BIOAVAILABILITY OF QUINIDINE IN CONGESTIVE HEART FAILURE

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1 The oral bioavailability of quinidine was evaluated in eight patients with moderate to severe congestive heart failure. Each patient was given a 400 mg dose of quinidine gluconate by intravenous infusion and orally in solution. Serial plasma samples and total urine for drug analysis were collected for 24 and 48 h after drug administration, respectively.

2 When compared to control cardiac patients, the rate of quinidine absorption was slower in the heart failure patients. The mean value for the apparent absorption half-life and time to achieve peak plasma quinidine concentration was 38 ± 18 min and 2.4 ± 1.5 h, respectively. The corresponding values observed in the control subjects were 18 ± 6 min and 1.0 ± 0.6 h.

3 The extent of quinidine absorption when evaluated by the AUC and urinary excretion methods was about 72% of the administered dose in the congestive heart failure patients. This value was similar to the extent of quinidine absorption (approximately 73%) observed in the control subjects.

4 A reduction in the plasma clearance rate and apparent volume of distribution for quinidine was observed in the congestive heart failure patients.

5 When compared with non-heart failure cardiac patients, the results of this study suggest that patients with congestive heart failure may require smaller oral quinidine dosages to achieve therapeutic drug concentrations in the plasma or serum.

Introduction

As a result of pathological changes of the intestinal wall (primarily oedema), reduced splanchnic blood flow, decreased gastrointestinal motility and other possible factors (Benet, Greither & Meister, 1976; Benowitz & Meister, 1976), oral drug absorption in patients with congestive heart failure can be reduced quite markedly. This has been shown for digoxin (Oliver, Tazman & Frederickson, 1973), hydrochlorothiazide (Anderson, Brettell & Aikawa, 1961; Beermann & Groschinsky-Grind, 1979) and metolazone (Tilstone, Dargie, Dargie, Morgan & Kennedy, 1974) in which the rate and/or extent of gastrointestinal absorption of these drugs were diminished in the heart failure patient.

Crouthamel (1974, 1975), analyzing the data of Bellet, Roman & Boza (1971), has suggested that the rate and extent of oral quinidine absorption is also decreased in patients with congestive heart failure. When compared to normal subjects, heart failure patients appeared to absorb only about one-half as much quinidine and at approximately one-third the rate. These conclusions were based, however, on

plasma concentration-time curves constructed from only four data points in a 24-h period, extrapolated urinary quinidine excretion data and the use of a nonspecific assay for quinidine in the original study.

In a previous study (Ueda & Dzindzio, 1978), we showed that the total body clearance rate of quinidine is reduced in patients with congestive heart failure. This was associated with a smaller apparent volume of distribution for quinidine in patients with this disease.

The therapeutic index of quinidine is relatively low. Additionally, the absolute bioavailability of orally administered quinidine is about 70% of the dose given and has been reported to vary substantially between patients (Ueda, Williamson & Dzindzio, 1976; Guentert, Holford, Coates, Upton & Riegelman, 1979). Thus, a further reduction in oral quinidine bioavailability in patients with congestive heart failure as suggested by Crouthamel (1974, 1975) would significantly influence the antiarrhythmic effectiveness of the drug after oral administration and the use of the drug clinically. For these reasons, quinidine absorption in patients with arrhythmias is an

Table 1 Patient population

Patient	Sex	Age (years)	Weight (kg)	AHA functional class*	Left ventricular ejection fraction echo or ventriculogram
1	M	74	82	III	35%
2	M	53	69	IV	10%
3	F	61	68	III	30%
4	M	79	55	III	32%
5	M	42	86	III	24%
6	F	47	56	III	36%
7	F	65	57	III	25%
8	F	61	78	II	35%

* At time of investigation.

important factor influencing the antiarrhythmic effectiveness of the drug. The purpose of this study was, therefore, to investigate the oral absorption characteristics of quinidine in congestive heart failure using extensive sampling and a specific assay procedure.

Methods

Patients

Using the following Institutional Review Board approved protocol and after the patients gave their informed consent, eight patients (four males and four females) with moderate to severe congestive heart failure (AHA functional class II–IV) at the time of the investigation were studied (Table 1). Their mean age was 60 years (range: 42–79). All had atrial and/or ventricular arrhythmias that warranted antiarrhythmic therapy. Historically, all patients noted symptoms of dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea and pedal edema. Pertinent physical findings included jugular distension, peripheral edema, bibasal rales and third heart sounds.

