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THE EFFECT OF QUINIDINE AND ITS METABOLITES ON THE ELECTROCARDIOGRAM AND SYSTOLIC TIME INTERVALS: CONCENTRATION—EFFECT RELATIONSHIPS

NICHOLAS H.G. HOLFORD, PETER E. COATES, THEODORE W. GUENTERT, SIDNEY RIEGELMAN & LEWIS B. SHEINER

Department of Medicine, Division of Clinical Pharmacology, Department of Pharmacy, and Department of Laboratory Medicine, University of California Medical Centre, San Francisco, California 94143

1 A combined pharmacokinetic and pharmacodynamic model has been used to analyze the relationship between electrocardiographic (ECG) and systolic time intervals (STI) and changes in plasma concentration of quinidine after oral and i.v. doses in ten normal subjects.

2 The major effects of quinidine were on cardiac repolarization. Contrary to previous descriptions, we found no important change in the U wave, but the T wave was split into two peaks. The amplitude of these two peaks (T and T′) was reduced, and the QT′ peak and QT intervals were prolonged. The QT peak interval and systolic time intervals did not change appreciably. There were small increases in the PQ and QRS intervals.

3 The effect of quinidine on the QT interval could be explained by a linear pharmacodynamic model. The equilibration between plasma and effect site had a half-time of 8 min. The slope of the pharmacodynamic model was 20.3 ms.mg l^{-1} after i.v. dosing and 33.5 ms.mg l^{-1} after oral dosing.

4 The difference in effect model slopes suggests pharmacologically active metabolites of quinidine are formed during absorption from the gut.

5 The total effect of a single oral dose of quinidine appears to be the same as the same dose given intravenously, even though only 70% of the oral dose reaches the systemic circulation as quinidine.

Introduction

Quinidine is one of the oldest anti-arrhythmic agents (Wenckebach, 1923), and its qualitative effect on the electrocardiogram was observed many years ago (e.g., in 1934 by Maher, Sullivan & Scheribel). Attempts have been made to relate the changes in the ECG to quinidine blood concentration, but have been limited by the use of nonspecific assays for quinidine and abbreviated descriptions of the time course of drug action (Cheng, Sutton, Swisher & Sutton, 1956; Heissenbuttel & Bigger, 1970; Josephson, Seides, Batsford, Weisfogel, Caracta, Lau & Damato, 1974; Cho, 1973; Edwards, Hancock & Sayner, 1974). The development of improved methods for measuring the ECG and specific assays for quinidine (Guentert, Coates, Upton, Combs & Riegelman, 1979) has allowed us to define quantitative relationships between quinidine concentrations and ECG changes in man and to extend the qualitative description of these changes.

The relationship between plasma quinidine concentration and its effect on the ECG can be quantitated by use of a linear pharmacodynamic model and recognition of the equilibration delay between plasma and effect site. It has been known for some time that quinidine is metabolized in man (Brodie, Baer & Craig, 1951). Several metabolites have been identified in urine (2′-quinidinone, Brodie *et al.*, 1951; 3-OH-quinidine, Carroll, Smith & Wall, 1974 and Beermann, Leander & Lindstrom, 1976; *o*-desmethyl-quinidine, Drayer, Lowenthal, Restivo, Schwartz, Cook & Reidenberg, 1978; and an N-oxide, Guentert, Coates & Riegelman, 1978). Recently all these metabolites have been measured in plasma except for *o*-desmethyl-quinidine (Drayer *et al.*, 1978; Guentert & Riegelman, 1978). It has been suggested that these metabolites may have pharmacological activity, based upon experiments in mice and rabbits (Drayer *et al.*, 1978). We have measured the effect of quinidine on cardiac repolarization after intravenous and oral administration in man, and conclude that one or more metabolites of quindine contribute to the ECG changes after a single oral dose.

