope value after single dose administration was 40.1 ± 21.7 ms (mg l⁻¹) and at steady state it was $72.2 \pm$

Table 2 Pharmacodynamic parameters obtained from total quinidine and 3-hydroxyquinidine concentrations

Subject	Single dose		Steady state	
	Slope	r value	Slope	r value
Quinidine				
1	15.2	0.60	27.2	0.80
2	29.6	0.79	29.5	0.93
3	67.3	0.54	103.1	0.53
4	66.8	0.81	116.7	0.58
5	33.6	0.77	—	—
6	28.3	0.60	84.7	0.49
Mean	40.1		72.2	
s.d.	21.7		41.7	
3-hydroxyquinidine				
1	133.0	0.77	92.4	0.68
2	156.4	0.92	92.5	0.90
3	307.7	0.55	-149.9	0.20
4	288.1	0.73	135.0	0.37
5	138.4	0.88	—	—
6	73.0	0.48	277.3	0.55
Mean	188		149.3 ^a	
s.d.	94		87.6	

^a Steady state data for subject 3 are not included in the mean calculation.

Table 3 Pharmacodynamic parameters obtained from unbound quinidine and 3-hydroxyquinidine concentrations

Subject	Single dose		Steady state	
	Slope	r value	Slope	r value
<i>Quinidine</i>				
1	152.4	0.60	120.9	0.80
2	246.5	0.79	148.1	0.77
3	489.8	0.56	734.3	0.53
4	485.6	0.82	827.3	0.57
5	226.6	0.78	—	—
6	176.8	0.60	704.9	0.49
Mean	296.3		525.0	
s.d.	152.0		319.0	
<i>3-hydroxyquinidine</i>				
1	231.6	0.61	263.3	0.64
2	458.8	0.96	286.6	0.86
3	335.9	0.37	—	—
4	795.0	0.74	356.6	0.33
5	276.0	0.82	—	—
6	174.8	0.48	716.2	0.53
Mean	378.7		405.6	
s.d.	226.0		210.8	

41.7 ms/(mg l⁻¹); $P < 0.05$. However, serum concentrations of quinidine and 3-hydroxyquinidine were higher at steady state. Similar results were seen when evaluating unbound concentrations (Table 3).

There was no consistent relationship between the change in the QTC interval and 3-hydroxyquinidine concentrations (Tables 2 and 3). At steady state a significant relationship between these two parameters was seen in only 3/6 subjects. Furthermore, the addition of 3-hydroxyquinidine to the quinidine concentration at various relative potencies did not result in an improvement in the correlation coefficient relating concentration to effect.

Discussion

This study investigated the pharmacokinetics and pharmacodynamics of quinidine and 3-hydroxyquinidine, using total and unbound serum concentrations following a single dose and after administration to steady state. The data showed differences in the pharmacokinetics of quinidine and 3-hydroxyquinidine when comparing the steady state with the single dose study. Pharmacodynamic differences were also observed.

Some reports (Russo *et al.*, 1982; Fremstad *et al.*, 1979; Gey & Levy, 1975) have indicated that

quinidine exhibits linear pharmacokinetics while others (Carliner *et al.*, 1979; Bolme & Otto, 1977; Guentert *et al.*, 1979) have suggested that its disposition is nonlinear. Thus, a nonlinear relationship between quinidine dose and steady state serum drug concentration has been reported (Bolme & Otto, 1977). Furthermore, steady state drug concentrations (Ochs *et al.*, 1978) are consistently higher than those predicted from single dose data. Our data support these observations in showing a lowering of oral and renal clearances upon dosing to steady state.

The AUC of 3-hydroxyquinidine was also increased at steady state together with a lowering of the renal clearance of this metabolite (Table 1). This is consistent with other data (Rahkit *et al.*, 1984) describing nonlinear excretion of 3-hydroxyquinidine.

