CORRELATION BETWEEN PLASMA QUINIDINE AND CARDIAC EFFECT

I.R. EDWARDS & B.W. HANCOCK

Academic Division of Medicine, Section of Therapeutics, Royal Infirmary, Sheffield S6 3DA

R. SAYNOR

Cardio-Thoracic Unit, Northern General Hospital, Sheffield S5 7AU

1 The relationship between serum quinidine levels and rate-corrected QT (QTc) interval after administration of single identical doses of quinidine was assessed. Quinidine concentrations were determined by a modification of Hamfelt & Malers' (1963) method. The significance and clinical application of our findings is discussed.

2 Individual responses (both in quinidine concentration and QTc prolongation) were variable, though the variation was no greater with QTc prolongation response than with serum quinidine levels. A significant peak in QTc prolongation occurred after quinidine administration and this was not accompanied by a similar peak in quinidine levels. There was some correlation ($r = 0.53$) between serum quinidine levels and QTc interval but a better correlation was found between rate of rise of quinidine concentration and QTc prolongation ($r = 0.87$).

3 One individual showed marked QTc prolongation with slow rate of rise of quinidine levels. Red cell quinidine levels were lower in this individual and he may be showing increased myocardial sensitivity to quinidine.

Introduction

Quinidine has long been recognized as a powerful anti-arrhythmic drug but its use has been limited by adverse effects, both idiosyncratic and because of the small therapeutic index. Blood quinidine levels may help control quinidine therapy but serious reactions still occur and a more effective means of control is yet to be found. The purpose of our study was to assess possible correlations between dose and serum levels of quinidine and cardiac effect, as judged by the rate corrected QT interval (QTc).

Methods

Seven healthy volunteers underwent the study. A test dose (equivalent to quinidine sulphate BP, 200 mg) was first given to each subject to exclude hypersensitivity. Several days later, after an 8 h fast, a resting ECG was recorded and blood taken for serum quinidine estimation. Quinidine bisulphate (500 mg), as slow release Kinidin Durules, Astra Chemicals Ltd (equivalent to quinidine sulphate BP, 400 mg) was then given and blood samples were taken after 0.5, 1, 2, 3, 4, 6, 8 and 24 hours. ECGs were recorded at the time of taking of each blood sample. The QT interval

(from the onset of the Q wave to the end of the T wave) was measured blind in seconds by two, and where possible three, observers from standard lead II. Correction for heart rate was made using the nomogram devised by Kissin, Schwarzschild & Bakst (1948). If a 'U' wave occurred, the maximum downslope of the T wave was extrapolated to the isoelectric line.

Quinidine levels ($\mu\text{g/ml}$) were determined by a modification of the photofluorometric method described by Hamfelt & Malers (1963). After removal of proteins by extraction with alcohol-acetone, a first fluorescent determination is made on the clear serum (a neutral medium later acidified by acetic acid). This gives the natural fluorescence of the serum. A second determination, after acidification with sulphuric acid, gives the total fluorescence of the serum. The difference between these determinations gives the fluorescence of quinidine and hydroxylated metabolites in the sample. Initially dilutions of standard serum are processed to obtain a calibration graph and these values must be periodically rechecked to ensure consistent and reproducible results.

The technique is as follows. Into a clean centrifuge tube distilled water (0.2 ml), serum (0.2 ml) and ethyl alcohol-acetone (equal

Fig. 1 Serum quinidine concentration against rate corrected QT interval, (QTc) in normal volunteers.

volumes) mixture (4.6 ml) are added. The well mixed solution is then centrifuged at 2000 rev/min for 10 min and the filtrate separated. Fluorometric measurements are made using an EEL fluorimeter. This has three compartments for small matching tubes containing blank serum, standard serum and unknown serum. The apparatus is first calibrated to zero with acidified blank serum and to 100 with an extract of standard serum solution containing quinidine (20 µg/ml) extracted as above and to which have been added two drops of glacial acetic acid and two drops of 20% sulphuric acid. The fluorescence of the serum sample is first determined directly after the addition of two drops of acetic acid and again after the addition of two drops of sulphuric acid. The difference between these determinations is directly proportional to the serum quinidine which is derived from the standard calibration curve.

The accuracy of this method is that of the Hamfelt & Malers (1963) method, the mean recovery of quinidine being 98% and variation coefficient (expressed as % mean value) being 5.6. Values for rate corrected QT interval (QTc) prolongation, serum quinidine and rate of rise of serum quinidine were correlated and the statistical significance of the results assessed.

Results

Only one subject complained of an adverse reaction to quinidine (mild colic).

Figure 1 shows the graph of QTc interval against serum quinidine level. The graph confirms a positive correlation ($r = 0.53$) between these two parameters but the scatter is wide. The upper limit of normal for the QTc interval is usually regarded as 0.42 seconds.

Figure 2 shows the graph of mean ($\pm$ s.d.) prolongation of QTc above resting values and mean ($\pm$ s.d.) serum quinidine levels against a time scale. There is a wide variation in both QTc response and quinidine levels but the correlation between these parameters is confirmed. The graph shows a rapid rise of QTc prolongation with a peak which then falls to a plateau of about the same slope as that of the quinidine levels. No overshoot occurs with quinidine levels. The difference between peak and plateau values for QTc prolongation is significant ($P < 0.01$ —paired t test), there being no significant difference between serum quinidine values at the same time intervals ($P > 0.4$). The peak in QTc prolongation was seen in each subject studied at between 5 and 7 hours.