Methods

The bioavailability of a quinidine sulphate solution was studied in ten normal volunteers (Guentert,

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Holford, Coates, Upton & Riegelman, 1979). Each subject received an intravenous infusion of quinidine gluconate (3.74 mg/kg quinidine base in 0.9% sodium chloride solution) over 25 min and an oral solution of quinidine sulphate (3.74 mg/kg quinidine base in water) administered via a nasogastric tube. At intervals of at least 1 week, each subject received quinidine (either intravenously or orally) or placebo (once only, either i.v. or oral). The sequence of the three treatments and choice of either i.v. or oral placebo was randomized. Intravenous and oral solutions were administered in a double-blind fashion between 08.00 h and 09.00 h after an overnight fast. Direct intragastric administration was used to mask the bitter taste of the solution. Subjects remained supine for 3 h after the dose, and received the first meal of the day at noon. Blood pressure was obtained by conventional sphygmomanometry for 45 min after the start of each intravenous infusion.

Blood samples were collected at 0, 5, 10, 15, 25, 30, 40, 45, 50, 60, 75, 90, 105, 120, 180, 240, 300, 360, 420, 480, 840 and 1440 min after administration of i.v. and oral doses of quinidine or placebo. Samples were drawn from an indwelling catheter or needle (Holford, Vozeh, Coates, Powell, Thiercelin & Upton, 1977) and put in heparinized containers (Venoject ®). Plasma was separated within 15 min and frozen at −20° C until analyzed using a specific assay for quinidine (Guentert, Holford *et al.*, 1979).

The ECG was recorded from a bipolar lead obtained from electrodes placed at the level of the fourth intercostal space in the mid-axillary line. This lead is similar to Standard lead I.

The ECG, phonocardiogram and ear lobe optical density were recorded on magnetic tape. Two-minute recordings of these signals were obtained on three to four occasions in the hour preceding the dose, and immediately preceding or following each blood sample, including an extra recording at 20 min. All recordings were made with the subject supine, the upper body supported at an angle of 30° to the horizontal. ECG and systolic time intervals were measured using a computer-assisted display system after signal averaging of ten cardiac cycles.

ECG and STIs corresponding to various heart rates were predicted using a model based on control observations on the day of placebo administration and observations of the effects of administering up to 1.4 mg atropine sulphate. The relationship between interval and heart rate was linear in the range of heart rates studied.

The effect of quinidine or placebo on each ECG measurement was determined by subtracting the heart rate predicted interval from the observed interval.

The rate-corrected effects after placebo administration did not remain constant throughout the day, confirming similar observations of Lewis (1975). The effect of quinidine on the intervals, was, therefore, calculated by subtracting the mean effect (from all subjects) seen following the corresponding placebo trial (i.v. or oral) at the corresponding time. The subject mean effect was used for correction because each subject did not receive both i.v. and oral placebo, and, therefore, individual correction for time-related variation could not be performed.

Plasma concentrations of quinidine were fit to a two-compartment pharmacokinetic model (Guentert, Holford *et al.*, 1979) using an interactive (Holford, 1979a) nonlinear least squares fitting program (Knott, 1979).

The relationship between plasma quinidine concentration and ECG effect was modelled in two ways. The simpler model described the pharmacologic effect as a linear function of concentration (Equations 1a and 1b) where plasma concentration (C1) is substituted for the concentration term (CONC), E is the change in ECG interval, and SLOPIV and SLOPOR are slope parameters for the i.v. and oral administration:

$$E = SLOPIV \cdot CONC + INTIV \qquad \text{Equation 1a - - i.v.}$$

$$E = SLOPOR \cdot CONC + INTOR \qquad \text{Equation 1b - - oral}$$

Because there appeared to be some delay in achievement of the ECG effect when the plasma concentration was changing rapidly, a more complex model was used to account for the rate of equilibration of concentration and effect (Sheiner, Stanski, Vozeh, Miller & Ham, 1979). In this model, the active site for quinidine's effects is modelled as if it were within a third 'compartment'. The concentration of quinidine in this compartment can be modelled as a function of the central compartment concentration, e.g., plasma, and a first-order elimination rate constant, K_{eo}, controlling loss of quinidine from the effect compartment (Figure 1). A function describing the concentration in the effect compartment can be derived in terms of the parameters of the pharmacokinetic model and this rate constant (Sheiner *et al.*, 1979; Whiting, Holford & Sheiner, 1980). The effect compartment concentration is the same as the steady state plasma concen-

