Tritiated Digoxin Excretion of Patients Following Renal Transplantation

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SUMMARY

Four patients with a single allografted kidney were given 1.0 mg of tritiated digoxin intravenously. Compared with patients with two normally functioning kidneys, these patients exhibited increased digoxin serum levels, modestly reduced renal excretion, and increased stool excretion of digoxin during a 7-day study. When administration of digoxin is indicated for a patient with a renal transplant, it may be necessary to reduce the dose even though renal function appears to be adequate.

Additional Indexing Words:
Urinary excretion  Stool excretion  Excretion in chronic heart failure

DIGOXIN is excreted primarily as the unchanged glycoside in the urine of patients with congestive heart failure1-3 and those with normal cardiovascular function.4 Digoxin excretion is prolonged in renal insufficiency5-7 and in renoprival human subjects.8 The renal excretion of digoxin is inversely related to the level of the blood urea nitrogen,5 and the ratio of creatinine clearance to digoxin clearance is unity in human subjects.7 Renoprival patients excrete larger quantities of digoxin in the stool, but this fails to compensate for the absence of urinary excretion and results in a prolonged serum half-time.

This study was designed to determine the functional capacity of the denervated allografted human kidney to excrete tritiated digoxin and to compare these findings with previous studies in these same patients during the renoprival period. Comparisons will be made with previous studies in our laboratory on patients with normal renal function.2

Methods

Tritiated digoxin was prepared by the Wilzbach hydrogen exchange method and had a specific activity of 66 to 112 µC/mg. A thin-layer radiochromatogram demonstrating the purity of the preparation, which was chemically pure, cardio-active, sterile, and pyrogen free, is shown in figure 1.

Four patients, none of whom were in congestive heart failure, were given 1.0 mg of tritiated digoxin intravenously after renal transplant. One patient was studied twice—one 32 days after the transplant and again 224 days after it. All patients were receiving immunosuppressive agents at the time of the study.

Frequent samples of urine and stools were...
Figure 1

Thin-layer radiochromatogram of tritiated digoxin. The sample of digoxin was applied at the left of the graph marked "origin." Digoxin is indicated by the dark spot on the lower portion of the diagram. The solvent front is at the far right. Note that radioactivity, indicated on the vertical axis, is localized to the area containing digoxin.

made for 7 days. Tritiated digoxin and its primary metabolites, digoxigenin monodigitoxoside and bisdigitoxoside, were extracted with chloroform, passed through an alumina column, eluted with a 2:1 chloroform-ethanol mixture, and evaporated. Counting solution* was added, and radioactivity was determined in a liquid scintillation counter.† This method will recover 96% of a known quantity of digoxin and its metabolites.

Results

Figure 2A illustrates the composite serum turnover on all four patients given tritiated digoxin following renal transplant. Curve A represents the actual counting rates of digoxin radioactivity, plotted on semilogarithmic paper on the vertical axis, and time on the horizontal axis. Three exponential functions are present when frequent early serum samples are obtained; however, in this study only the latter two were determined. The first exponential, with a half-time of 2 min, requires 3-min samples for adequate demonstration and represents serum distribution of digoxin. It depends on such variables as blood volume, cardiac output, and speed of digoxin injection, and was relatively unimportant to this study. Line B is the dominant serum half-time, which is 50 hours, and represents metabolism and excretion of digoxin. Line C represents the distribution and tissue binding of intravenous tritiated digoxin and has a half-time of 60 min. This turnover curve is compared with that obtained from the same patients when anephric, and a group of 12 patients with normal renal function and congestive heart failure in figure 2B. Note that serum levels of digoxin are highest during the anephric state with a dominant half-time of 82 hours, intermediate after transplantation with a half-time

*Counting solution: 4.0 g of 2,5 diphenyloxazol; 0.1 g of p-bis 2-(5-phenyloxazolyl)-benzene; 1.0 g of Hyamine-10X; 3.5 ml of methanol brought to 1 L with toluene.

†Packard Instrument Company, Downer’s Grove, Illinois.

Figure 2

(A) Serum digoxin turnover in post-transplant patients. Radioactivity is plotted on the vertical axis as percentage of the 15-min specimen, on a semilogarithmic scale with time on the horizontal axis. Curve A represents the actual counting rates; line B represents an extension to zero time of curve A after the equilibration plateau was reached. This exponential indicates metabolism and excretion and has a half-time of 50 hours. Line C represents a second exponential function with a half-time of 60 min, representing tissue distribution and binding.

(B) Composite serum digoxin turnover. Radioactivity is plotted on a semilogarithmic scale on the vertical axis as in figure 2A; time, on the horizontal axis. Serum levels of digoxin are higher in anephric state, intermediate post transplant, and lowest with normal renal function.

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of 50 hours, and least in patients having normal renal function with a half-time of 33 hours. These values for serum half-time were determined over a 7-day period, of which only the first 36 hours are shown in the figure.

Figure 3 compares the 7-day urine excretion of digoxin in the same three groups as shown in figure 2. There is, of course, no urinary excretion in the anephric patients, but there is 42% excretion in the post-transplant patients, and 80% in the patients with congestive heart failure and normal renal function. Figure 3 also shows the 7-day fecal excretion of tritiated digoxin in these same patients. Thirty-one percent of the total administered dose was excreted in 7 days in the stool of anephric patients, 21% in the post-transplant state, and 12% in patients with normal renal function after comparable doses of digoxin. The total digoxin excretion by these patients is indicated. Anephric patients who were maintained on dialysis excreted a total of only 34% of the total administered dose of digoxin in 7 days. After renal transplantation, these same patients excreted 63% of the digoxin over a similar period. These data are in contrast to the 92% excreted by patients with congestive failure and normal renal function.

