Digoxin-Quinidine Interaction in Patients with Chronic Renal Failure

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SUMMARY We evaluated the effect of quinidine on digoxin pharmacokinetics in six patients with severe renal failure. Quinidine reduced the total body clearance of digoxin from 1.87 to 1.06 l/hour (p < 0.001), and prolonged the digoxin half-life of elimination from 5.20 to 9.61 days (p < 0.01). The digoxin volume of distribution was unchanged. Renal clearance of digoxin was negligible; thus, the decrease in total body clearance was due to a decrease in the nonrenal clearance of digoxin. The mean trough serum concentrations of quinidine ranged from 1.0 to 3.0 µg/ml. We conclude that in patients with chronic renal failure, the dose of digoxin should be decreased by 50% if quinidine therapy is initiated.

QUINIDINE increases digoxin serum concentrations approximately twofold.1 This elevation in concentration occurs primarily as a result of a decrease in the total body clearance of digoxin and volume of distribution of digoxin.2 A decrease in digoxin nonrenal clearance has also been reported.3-6 However, the magnitude of the change in nonrenal clearance has varied widely.3-6

In renal failure patients, the renal clearance of digoxin is small relative to the nonrenal clearance. If the quinidine effect on digoxin nonrenal clearance is small, then in patients with chronic renal failure, quinidine may induce only a small change in digoxin total body clearance. In addition, these patients demonstrate a decreased digoxin volume of distribution7 due to decreased tissue binding of digoxin.8 Whether quinidine alters this already decreased digoxin volume of distribution is not known. We therefore evaluated the effect of quinidine on digoxin kinetics in chronic dialysis patients to assess the effects of renal failure on this drug interaction and to gain further insight into the mechanisms of this interaction.

Methods

Patients
Six adults gave informed, written consent to participate in the study, which was approved by the Human Subjects Committee of the Arizona Health Sciences Center. The clinical characteristics of the subjects are listed in Table 1. All subjects had end-stage renal disease. Five subjects were on chronic hemodialysis; one (subject 5) was on continuous ambulatory peritoneal dialysis during the first half of the study and hemodialysis during the second half. Five patients were males and one was female, ages 30-58 years (mean 47 years). Serum creatinine levels ranged from 10.2 to 16.8 mg/dl (mean 13.4 mg/dl). No subject was on digoxin or quinidine or any drug known to affect the pharmacokinetics of intravenously administered digoxin at the time of enrollment.

Protocol
Subjects were given quinidine gluconate, 324-mg tablets containing 202 mg of quinidine, twice daily. After 3 days of quinidine, a single dose of digoxin, 0.6 or 0.8 mg, was administered intravenously over 10 minutes. Blood samples were obtained 0.5, 1, 2, 4, 6 and 8 hours, and once on days 2, 3, 4, 7, 9, 11, 14, 16, 18, 21, and 23 after the digoxin dose. The blood samples were drawn immediately before a quinidine dose on these days. Quinidine was then discontinued. Two weeks after completion of the blood sampling and discontinuation of quinidine, a second digoxin dose identical to the first was administered intravenously. Blood samples were obtained as described after the first dose. Three patients were totally anuric; urine production in the other three was negligible. Therefore, urine samples were not analyzed.

Serum samples were stored frozen at -20°C until assayed. All samples were assayed for digoxin. Quinidine serum trough concentrations were determined once each week during quinidine treatment, and once before the second digoxin injection to assure that no quinidine was present.

Analytical Methods
Digoxin serum concentrations were determined using the Becton-Dickinson 125I radioimmunoassay, with the following modifications. Standard solutions of digoxin (Boehringer-Mannheim) were diluted in pooled human plasma and a standard curve (range 0-4 ng/ml) was prepared for each assay. All samples and standards were run in duplicate. The charcoal suspension contained 0.15 M NaCl, 3.6 mM sodium barbital, 3.6 mM sodium acetate, 0.03% dextran T-80, and 1.25% Norit-A activated charcoal pH 7.2. After cen-
trifugation to precipitate the charcoal, a 1-ml sample of supernatant containing antibody-bound digoxin was pipetted into another tube and the radioactivity was counted for 4 minutes in a gamma counter. The coefficient of variation for the digoxin assay was 2.6% at 2 ng/ml. The average minimal detectable serum concentration was 0.25 ng/ml.

Quinidine was analyzed by an enzyme mediated immunoassay system (EMIT®-Syva).

**Data Analysis**

The logarithm of the digoxin serum concentration was plotted against time for each digoxin injection in each subject. The slope (β) of the terminal portion of the curve was determined by linear regression. Half-life (t1/2) was calculated from β by the relationship t1/2 = 0.693/β. The total area under the serum concentration vs time curve (AUC) was determined using the trapezoidal rule and Cβ/β, where Cβ is a serum concentration in the terminal log linear phase of the concentration-time curve. Total body clearance (Clb) was calculated from the relationship Clb = dose/AUC. The volume of distribution (Vd) was calculated from the equation Vd = Clb/β. The volume of distribution at steady state (Vss) was calculated from the equation Vss = (Dose·AUMC)/(AUC)2, where AUMC is the total area under the first moment of the serum concentration-time curve.9

Statistical comparisons of the pharmacokinetic variables in the presence and absence of quinidine were made by a paired t test.