Roentgenographic findings diagnostic of heart failure (cardiomegaly and signs of pulmonary venous hypertension), cardiac catheterization and/or echocardiography supported the clinical impression of heart failure in each case. Since all subjects were admitted to University Hospital in uncompensated severe congestive heart failure, initiation of the individual studies was delayed until medical management brought them into an acceptable degree of compensation. With the exception of Patient 4 whose creatinine clearance was 21 ml/min, all had normal hepatic and renal functions as determined by standard clinical laboratory tests. During the study, all patients were also taking digitalis preparations, diuretics and potassium supplements.

The controls consisted of ten cardiac patients (six

males and four females) who also required antiarrhythmic therapy. They ranged in age from 40 to 78 years (mean: 54 ± 12) and weighed between 45 and 88 kg (mean: 69 ± 15). All had normal hepatic and renal functions and none exhibited evidence of clinical heart failure or intestinal malabsorption. These patients were taking no other cardiovascular drugs.

Quinidine administration

Single 400 mg doses of quinidine gluconate were given to each patient by intravenous infusion and as an oral solution in a completely random fashion. Both doses were prepared from the same source and in the same manner as discussed below. A period of 72 h separated the two drug treatments. Plasma and urine samples for drug analysis were collected and stored as previously described (Ueda *et al.*, 1976).

For the intravenous dose, 6 ml quinidine gluconate 80 mg/ml injection was diluted with 42 ml of 5% dextrose in water in a 60 ml disposable syringe. After mixing, 40 ml was given at a constant rate over 22 min with an infusion pump (Harvard Apparatus Co.) through a superficial arm vein. Serial blood samples were drawn from the opposite arm at 0 min, during the infusion at 5 min intervals, at the time drug infusion was terminated and 5, 10, 15 and 20 min and 1, 2, 4, 6, 8, 10, 12 and 24 h post infusion. Systolic and diastolic blood pressures were monitored at 5-min intervals during quinidine infusion and for 20 to 30 min after cessation of the infusion.

The oral quinidine doses, 400 mg/40 ml, were given on an empty stomach after an overnight fast. The dose cups were rinsed with 90 ml water and the rinsings were also given. Serial blood specimens for quinidine analysis were drawn at 0, 15, 30, 45, 60 and 90 min and at 2, 3, 4, 5, 6, 8, 10, 12 and 24 h post dose. Food was permitted 3 h after drug ingestion.

With both doses, control urine specimens were obtained and all spontaneously voided urine collected for the 48-h period following drug administration.

Aliquots of each drug solution were also assayed to verify the amount of quinidine given.

Quinidine assay

Quinidine concentrations in the collected samples were determined with the thin layer chromatography-fluorometric assay procedure previously described (Ueda *et al.*, 1976). The method is specific for quinidine (Ueda, Ballard & Rowland, 1977). Dihydroquinidine and other benzene extractable species (e.g., metabolites) are effectively separated from intact drug.

Data analysis

The rate of quinidine absorption was evaluated by fitting the plasma concentration-time data obtained after the oral doses to Equation 1 or 2 using the nonlinear least-squares regression program NONLIN (Metzler, Elfring & McEwen, 1974) and IBM 360/65 computer.

$$C_p = B[e^{-\beta(t-t')} - e^{-k_a(t-t')}] \quad (1)$$

$$C_p = -(A + B)e^{-k_a(t-t')} + Ae^{-\alpha(t-t')} + Be^{\beta(t-t')} \quad (2)$$

C_p is the plasma quinidine concentration at time t after the dose, t' is the lag time before absorption, A and B are ordinate intercepts for the two dispositional processes, k_a is the apparent first-order absorption rate constant, and α and β are first-order disposition rate constants. Initial estimates of A , B , k_a , α and β were obtained using the computer program CSTRIP (Sedman & Wagner, 1976). A one-minute estimate for t' was used. The equation of best fit was determined by the F test described by Boxenbaum, Riegelman & Elashoff (1974) and Runs Test (Weinberg & Schumaker, 1974) for the randomness of distribution of the experimental data points about the best-fit curve.