Table 1 lists each patient's age, sex, and dates of post-transplant study of blood urea nitrogen, serum potassium, and creatinine clearance.

Table 2 indicates the excretion data and half-time of digoxin while the patients were anephric and after transplant.

Discussion

Digoxin, a polar digitalis glycoside, is excreted primarily by the kidney. Eighty percent of the administered dose of tritiated digoxin and its metabolites can be recovered from the urine during a 7-day collection period following intravenous administration into human subjects with congestive heart failure. A small amount, roughly 10 to 12%, is recovered from the stool in this same period of time. Renal insufficiency has been shown to prolong digoxin excretion and may result in digitalis toxicity. Digoxin excretion can be related inversely to the level of the blood urea nitrogen (BUN), or proportionally to the creatinine clearance. Figure 4 illustrates the relationship of the BUN to digoxin clearance. Note the reduction in digoxin clearance when the BUN reaches 50 to 75 mg%.

The data which have been presented indicate that urinary excretion of digoxin in the allografted kidney was roughly proportional to that expected for a single kidney, 42% being

Table 1

Clinical Information

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Race</th>
<th>Donor</th>
<th>Blood urea nitrogen (mg%)</th>
<th>Potassium (mEq/L)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Days post-transplant</th>
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<td>1</td>
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<td>M</td>
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<td>49</td>
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<td>F</td>
<td>C</td>
<td>Cadaver</td>
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<td>4.6</td>
<td>53</td>
<td>51</td>
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<tr>
<td>3</td>
<td>25</td>
<td>M</td>
<td>C</td>
<td>Mother</td>
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<td>4.1</td>
<td>64</td>
<td>53</td>
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<tr>
<td>4</td>
<td>38</td>
<td>M</td>
<td>C</td>
<td>Mother</td>
<td>28</td>
<td>5.2</td>
<td>57</td>
<td>32</td>
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</table>

N = Negro; C = Caucasian.

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Digoxin Turnover and Excretion in Four Patients after Renal Transplants

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cumulative urine excretion*</th>
<th>Urine half-time (days)</th>
<th>Digoxin clearance (ml/min)</th>
<th>Digoxin-creatinine clearance ratio</th>
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<tr>
<td>1</td>
<td>Day 1 18.54 Day 3 26.88 Day 5 32.60 Day 7 34.26</td>
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<td>2</td>
<td>Day 1 12.00 Day 3 21.19 Day 5 26.71 Day 7 30.94</td>
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<td>49</td>
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<td>3</td>
<td>Day 1 28.82 Day 3 45.07 Day 5 53.46 Day 7 57.50</td>
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<td>1.05</td>
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<td>4 (a)</td>
<td>Day 1 23.54 Day 3 38.58 Day 5 45.56 Day 7 49.20</td>
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<td>59</td>
<td>1.03</td>
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<tr>
<td>4 (b)</td>
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<tr>
<td>Mean</td>
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<td>Mean for anephric patients</td>
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<td>—</td>
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<td>Mean for CHF patients</td>
<td>Day 1 38.1 Day 3 62.2 Day 5 70.0 Day 7 80.0</td>
<td>1.85</td>
<td>90</td>
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</table>

*Percent of total administered dose.

Figure 4

The relationship of digoxin clearance to blood urea nitrogen (BUN). The BUN is plotted on the vertical axis, digoxin clearance on the horizontal. Note the sharply reduced digoxin clearance when the BUN approaches 50 to 75 mg%.

recovered from the urine in a 7-day collection after administration, compared with 80% in patients with two kidneys and normal renal function.

Stool excretion of digoxin by the patients after transplantation was increased to 21% of the total administered dose during the 7 days' collection, compared with 12% by patients with two normal kidneys. For patient 4 the increase in stool excretion of digoxin persisted for as long as 224 days following transplantation. Whether the increased fecal excretion of digoxin in such patients is the result of an "adaptive" alternate route of excretion is currently under investigation. It is possible that the increased fecal excretion of the drug is simply associated with the longer persistence of digoxin within the plasma and tissues of these patients.

Management problems of digitalis in patients with renal failure have been noted for many years and may be related to subtle (or overt) digitalis intoxication resulting from the prolonged urinary excretion of digoxin. This is in part compensated for by increased stool excretion.5, 6 The fact that many patients with renal insufficiency survive therapy with "average" doses of digoxin is probably related to reduced absorption, increased fecal excretion, and perhaps a competitive relationship between digitalis and potassium, as shown by Marcus and associates10 and suggested by Lown and Levine.11

Patients with a single functioning renal transplant excrete 63% of a total dose of tritiated digoxin in 7 days, compared with 92% by patients with two normal kidneys. The ratio of the creatinine to digoxin clearance averaged 0.93, a value similar to that reported by Bloom and Nelp7 both in normal subjects and in patients with reduced renal function. Thus it appears that there is no apparent gross difference in the handling of digoxin by the transplanted, as compared to the intact, kidney at the same level of renal function. However, because of the reduced glomerular filtration rate associated with a single kidney,
caution is advisable in determining maintenance dose requirements for these patients.

References


<table>
<thead>
<tr>
<th>Day 1</th>
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<th>Day 5</th>
<th>Day 7</th>
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<td>Stadium excretion*</td>
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<td>Total serum half-time (days)</td>
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<td>18.04</td>
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<td>Total serum half-time (min)</td>
<td>13.82</td>
<td>18.92</td>
<td>20.14</td>
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<td>Serum half-time (min)</td>
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<td>53</td>
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<td>Line C</td>
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