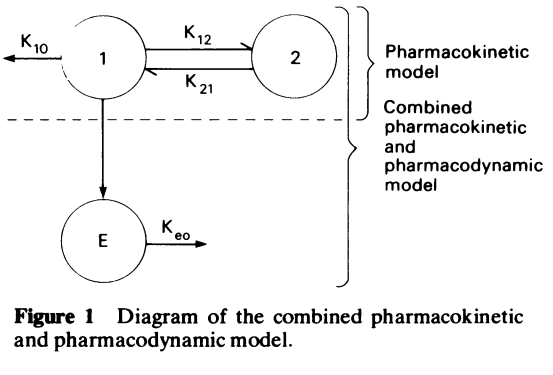

Figure 1 Diagram of the combined pharmacokinetic and pharmacodynamic model.

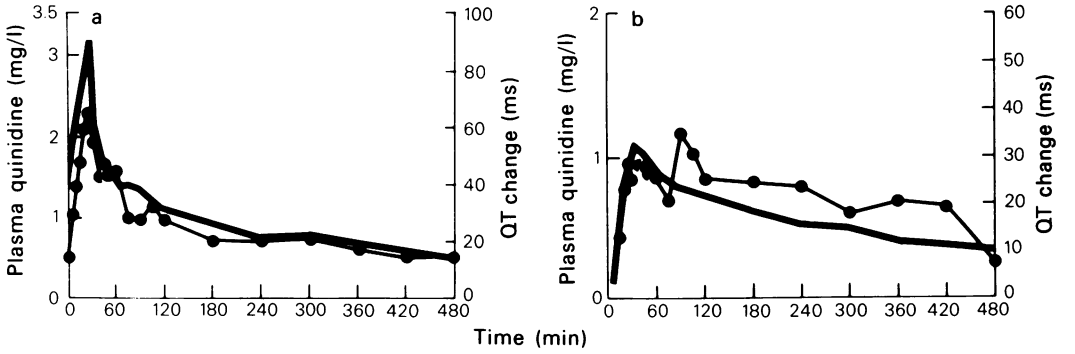

Figure 2 Change in quinidine plasma concentration (——) and rate-corrected QT interval (-•-) after a) i.v. and b) oral doses of quinidine. Each point is the mean of data from 10 subjects.

tration that would be associated with the observed effect. The ECG effect can then be fit to a linear pharmacodynamic model (Equations 1a and 1b) using the effect compartment concentration as CONC. The pharmacodynamic model is thus a function of three unknown parameters - - SLOPIV, INTIV, K_{eo}IV for i.v. doses, and SLOPOR, INTOR, K_{eo}OR for oral doses. By fitting i.v. and oral data sets simultaneously using the data from ten subjects, the effect of combining or eliminating parameters from the model could be tested. Parameter estimation was performed with a nonlinear least squares fitting program (Knott, 1979, Holford, 1978b). Models were compared using the F statistic (Neter & Wasserman, 1974).

Results

Pharmacokinetics

The pharmacokinetic model chosen to fit each individual's i.v. and oral plasma quinidine concentrations is described elsewhere (Guentert, Holford *et al.*, 1979). The pooled data obtained from the ten individuals *v.* time is shown in Figure 2.

Pharmacodynamics

The pooled QT interval changes during quinidine infusion and oral administration are shown in Figure 2. The time course of changes in heart rate and QT interval after placebo are shown in Figures 3 and 4. The abrupt change in heart rate after 200 min occurred following the mid-day meal.