The amount of quinidine reaching the systemic circulation after the oral dose or extent of drug absorption was evaluated by determining the ratio of the total areas under the plasma concentration-time curves (AUC) obtained after the oral and intravenous doses according to the relationship,

$$F_{AUC} = \frac{(AUC/Dose)_{oral}}{(AUC/Dose)_{i.v.}} \quad (3)$$

where F_{AUC} is the fraction of the oral dose that reached the systemic circulation. The values of AUC were determined by calculating the area from 0 to 24 h with the trapezoid rule and estimating the area from 24 h to infinity by dividing the 24-h plasma concentration by the terminal first-order rate constant, β .

The extent of oral quinidine absorption was also assessed by comparing the amount of quinidine excreted in the urine in 48 h (Au^{48}) after drug administration by the two routes according to:

$$F_{Au^{48}} = \frac{(Au^{48}/Dose)_{oral}}{(Au^{48}/Dose)_{i.v.}} \quad (4)$$

The results are expressed as the mean $\pm$ s.d. The Student's t -test was used to evaluate the significance of the observed differences.

Results

The results of the oral absorption studies are summarized in Table 2. In seven of the patients with congestive heart failure and eight of the control subjects, the plasma concentration-time curves obtained with the oral quinidine doses were described by Equation 1. In all patients, the lag time varied from 0 to 10 min (1.2 ± 2.2) and with no difference between the two patient groups. The mean plasma quinidine concentration-time curves obtained with the oral doses in the two groups of patients are shown in Figure 1.

Peak plasma concentrations of quinidine ranging from 0.65 to 2.29 $\mu\text{g/ml}$ (1.31 ± 0.56) were observed in the heart failure patients at 141 ± 89 min (range: 45–258) after drug ingestion. The values of k_a and corresponding apparent absorption half-life were 0.011 to 0.057 min^{-1} (0.024 ± 0.015) and 12 to 63 min (38 ± 18), respectively. $T_{1/2\beta}$ varied between 4.84 and 8.90 h (6.98 ± 1.29).

The ratio of AUC obtained after the oral and intra-

Figure 1 Mean plasma quinidine concentration-time curves obtained after oral doses of 400 mg quinidine gluconate in cardiac patients with (●) and without (▲) congestive heart failure.

Table 2 Mean $\pm$ s.d. plasma and urine quinidine data after oral and intravenous drug administration in congestive heart failure and control patients

Patients	Intravenous			Oral			Bioavailability	
	$T_{1/2\beta}$ (h)	fe^*	Peak plasma concentration ($\mu\text{g/ml}$)	Peak time (min)	k_a (min^{-1})	$T_{1/2a}$ (min)	F_{AUC}	F_{Ait}^{**}
CHF	6.73 ± 1.69	0.15 ± 0.06	1.31 ± 0.56	141 ± 89	0.024 ± 0.015	38.2 ± 18.3	0.74 ± 0.13	0.72 ± 0.09
Controls	6.23 ± 1.53	0.17 ± 0.05	1.14 ± 0.35	62 ± 35	0.044 ± 0.019	18.0 ± 6.4	0.74 ± 0.15	0.70 [†] ± 0.14
Significance level	NS§	NS	NS	$P < 0.025$	$P < 0.01$	$P < 0.01$	NS	NS

* fe = fraction of dose in urine.† $n = 7$; Complete 48h urine samples were not available for three patients.

§ Not significant at 0.05 level.

venous quinidine doses ranged from 0.54 to 0.92 (0.74 ± 0.13). F assessed by the urinary drug excretion method was 0.72 ± 0.09 (0.57 to 0.83) and in excellent agreement with the area estimate of drug absorption ($t_{\text{paired}} = 0.50$; $df = 7$). In these patients, 11 ± 4 and $15 \pm 6\%$ of the oral and intravenous doses were excreted in the urine as intact drug after 48 h, respectively.

The maximum plasma quinidine concentrations reached in the control cardiac patients of 0.54 to 1.44 $\mu\text{g/ml}$ (1.14 ± 0.35) were similar to the peak drug concentrations seen in the congestive heart failure patients. The time at which these peak concentrations (t_{max}) were reached of 62 ± 35 min, however, was significantly earlier in the non-heart failure subjects ($P < 0.025$).

The apparent first-order rate constant for quinidine absorption in the non-heart failure patients ranged from 0.022 to 0.089 min^{-1} (0.044 ± 0.019) and were significantly larger than the values of k_a observed in the patients with congestive heart failure ($P < 0.01$). Correspondingly, the apparent absorption half-life which varied between 8 and 31 min (18 ± 6) was significantly shorter in the control subjects. These observations coupled with the larger values for t_{max} showed that the rate of quinidine absorption was diminished in the presence of congestive heart failure.