The free fraction of quinidine found by ultrafiltration was similar to that obtained by equilibrium dialysis in healthy volunteers (Edwards *et al.*, 1986). The free fraction of 3-hydroxyquinidine was almost four times higher than that of quinidine and was not different when comparing single dose with steady state (Table 1). In patients we have observed a mean free fraction of 0.42 ± 0.13 for 3-hydroxyquinidine, similar to that obtained in healthy subjects (Wooding-Scott *et al.*, 1987).

The differences in protein binding between quinidine and 3-hydroxyquinidine are significant in relation to the relative contribution of this metabolite to the activity of the parent compound. When comparing total drug concentrations, the $C_{\max}$ of 3-hydroxyquinidine is considerably lower than the $C_{\max}$ of quinidine. In contrast, when comparing unbound concentrations, 3-hydroxyquinidine concentrations approach and frequently exceed those of unbound quinidine. In patients we have observed that the ratio of 3-hydroxyquinidine to quinidine is dependent on the clearance of quinidine (Wooding-Scott *et al.*, 1987). At low clearance values (unbound clearances less than 90 l h⁻¹) this ratio is low and at high clearance values (unbound clearances greater than 160 l h⁻¹) it exceeds 1.0. Some patients have unbound 3-hydroxyquinidine values 4–5 times higher than those of unbound quinidine. Therefore, if this metabolite possesses antiarrhythmic activity, it may represent a significant component of the pharmacologic effect produced by quinidine.

In this study, the change in the QTc interval was used as an expression of the pharmacologic effect of quinidine. While prolongation of the QTc interval does not predict that quinidine will suppress arrhythmias, it does indicate that quinidine has a prolonged effect on cardiac repolar-

ization. It has also been suggested (Reiter *et al.*, 1986) that the higher risk of developing torsades de pointes and syncope with quinidine as compared with procainamide is related to its greater effect in prolonging the QTc interval. Thus, the QTc interval seems to be a useful marker of the clinical effect of quinidine. The change in the QTc interval correlated with quinidine concentration in all volunteers, with the exception of one (number 5) at steady state. The slope, of the concentration-effect relationship for total quinidine after the single dose averaged 40.1 ± 21.7 ms/(mg l⁻¹). This is similar to that reported by Holford *et al.* (1981). They reported a mean slope value of 35.0 ± 12.8 ms/(mg l⁻¹) describing the relationship between quinidine concentration in an 'effect compartment' and the change in QTc interval after administration of a single oral dose equivalent 3.74 mg kg⁻¹ quinidine base. The range of total quinidine concentrations was 0 to 3 mg l⁻¹, which is similar to that observed in our study. The slope value which we observed at steady state was nearly twice that observed after the single dose (Table 2). Since quinidine and 3-hydroxyquinidine concentrations increased on average by 41% and 77% respectively, this may simply reflect moving up the sigmoid concentration-response curve under steady state conditions. Alternatively, the presence of higher concentrations of metabolites in serum as previously suggested (Holford *et al.*, 1981), may account for this observation. In five of six volunteers the ratio of 3-hydroxyquinidine to quinidine was

higher at steady state than after the single dose. Further analysis of the concentration-effect data for 3-hydroxyquinidine, however, did not suggest a contribution to activity from this metabolite in all subjects. In three subjects (numbers 1, 2 and 5) after single dose administration a closer correlation was observed when concentrations of 3-hydroxyquinidine were used alone (Tables 2 and 3). Whereas at steady state, the addition of 3-hydroxyquinidine concentrations and assuming different potency values did not improve the goodness of fit over that seen using quinidine concentrations alone. In man, Huffman *et al.* (1977) showed that oral administration of 3-hydroxyquinidine does not prolong the QTc interval. In contrast, other data indicate a prolongation in two of four subjects (Vozech *et al.*, 1985).

We conclude that the pharmacokinetics of both quinidine and 3-hydroxyquinidine are changed after chronic dosing. This is partly caused by a reduction in the renal clearance of both compounds. A greater pharmacodynamic effect is observed at steady state for a given quinidine concentration. These changes in pharmacokinetics and pharmacodynamics of quinidine upon chronic dosing indicate that it is most appropriate to evaluate the response to quinidine under steady state conditions.

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