The principal qualitative changes in the ECG with quinidine are illustrated in Figure 5. The major changes are in the duration of repolarization and the T wave complex. All phases of repolarization are prolonged except for the peak of the T wave, which remains fixed in relation to the onset of the Q wave. The T wave complex amplitude is reduced to about

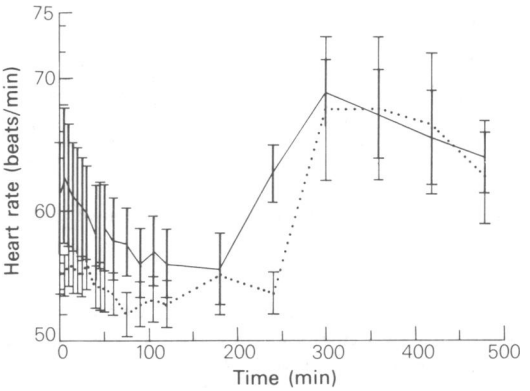

Figure 3 Change in heart rate after i.v. (·····) and oral (——) placebo over the first 500 min. Each point is the mean of nine subjects.

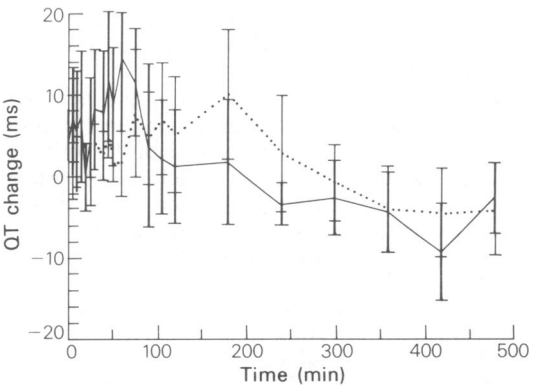

Figure 4 Change in QT interval after i.v. (·····) and oral (——) placebo over the first 500 min. Each point is the mean of nine subjects.

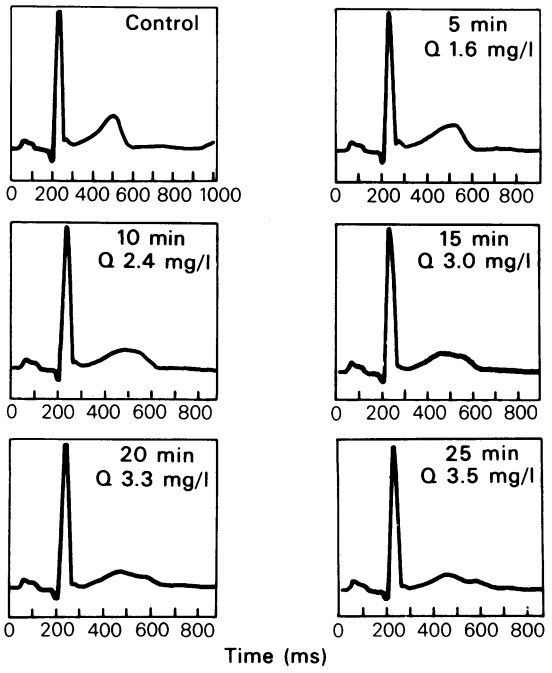

Figure 5 The effect of intravenous infusion of quinidine (Q) on the electrocardiogram.

one third at peak quinidine concentrations, and it is split into two distinct components. We call the interval from the onset of the Q wave to the peak of the first component the QT PEAK, and the interval to the peak of the second component the QT′ PEAK.

The area under the QT change *v* time curve was calculated for each individual from 0 to 24 h. The mean (s.d.) area under the curve for the ten volunteers after i.v. quinidine was 162 (110) ms h, after oral quinidine 162 (144) ms h, after i.v. placebo 11 (118) ms h and, after oral placebo 17 (119) ms h. The ratio of oral to i.v. under the curve after correction for placebo effects was 0.96.

One might expect that the relationship between QT interval change and change in quinidine concentration would be the same regardless of the route of drug administration; however, models incorporating different slope parameters for i.v. and oral dosing fit the data better than those with common slopes. There was no apparent requirement for different K_{eo} parameters with different routes of dosing.

The effect of quinidine on these and other ECG and systolic time intervals, determined by fitting the pooled data from all subjects for those effects to the pharmacodynamic model, is shown in Table 3. Figure 6 is a plot of the predicted QT change after i.v. and oral dosing against the predicted plasma quinidine concentration. Note the anti-clockwise hysteresis loop, which points to the need to model the delay between plasma concentration and effect, and also the leftward shift of the oral curve compared to the i.v. curve.