**Results**

Table 2 is a summary of the pharmacokinetic values for digoxin in the presence and absence of quinidine in the six subjects. In each subject, quinidine reduced the total body clearance of digoxin, resulting in a prolonged digoxin half-life. There was no significant change in the volume of distribution of digoxin. For the group, digoxin total body clearance was reduced by 43%, from 1.87 ± 0.36 to 1.06 ± 0.28 l/hour (p < 0.001). Digoxin half-life was prolonged by 85%, from 5.20 to 9.61 days (harmonic mean10) (p < 0.01). The log serum digoxin concentration vs time curves for subject 5 are shown in figure 1.

Trough quinidine serum concentrations are shown in table 2. The trough levels were consistent within each subject during the 3 weeks of quinidine therapy, indicating good compliance. There was no detectable quinidine in the serum before the second digoxin injection.

No subject experienced significant adverse effects. Two subjects developed mild diarrhea on quinidine. This did not interrupt the protocol, nor was treatment required.

**Discussion**

Our study demonstrates that the major effect of quinidine on digoxin pharmacokinetics in patients with severe renal failure is to decrease the total body clearance of digoxin. The magnitude of this effect in renal failure patients is comparable to that in subjects with normal renal function.2 However, since digoxin renal clearance in the subjects in the present study is negligible, the decrease in total body clearance must be due to a quinidine-induced decrease in digoxin nonrenal clearance. Both hepatic metabolism and biliary secretion of digoxin have been suggested in man. Either or both of these processes could be affected by quinidine.

In persons with normal renal function, a variable

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**TABLE 1. Clinical Characteristics of Study Subjects**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
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<td>M</td>
<td>73.6</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>M</td>
<td>72.0</td>
<td>Glomerulonephritis</td>
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<tr>
<td>3</td>
<td>58</td>
<td>F</td>
<td>62.2</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>46</td>
<td>M</td>
<td>95.9</td>
<td>Hypertension</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>M</td>
<td>69.5</td>
<td>Glomerulonephritis</td>
</tr>
</tbody>
</table>

**TABLE 2. Pharmacokinetic Parameters for Digoxin Alone and in the Presence of Quinidine**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Half-life (days)</th>
<th>Total body clearance (l/hour)</th>
<th>Volume of distribution (l/kg)</th>
<th>Steady-state volume (l/kg)</th>
<th>Quinidine trough* concentration (µg/ml)</th>
<th>Mean ± sd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D</td>
<td>D + Q</td>
<td>D</td>
<td>D + Q</td>
<td>D</td>
<td>D + Q</td>
</tr>
<tr>
<td>1</td>
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<td>5.57</td>
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<td></td>
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<td>8.93</td>
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<tr>
<td>3</td>
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<td>7.48</td>
<td>1.76</td>
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<tr>
<td>4</td>
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<td>8.36</td>
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<td>1.70</td>
<td>1.00</td>
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<td></td>
<td></td>
<td>4.15</td>
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<td>1.50</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>5.05</td>
<td>11.94</td>
<td>2.23</td>
<td>1.24</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>5.20*</td>
<td>9.61*</td>
<td>1.87</td>
<td>1.06</td>
</tr>
</tbody>
</table>

*Harmonic mean.10
†Mean of three measurements.
Abbreviations: D = digoxin alone; D + Q = digoxin with concurrent quinidine.
effect of quinidine on digoxin nonrenal clearance has been reported. In a previous study in normal volunteers, we demonstrated a statistically insignificant decline in digoxin nonrenal clearance during quinidine administration. Leahey et al. found a similar decrease in digoxin nonrenal clearance in a group of normal subjects. Steiness et al. reported a marked reduction in digoxin nonrenal clearance during quinidine treatment in six healthy subjects. In that study, the decrease in nonrenal clearance was the major pharmacokinetic effect of quinidine. The quantitative differences in these findings are not explained by the serum concentration of quinidine. The present study demonstrates that in patients with severe renal failure, a low dose of quinidine reduces digoxin nonrenal clearance, produces a 43% decrease in digoxin total body clearance, causes digoxin serum levels to increase and prolongs digoxin half-life.