The findings in Fig. 2 suggested that the rate of rise of quinidine concentration may be important in determining the maximum QTc response. Figure 3 shows the graph of rate of rise of serum quinidine ($\mu\text{g}/3\text{ h}$) against maximum QTc prolongation above resting values in each subject and shows a good positive correlation ($r = 0.87$). Figure 4 shows the same graph as in Fig. 3 but includes the one exception to the positive correlation—individual A who showed a marked increase in QTc prolongation with a slow rate of rise of quinidine concentration. At this stage, it was decided to repeat the study measuring serum and red cell quinidine concentrations on subject A and also on subject B who had marked QTc prolongation with rapid rate of rise of serum quinidine, in an effort to explain the difference between them. The values for serum quinidine and QTc prolongation were not significantly different from values obtained in the first studies on these individuals.

Figure 5 is the graph showing serum and red cell levels of quinidine against a time scale in

Fig. 2 Mean rate corrected QT prolongation (QTc) and serum quinidine concentration ($\pm$ s.d.) against time in seven normal volunteers. * Difference significant, $P < 0.01$.

Fig. 3 Maximum rate corrected QT prolongation (QTc max) against rate of rise of serum quinidine concentration in each normal volunteer ($r = 0.87$).

Fig. 4 Maximum rate corrected QT prolongation (QTc max) against rate of rise of serum quinidine concentration, as shown in Fig. 3, including values for two studies on subjects A (○) and B (Δ).

Fig. 5 Serum (■, □) and red cell (●, ○) quinidine concentrations against time for subjects A (●, ■, QTc max 0.08 s) and B (○, □, QTc max 0.075 s).

subjects A and B. The differing rates of rise were confirmed and the eventual red cell levels of quinidine were lower with the slower rate of rise of serum quinidine in subject A than in subject B.

Discussion

The cardiac effects of quinidine are well known but the detailed mechanism underlying these effects has not yet been elucidated. Myocardial cell membrane permeability is reduced, possibly

through binding of quinidine to membrane lipoproteins thus impairing the outflow of intracellular potassium with inhibition of depolarization. The formation of quinidine chelates (e.g., with calcium) may inhibit cyclic AMP formation resulting in reduction of oxidative metabolism and depression of myocardial contraction (Conn, 1964). As a result of such biochemical changes electrical conduction, impulse formation and vagal tone are depressed, the refractory period prolonged and myocardial contractility reduced. The ECG changes are therefore of PR, QRS and QT prolongation with ST depression and T wave flattening.

It has been shown that myocardial toxicity correlates better with serum levels than with dosage of quinidine (Hamfelt & Malers, 1963). The therapeutic range for quinidine concentration is about 3-7 $\mu\text{g/ml}$ using our technique. Although toxicity is usually associated with concentrations above 8 $\mu\text{g/ml}$, fatal reactions have occurred after small initial oral doses while concentrations as high as 20 $\mu\text{g/ml}$ have been tolerated in other individuals (Prescott, 1972). Such variations are understandable since many factors, such as intestinal absorption, plasma albumin binding, potassium status, hepatic degradation and renal excretion, may influence the actual levels of quinidine available to the myocardial cell (Conn, 1964; Hartel & Frick, 1971; Prescott, 1972; Kessler, Lowenthal, Warner, Gibson, Briggs & Reidenberg, 1974).

Our study confirms the wide variation in individual responses to quinidine (Figs. 1 and 2). The lack of a better correlation between serum quinidine and QTc interval may be because our method measured both quinidine and its less cardio-active metabolites, those samples taken later in each study containing increasing proportions of metabolites.

The variation in QTc prolongation (Fig. 2) was certainly no greater than that found with serum quinidine levels, the former being by far the simpler of these parameters to measure. The rapid rate of rise of serum quinidine concentration and QTc prolongation after quinidine administration is associated with an overshoot of QTc prolongation at a time when serum quinidine levels are stabilizing (Fig. 2). Such peaks of QTc prolongation may be dangerous if excessive, or cumulative if dose schedules are not regularized so that the drug should be given at regular time

intervals rather than just three times daily or four times daily as commonly prescribed. Figure 2 also shows a decline in cardiac effect before quinidine levels start to fall. This finding may also be explained by the later assays measuring increasing proportions of less cardio-active metabolites. The good correlation between rate of rise of serum quinidine and maximum QTc prolongation after quinidine administration (Fig. 3) becomes clinically important particularly in relationship to meals. Quinidine taken on an empty stomach will be absorbed more rapidly than if taken after meals, thus enhancing the cardiac effect. The rapid rise with subsequent peak of QTc prolongation is obviously lessened by the use of sustained release preparations of quinidine.

In the subjects (A and B) with marked QT prolongation yet differing rates of rise of quinidine levels (Fig. 5), eventual red cell quinidine levels were lower in the individual A with the slower rate of rise. It has been shown that red cell quinidine levels correlate well with those in myocardial tissue (Härtel & Frick, 1971) and it is possible that a result such as that observed in subject A may indicate increased myocardial sensitivity to the action of quinidine.

The reproducibility of results in the two studies on subjects A and B indicates that whilst the responses of different individuals to quinidine are variable, the response within each individual seems constant.

Our study indicates that the measurement of the QTc prolongation is probably as reliable as serum quinidine determination for controlling therapy, though responses vary. The measurement is simple, non time-consuming and enables immediate decisions to be made on changes in therapy.

In patients being considered for quinidine therapy, an evaluation such as we have described with serial quinidine levels and simultaneous QTc measurements after a single dose of quinidine may bring to notice those who tend to have rapid rates of absorption and, therefore, increased cardiac effect and those who may have increased myocardial sensitivity to quinidine with lower rates of rise of quinidine levels and marked QT prolongation.

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ADDENDUM

Since we have completed this study, we have successfully applied our findings in patients with paroxysmal arrhythmias started on quinidine. Their results agreed well with those obtained in our normal volunteers.