Table 1 Individual pharmacodynamic parameter estimates from measurements of QT interval change*

Subject	K_{eo} (min^{-1})	*SLOPIV* (*ms. mg* l^{-1})	*SLOPOR* (*ms. mg* l^{-1})	*R**2*
1	0.59	29.5	46.2	0.67
2	0.02	0.0	49.0	0.67
3	1.6	23.0	39.5	0.58
4	0.08	29.3	26.5	0.68
5	0.07	15.6	13.7	0.93
6	0.23	12.0	34.2	0.53
7	73.3	37.0	35.6	0.65
8	0.15	30.3	52.4	0.83
9	0.08	16.0	17.7	0.78
10	0.14	16.9	34.7	0.44

*Model is: Effect = Slope (Ce, mg/l) + Intercept, where Ce is concentration in the 'effect compartment' (see text).

Estimates of K_{eo}, SLOPIV and SLOPOR were made for each of the individual subjects using changes in QT and QT′ peak intervals as a measure of pharmacologic effect (Table 1). The inter-individual variability in these parameter estimates is composed of both true inter-individual differences and parameter estimation error. An estimate of the (pure) estimation error was obtained as the standard error of the parameters (Knott, 1979). An estimate of the (pure) inter-individual variance of the parameters was obtained by using an estimation, procedure incorporating a mixed effect model (Sheiner, Rosenberg & Marathe, 1977). The slope parameters (i.v. *v* oral) were different for both QT and QT′ peak ($P < 0.05$) changes, but within one route of administration similar values for both measures of effect were obtained for the slopes (Table 2). The estimate of K_{eo} was smaller for QT changes than for QT′ peak changes.

Discussion

The measurements of the ECG and systolic time intervals we made were corrected in two ways before analyzing them for the effect of quinidine.

First, the effect of heart rate on the intervals was assessed by predicting the interval based on the heart rate at the time of the measurement. The difference between the observed and predicted intervals was used as a first approximation to a measure of quinidine effect.

The difference between observed and predicted measurements was then corrected for the effect of time-related and other effects by subtracting the corresponding (rate-corrected) values found during

Table 2 Mean pharmacodynamic parameters and estimates of inter-individual variation using parameters from ten individuals derived from QT and QT' peak measures *

Parameter	*Mean*	*Standard error*	*Interindividual standard deviation*
K_{eo} (min^{-1})			
QT	0.08	0.01	0.03
QT' PEAK	0.16	0.04	0.06
SLOPIV ($ms.mg\ l^{-1}$)			
QT	20.3	0.5	8.9
QT' PEAK	21.6	4.8	13.4
SLOPOR ($ms.mg\ l^{-1}$)			
QT	33.5	2.0	9.4
QT' PEAK	33.5	3.7	9.4

* Estimates derived from parameters obtained from separately fitting data from each of ten individuals.

placebo administration. This last correction was of considerable magnitude, and emphasizes the need for adequate control studies when following physiologic variables over the course of a day. Without such studies, large time-related changes (Figures 3 and 4) in ECG and systolic time intervals on the placebo days due to intravenous infusion, nasogastric intubation and meals would have distorted our estimates of pharmacological effect, their magnitude and time course.

Within the range of concentrations studied, quinidine has no effect on systolic time intervals despite causing marked changes in the T wave complex. This is compatible with the lack of effect of quinidine on contractility in man when measured after cardiac denervation (Markiewicz, Winkle, Binetti, Kernoff & Harrison, 1976). In contrast, increases in cardiac output seen in normal subjects after quinidine (Ferrer, Harvey, Werkö, Dresdale, Cournand & Richards, 1948) are attributable to a drop in blood pressure following α-adrenoceptor blockade by the drug (Schmid, Nelson, Mark, Heistad & Abboud, 1974; Nelson, Schmid, Holmstein, Mark, Heistad & Abboud, 1974). The changes in blood pressure seen in our subjects were small and were fully compensated at peak quinidine concentrations. Any change in contractility or vascular tone was presumably too small to cause appreciable changes in systolic time intervals.