The extent of quinidine absorption determined by comparing the areas under the oral and intravenous plasma concentration-time curves indicated that $74 \pm 15\%$ of the oral doses reached the systemic circulation in the non-heart failure patients. By the urinary drug excretion method, F was 0.70 ± 0.14 in these patients. From these results, it was observed that oral quinidine availability was the same in the presence or absence of congestive heart failure.

The terminal half-life in the control subjects after the oral dose was 6.55 ± 2.07 h.

From the intravenous studies, the plasma clearance rate (Cl) and apparent volume of distribution (V_d) for quinidine were determined for each patient with Equations 5 and 6, respectively.

$$Cl = \text{Dose}/AUC \quad (5)$$

$$V_d = Cl/\beta \quad (6)$$

Quinidine clearance in this study in patients with and without congestive heart failure was 3.51 ± 1.02 and 5.20 ± 1.31 $\text{ml min}^{-1} \text{kg}^{-1}$, respectively. It was also observed that V_d was smaller in the heart failure patients (1.88 ± 0.53 v 2.87 ± 1.12 l/kg). These differences in Cl and V_d between the two groups of patients were significant at the 0.05 level.

Discussion

A number of studies have shown that drug absorption and disposition can be markedly different in patients

with congestive heart failure (Benet *et al.*, 1976; Benowitz & Meister, 1976; Thomson, Melmon, Richardson, Cohn, Steinbrunn, Cudihee & Rowland, 1973). The precise mechanisms behind these differences, however, are not clearly understood. Presumably, altered haemodynamics as a result of a reduction in cardiac output is a major underlying factor. A reduction in hepatic blood flow has been shown to affect the removal rates of lignocaine and propranolol, antiarrhythmic agents whose clearances by the liver are dependent on the rate of blood flow to this organ (Boyes, Adams & Duce, 1970; Stenson, Constantino & Harrison, 1971; Nies, Evans & Shand, 1973; Kornhauser, Wood, Vestal, Wilkinson, Branch & Shand, 1978). The effects of decreased intestinal blood flow on reducing the rate of gastrointestinal drug absorption has recently been discussed by Benet *et al.* (1976).

In this study, the rate of quinidine absorption in patients with congestive heart failure was about 50% of the absorption rate observed in the non-heart failure patients (Table 2). Crouthamel (1975) noted a similar reduction in the rate at which quinidine was absorbed by the congestive heart failure patient and suggested that the disease impairs drug absorption by decreasing splanchnic blood flow. Working on this assumption, Kates & Blanford (1979) investigated the effects of propranolol on the absorption and disposition of orally administered quinidine. Since propranolol alters splanchnic blood flow and thereby decreases gastrointestinal perfusion, they hypothesized that the coadministration of propranolol might serve as a model for quinidine absorption and disposition in congestive heart failure. The results of their study showed, however, that propranolol had little effect on the absorption and disposition of quinidine. In fact, it appeared to promote rather than retard the rate of quinidine absorption.

In light of the findings of Kates & Blanford (1979), although a reduction in splanchnic blood flow may contribute to the slower rate of quinidine absorption observed in the congestive heart failure patients, it does not appear to be the most dominant factor. As an alternative explanation, impaired transfer of drug across an edematous bowel, delayed gastric emptying, and/or decreased gastrointestinal motility are all possible causes (Benet *et al.*, 1976).

In the patients with congestive heart failure, about 74% of the orally administered quinidine doses reached the systemic circulation. This value for the absolute bioavailability of quinidine in congestive heart failure was nearly identical to the extent of quinidine absorption observed in the non-heart failure subjects and was indicative of the apparent lack of effect by congestive heart failure on the amount of drug absorbed from the gastro-intestinal tract.

Analyzing the urine quinidine excretion data of

Bellet *et al.* (1971), Crouthamel (1974, 1975) suggested that patients in congestive heart failure absorb a significantly smaller fraction (about 50%) of an orally administered dose of quinidine when compared with normal subjects. The present study, however, did not detect any difference in the extent of quinidine absorption between patients with and without congestive heart failure. The explanation for these divergent observations is most likely related to the differences in renal status of the patients in the two studies. In the present investigation, all but one patient had normal renal function. The heart failure patients in the Bellet *et al.* (1971) study, on the other hand, had creatinine clearance rates that were approximately 50% of the clearance values found in the normal subjects. Thus, this latter observation could have accounted for the reduction in 24-h urinary quinidine output (and therefore the reduced quinidine availability reported by Crouthamel 1974, 1975) by the heart failure patients in the Bellet study (1971).