We examined the effects of quinidine on digoxin given in a single i.v. dose. The interaction also occurs during chronic oral dosing with digoxin in patients with renal failure. Hirschberg et al. measured steady-state serum digoxin concentrations before and 4 days after initiation of quinidine treatment in 15 patients with varying degrees of renal insufficiency. A marked increase in serum digoxin concentration of 27–150% was observed in all but one patient. The mechanism of interaction was not investigated. Similarly, Doering et al. reported that quinidine in a dose of 750 mg/day raised steady-state serum digoxin concentrations in eight anuric patients from 0.84 ± 0.37 to 1.58 ± 0.72 ng/ml. They also found that quinidine did not alter the serum protein binding of digoxin.

The volume of distribution of digoxin is decreased in chronic renal failure. This is presumably due to a decrease in tissue affinity for digoxin, and a decrease in digoxin tissue to serum concentration ratio has been demonstrated. The same mechanism has been proposed to explain the quinidine-induced decrease in digoxin volume of distribution, observed in subjects with normal renal function. In our study, quinidine did not further decrease the digoxin volume of distribution in patients with severe renal failure. This suggests that the tissue-bound digoxin in renal failure patients is not further displaced by quinidine. However, the lack of an effect on digoxin volume of distribution reported here may be related to the low quinidine serum concentrations. The concentrations are lower than those we reported in subjects with normal renal function who demonstrated a significant decrease in digoxin volume of distribution. We deliberately used a low dose of quinidine to avoid adverse reactions in this population of chronically ill patients. Leahey et al. found a greater decrease in digoxin volume of distribution in a group of normal subjects with a mean quinidine level of 2.33 µg/ml compared with a group with a mean level of 1.11 µg/ml.

The clinical consequences of this interaction in renal failure were not assessed in this study. However, the rise of digoxin levels due to quinidine has been associated with evidence of toxicity. Therefore, to maintain the same serum concentration of digoxin in patients with severe renal failure, the present data suggest that the digoxin dose should be decreased by about 50% if quinidine therapy is initiated.

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Transcutaneous Angioplasty of Experimental Aortic Coarctation

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SUMMARY A dilatable form of juxtaglucal ductal aortic coarctation was surgically created in 29 newborn lambs. Of the 17 long-term survivors, four lambs served as controls and 13 underwent transcutaneous balloon dilation angioplasty with either polyvinylchloride or polyethylene catheters after 7–10 weeks of recovery. During growth before dilation, there was little change in the systolic gradient across the coarctation (36.6–35.3 mm Hg) despite an increase in animal weight from 3.8 to 19.3 kg. This systolic gradient remained constant in undilated lambs throughout a 6-month follow-up. Dilation produced an immediate 65% increase in the diameter of the coarctation and a 68% decrease in the systolic gradient across the coarctation site. Successful dilation required very high (6–8 atmospheres) dilating pressures. This gradient relief persisted throughout a follow-up of up to 1 year. Although no late sequelae could be attributed to the angioplasty, one lamb suffered an anterior aortic tear (associated with a difficult postdilation wire passage across the dilation site), which resulted in fatal intrathoracic hemorrhage. Gross pathologic inspection demonstrated intimal and medial tears in successfully dilated lambs in the first 3 days after dilation; on late pathologic examination, the intima appeared completely healed, without evidence of aneurysm or accelerated atheroma formation, within 2 months. These results, in conjunction with previous human in vitro studies, support the hypothesis that human aortic coarctation may be a dilatable lesion, although the safe limits and optimal protocols for dilating human coarctations are not known.

THE OPTIMAL medical and surgical management of infants and children with aortic coarctation is controversial. Early surgery seems to prevent the development of sustained, lifelong hypertension,1 but may result in a significant gradient later in life.2,3 Late surgery results in excellent long-term technical success,3,4 but may leave the child with lifelong arterial hypertension.1–5 A two-stage surgical approach (operating when necessary on recoarcted aortas) is not optimal because reoperation for recoarctation is, despite recently improved results,1,6 a difficult and hazardous procedure.6–7 The advent of a successful balloon dilation catheter for the treatment of peripheral athereosclerotic lesions8,9 appears to offer a fourth alternative: One could initially dilate the coarctation transcutaneously (thus eliminating the gradient) and still allow a clean and safe operative field for subsequent definitive repair at an optimal age.

The feasibility of such an approach was first suggested by the successful dilation of a postmortem human coarctation by Sos et al.10 in 1979. That study was confirmed and extended in excised human specimens;11 in the latter study, however, native human coarctations required high dilating pressures (8 atmospheres), suggesting that the technique for successful dilation of coarcted aortas might differ from that of acquired arterial lesions.

Despite the encouraging results obtained from in vitro studies, several important questions can only be addressed by in vivo investigations: Will dilation weaken the aortic wall to the point of rupture? Will the intimal and medial injury (known to occur with balloon angioplasty)12,13 result in accelerated atheroma or aneurysm formation? Will the dilated segment restenose with time, or will it grow along with the growing child?

To address these and similar questions, we developed a dilatable form of aortic coarctation in growing lambs. In this report we outline our preparation and its “unnatural” history using hemodynamic, angiographic and pathologic techniques; determine the safe-
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