The use of a specific assay for quinidine and repeated measurements of ECG and systolic time intervals has allowed us to make new qualitative observations of the pharmacologic effects of quinidine in man. By observing the consecutive changes in repolarization produced by quinidine, we note that the usual description of the quinidine effect as the appearance of a U wave (e.g. Cheng *et al.*, 1956; Surawicz & Lasseter, 1972) is incompatible with current ECG nomenclature (AHA Committee on Electocardiography, 1975). The series of ECG tracings shown in Figure 5 shows the typical effects of quinidine observed in normal volunteers receiving the drug either by the i.v. or oral route. The small positive wave after the T wave in the control record is usually designated the U wave. We continue to use this terminology, but have had to name the secondary wave appearing in the presence of quinidine the T' wave to distinguish it from the T wave, which clearly precedes it, and the U wave, which follows it. We have chosen to call the interval from the beginning of the Q wave to the end of the T or T' wave (when present) the QT interval, and to the end of the U wave, the QU interval. Contrary to earlier descriptions, the characteristic effect of quinidine on the ECG is not to enhance the U wave, but to cause splitting of the T wave. Delay in repolarization of Purkinje fibers is typical of quinidine's electrophysiologic effects *in vitro* and may be responsible for the appearance of the T' wave *in vivo* (Watanabe, 1975). The changes in QT and QT' PEAK intervals parallel one another

Table 3 Parameter estimates for pharmacodynamic model for quinidine effects *

	K_{eo} (min^{-1})	*SLOPIV* ($ms.mg\ l^{-1}$)	*SLOPOR* ($ms.mg\ l^{-1}$)	r^2
PQ	10.8	3.1	4.5	0.39
QRS	0.13	3.7	3.9	0.64
QT' PEAK	0.20	18.9	35.5	0.96
QT	0.19	19.4	33.4	0.87
QS_2	5.7	1.3	4.7	0.18
LVET	0.57	10.1	5.0	0.46
PEP	2.8	−1.0	−7.3	0.20

* Model is: Effect = Slope (Ce, mg/l) + Intercept, where Ce is concentration in 'effect compartment', see text.

and are the most prominent effects of quinidine on ECG intervals.

The effect of quinidine on other ECG and STI's was evaluated using the combined pharmacokinetic-pharmacodynamic model. The lack of correlation of changes with drug concentration indicates the general lack of effect on these measurements and contrasts strongly with the marked effects on repolarization (Table 3). The positive slope parameters for the PQ and QRS measurements are compatible with a small increase in these intervals attributable to quinidine. Such changes are compatible with *in vitro* observations of a decrease in depolarization rate by quinidine (Chen, Gettes & Katzung, 1975) and QRS measurements in patients (Heissenbuttel *et al.*, 1970; Pifano, Feo, Fuenmayor & Lexague, 1979). We observed no consistent changes in systolic time intervals, in contrast to the findings of Fieldman, Beebe & Chow (1977), who claimed a 30 ms increase in QS_2 2 h after 400 mg of quinidine sulphate taken orally. Their observations were uncontrolled, and may be explained in part by time-related variation in QS_2. In agreement with our findings, a lack of quinidine effect on QS_2 or LVET has been seen by others in normal volunteers (Breithardt, Jochum, Kuhn and Seipel, 1978) and patients (Pifano *et al.*, 1979).

The quantitative effect of other anti-arrhythmic agents on the ECG has been related to drug concentration (procainamide, Galeazzi, Benet & Sheiner, 1976; disopyramide, Whiting *et al.*, 1980; lorcainide, Meinertz, Kasper, Kersting, Just, Bechtold & Jähnchen, 1979). After intravenous dosing, plots of drug concentration against QT or QRS change have all shown anti-clockwise loops ('hysteresis') characteristic of a time delay between ECG effect and plasma concentration (e.g., Figure 6). The delay is particularly prominent when drug concentration is changing rapidly, suggesting that disequilibrium between plasma and effect site (biophase) concentration is responsible.