The incomplete availability of the oral quinidine doses seen in this study and by others (Conrad, Molk & Chidsey, 1977; Greenblatt, Pfeifer, Ochs, Franke, MacLaughlin, Smith & Koch-Weser, 1977; Guentert *et al.*, 1979) in patients with no evidence of congestive heart failure has been attributed to pre-systemic or first-pass clearance of the drug by the liver. Quinidine is eliminated from the body primarily by metabolism. Less than 20% of a given dose is excreted in the urine as unchanged drug. However, the hepatic extraction ratio of quinidine in the non-heart failure patient is relatively low and drug clearance by this organ is therefore independent of liver blood flow. Thus, in spite of a possible decrease in hepatic blood flow in

Figure 2 Simulated plasma quinidine concentration-time curves following oral administration of 233 mg quinidine every 6 h in the presence (dash line) and absence (solid line) of congestive heart failure. The following values were used to simulate both curves: $F = 0.70$; dose = 233 mg; dosing interval = 6 h; $\beta = 0.11 \text{ h}^{-1}$. The values of k_a and apparent volume of distribution for the heart failure and non-heart failure curves were, respectively, 1.44 and 2.64 h^{-1} and 130 and 190 l .

patients with congestive heart failure, the absence of blood flow-dependent elimination of quinidine by the liver would predict that the fractional rate of drug removal is unaffected in congestive heart failure. This was the case in this study. The values of $T_{1/2}\beta$ for the two groups of patients were nearly the same.

Although two- and three-compartment models have been previously shown to describe the disposition of quinidine after intravenous administration (Conrad *et al.*, 1977; Greenblatt *et al.*, 1977; Guentert *et al.*, 1979; Ueda, Hirschfeld, Scheinman, Rowland, Williamson & Dzindzio, 1976; Ueda & Dzindzio, 1978), the results of this investigation demonstrated that in 15 of the 18 patients studied (83%), a single compartment model was all that was needed to characterize the absorption and disposition of orally administered quinidine. This finding is completely in agreement with the rapid α -phase seen after intravenous quinidine (Conrad *et al.*, 1977; Greenblatt *et al.*, 1977; Guentert *et al.*, 1979; Ueda *et al.*, 1976; Ueda & Dzindzio, 1978) and the recent suggestion by Guentert *et al.* (1979) that for individualized dosage adjustments, application of the one-compartment model is adequate.

The antiarrhythmic effects of quinidine have been shown to be related to its concentration in the plasma and serum (Sokolow & Ball, 1956; Heissenbuttel & Bigger, 1970). Preliminary observations with a small number of patient samples suggest that the binding of quinidine to plasma proteins is not altered in the presence of congestive heart failure. Thus, assuming that the interactions of quinidine and plasma proteins

are the same in patients with and without congestive heart failure, the reduced rate of drug clearance and unaltered extent quinidine bioavailability would suggest that congestive heart failure patients require smaller oral quinidine dosages than non-heart failure cardiac patients to treat their arrhythmias. This is illustrated in Figure 2. Using the results obtained with the intravenous and oral doses, this figure shows the predicted plasma concentration-time profiles for quinidine when equivalent oral drug dosage regimens (i.e. 233 mg quinidine every six hours) are used in patients with and without congestive heart failure. These simulations were made using a continuous system modeling program (Program No. 360A-CX-16X, IBM Corporation, 1972) and digital computer and assuming a one-compartment model with first-order drug absorption and elimination. From the two predicted curves, it can be seen that plasma quinidine concentrations are higher in the presence of congestive heart failure. The predicted maximum, minimum, and average plasma quinidine concentrations at steady state are 2.22, 1.45 and 1.90 $\mu\text{g/ml}$, respectively, in the presence of the disease and 1.60, 0.96 and 1.30 $\mu\text{g/ml}$ in its absence. From this information, it would appear that therapeutic plasma or serum concentrations of quinidine are achieved with lower oral dosages in patients with congestive heart failure.

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