The delay in achievement of effect may arise for several reasons: e.g., time taken for quinidine to reach its active site in the heart, time taken for biochemical changes induced by quinidine to affect the heart. We have modelled this process by postulating equilibration of plasma and biophase concentrations through a first-order rate mechanism. Under this model, given a sudden stepwise change in plasma concentration to a new constant value, the biophase concentration will approach a new equilibrium value in a gradual fashion characterized by a half-life inversely proportional to a single rate constant (K_{eo}, Figure 1). The new biophase concentration, and thus pharmacologic effect, will approach equilibrium in about four such half-times.

The equilibration half-time estimated by this model includes all factors contributing to the delay, whether they arise from drug penetration to the active site or activation of cellular processes leading to the ultimate effect. The half-time for achievement of QT changes caused by quinidine is about eight minutes (Table 3). This would predict that the QT interval will reach its equilibrium value in about 30 min after a change in the steady state concentration of quinidine in plasma. A similar model has been applied to concentration-effect relationships of procainamide and disopyramide. The equilibration rate constant corresponds to a half-time of 6 min for procainamide (Galeazzi *et al.*, 1976) and 1.5 min for disopyramide (Whiting *et al.*, 1980).

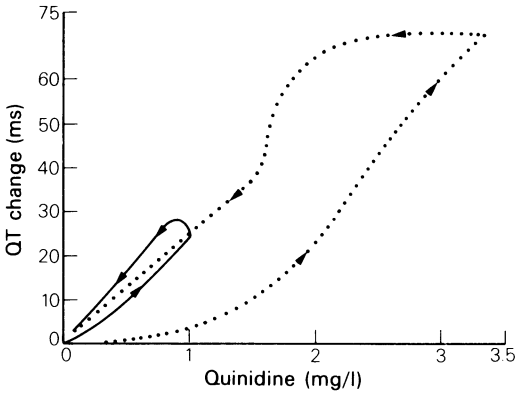

Figure 6 Change in QT interval predicted by the combined pharmacokinetic and pharmacodynamic model after i.v. (·····) and oral (——) administration of quinidine. Relationship to plasma concentration predicted from pharmacokinetic model.

The effect-compartment 'concentrations' are equivalent to the steady state plasma concentrations causing the same effect. Plasma concentrations are modelled by standard two-compartment pharmacokinetic models (Guentert, Holford *et al.*, 1979; Ueda & Dzindzio, 1978). The relationship between effect-compartment concentration and effect is evaluated using a simple linear pharmacodynamic model (Equations 1a and 1b). More complex pharmacodynamic models have been proposed (Wagner, 1968) and tested (Sheiner *et al.*, 1979), but these models require estimation of maximal pharmacological effect. When the effect of quinidine is plotted against the effect-compartment concentration predicted by the combined pharmacokinetic and pharmacodynamic model (Figure 7), the simple linear relationship appears to be adequate. There is no suggestion that a maximum effect is being reached, and the effect-intercept is quite close to zero at zero predicted effect-compartment concentration. This is in contrast to the observations of Kramer, Kolibash, Lewis, Bathala, Visconti & Reuning (1979), who

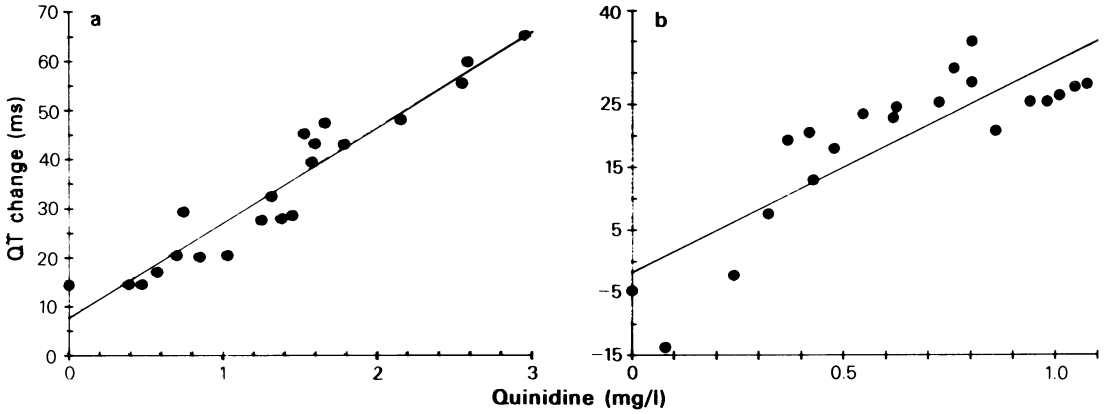

Figure 7 a) Change in QT interval observed and predicted by the combined model after i.v. infusion of quinidine. b) Change in QT interval observed and predicted by the combined model after oral administration of quinidine.

found that a simple linear model was not adequate to describe changes in QS_2 produced by digoxin. They based this conclusion upon the relatively large effect predicted by the model when no drug was predicted at the effect site.

By testing a variety of models using the simple linear relationship, it became clear that the apparent proportionality between plasma quinidine concentration and ECG effect was greater after oral dosing. The mean oral slope of QT interval prolongation is 34 ms. mg l^{-1}, compared with 20 ms. mg l^{-1} after an i.v. dose (Table 2 and Figure 6). This difference could not be explained by postulating different equilibration constants.

Quinidine is extensively metabolized after oral administration (up to 30% during absorption) (Guentert, Holford *et al.*, 1979) and levels of some of the metabolites after oral dosing to steady state may equal or exceed quinidine in serum water (Drayer *et al.*, 1978). A new metabolite of quinidine, an *N*-oxide, was found in the plasma of our subjects (Guentert *et al.*, 1978), and, in some, reached 30% of simultaneous quinidine concentrations after oral dosing. Much smaller concentrations of known metabolites are seen after i.v. dosing due to lack of first-pass metabolism by this route. We believe that the apparent change in sensitivity to quinidine after an oral dose, when compared to an i.v. dose, is attributable to one or more active metabolites of quinidine that are present in higher concentrations because of first-pass metabolism of quinidine during absorption. More than 35% of the QT and QT′ peak changes seen after an oral dose cannot be explained by the plasma quinidine concentrations when activity is estimated from the i.v. data.

The increased apparent activity after oral doses of quinidine is confirmed by the estimates of area under the effect v. time curve for the QT interval. The oral bioavailability of quinidine in these subjects was 70% (Guentert *et al.*, 1979), yet the pharmacodynamic 'bioavailability' was 96%. The pharmacodynamic 'bioavailability' suggests that the oral activity of quinidine is 37% greater than the effect seen after an i.v. dose. This agrees very closely with the estimates made from comparison of the slopes of the explicit pharmacodynamic model (35%). If a linear pharmacodynamic model for quinidine effect on the heart is accepted (Figure 7), then we would predict that single oral and i.v. doses of quinidine have the same total effect, even though only 70% of the oral dose reaches the systemic circulation.

Activity of three quinidine metabolites in preventing arrhythmias in animal models has been reported (Drayer *et al.*, 1978). Huffman, Hignite & Tschanz (1977) were unable to demonstrate an effect of the known metabolite 3-OH-quinidine on the QT interval at steady state after oral dosing in man, but the effect of an intravenous dose of quinidine was not tested and our study does not rule out a contribution of this metabolite to the ECG effects seen after quinidine.

We conclude that changes in repolarization of the ECG are sensitive indicators of quinidine-like activity in the plasma. The nature of the changes in normal volunteers after single doses is easily defined, and may be a useful index of quinidine's effect on the myocardium. The magnitude of these changes may be of potential value in predicting desired antiarrhythmic activity and they could, in this regard, even be superior to measurements of quinidine concentration alone. Metabolites of quinidine appear to be pharmacologi-

cally active in man, and may contribute to the antiarrhythmic activity of the drug.

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All computation in this work was performed using the PROPHET system except for use of NONMEM, which was used on a CDC-7600 computer at Lawrence Berkeley Laboratories, Berkeley, California.

The PROPHET system is a specialized computer resource developed by the Chemical/Biological Information Handling Program of the National Institutes of Health (PROPHET, 1974).

Human studies were performed in the General Clinical Research Center at Moffitt Hospital, University of California Medical Center.

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