Tritiated Digoxin

XIV. Enterohepatic Circulation, Absorption, and Excretion Studies in Human Volunteers


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SUMMARY

Metabolic turnover studies performed on six patients with surgically induced biliary fistula given tritiated digoxin reveal virtually all stool excretion of digoxin to be derived from bile. This establishes the relative lack of recycling of digoxin as an important factor in digoxin metabolism. This is probably related to its polar chemical structure and is a determinant of its clinical duration of action in human subjects. The amount of digoxin in the enterohepatic circulation (recycling) was calculated to be 6.5% of the administered dose and absolute absorption to be 85% in human subjects.

Additional Indexing Words: Biliary fistula Digoxin, metabolism of

The availability of 3H digoxin for experimental clinical use has made possible a number of meaningful studies during the last decade. These studies have outlined the serum turnover rates, serum half-time (the time required for one half of the radioactivity identified with the drug to disappear from the serum) and serum digoxin levels. The urinary and fecal excretion of digoxin was characterized, and the larger portion of the drug was found to be excreted unchanged in the urine. Comparative studies in patients given 3H digoxin by oral, intramuscular, and intravenous routes suggested that digoxin was more completely absorbed than previously supposed, as there were only small differences in stool excretion after different routes of administration.

Patients with surgical T-tube drainage provide a method for determining the contribution of biliary excretion to total stool excretion and provide an index of recycling of the drug in the intestine and its contribution to the metabolism of digoxin.

The purpose of this paper is to report tritiated digoxin turnover and excretion studies on six patients with surgically induced biliary fistula and T-tube drainage and to apply these data to the calculation of the enterohepatic circulation and absorption of tritiated digoxin. Previous studies with tritiated digoxin are utilized in these computations.

Methods

Six male patients with biliary tract disease who were candidates for T-tube drainage postoperatively were selected for study. Clinical diagnoses
Table 1

Clinical Information

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Weight</th>
<th>Race</th>
<th>BUN (mg/100 ml)</th>
<th>Dose of digoxin (mg)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>118</td>
<td>N</td>
<td>15</td>
<td>1.0</td>
<td>Cholelithiasis (preoperative), chronic pancreatitis (postoperative)</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>160</td>
<td>W</td>
<td>14</td>
<td>1.0</td>
<td>Chronic cholecystitis, cholelithiasis</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>159</td>
<td>W</td>
<td>14</td>
<td>1.0</td>
<td>Cholangitis, chronic pancreatitis, hepatitis</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>170</td>
<td>W</td>
<td>12</td>
<td>0.75</td>
<td>Chronic cholecystitis, cholelithiasis, muscular dystrophy</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>173</td>
<td>W</td>
<td>14</td>
<td>0.5</td>
<td>Chronic cholecystitis, cholelithiasis</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>146</td>
<td>W</td>
<td>18</td>
<td>1.0</td>
<td>Choledocholithiasis</td>
</tr>
</tbody>
</table>

are shown in table 1. None were in congestive heart failure, nor did they exhibit any cardiac arrhythmia. They were not jaundiced at the time of the surgical procedure. Cholecystectomy, exploration of the common bile duct, or both were performed under general anesthesia, with barbiturate induction and halothane anesthesia supplemented with succinylcholine chloride, agents not known to affect digoxin metabolism. Cyclopropane was used to anesthetize one patient (case 2). A T-tube was placed in the common bile duct and drained externally. None of the bile was returned to the patients. The patients were taken from the operating suite to the recovery area, and about 1 hour following closure of the abdominal incision, when consciousness had returned, each was given 0.5 to 1.0 mg of $^3$H digoxin intravenously. The $^3$H digoxin was 99.5% chemically pure by the manufacturer's statement,* and radiochromatographically pure. The specific activity was 125 $\mu$g/mg. Serum samples were obtained at 5, 10, 15, 30, 45, 60, and 90 min and 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours, and daily thereafter for a total of 7 days. All urine, stools, bile, and nasogastric aspirate were saved in aliquots for 7 days. Stool markers were not used because of the nasogastric suction and limited oral intake dictated by the surgical procedure. The radioactivity present in the samples representing digoxin and its major metabolites (digoxigenin mono- and bis-digitoxside and digoxigenin) was extracted by a method of column chromatography previously described.1 Total recovery of radioactivity was verified by a modification of the Schoniger combustion technic.18 Metabolites were searched for by thin-layer chromatography with silica gel plates immersed in a solvent system which consisted of 65.3% cyclohexane, 32.7% acetone, and 2.0% glacial acetic acid.19 These data were analyzed and compared with those from patients receiving $^3$H digoxin intravenously2, 6 and orally4, 10 to compute equations for enterohepatic circulation, absorption, and excretion of tritiated digoxin. The basic techniques of study did not vary greatly between studies, and the data obtained are felt to be reliable and comparable to those of the current investigation. A total of 54 studies of tritiated digoxin turnover in human beings were analyzed in the computations included in this communication and are annotated in table 2. All the patients except those in the current study were in congestive heart failure and required digoxin for therapy.

Results

The clinical information on each of the patients with biliary fistula is recorded in table 1. None of the patients were in congestive heart failure; however, previous studies10, 16 have shown that there is no alteration in serum levels, turnover, and excretion rates of $^3$H digoxin between patients with and without

Table 2

Tritiated Digoxin Half-Times and Excretion

<table>
<thead>
<tr>
<th></th>
<th>Oral (20%)</th>
<th>Intravenous (28%)</th>
<th>Intravenous biliary fistula (6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum T 1/2</td>
<td>33.8 hr</td>
<td>33 hr</td>
<td>32.3 hr</td>
</tr>
<tr>
<td>Urine T 1/2</td>
<td>1.7 days</td>
<td>1.8 days</td>
<td>1.35 days</td>
</tr>
<tr>
<td>Stool T 1/2</td>
<td>1.4 days</td>
<td>1.6 days</td>
<td></td>
</tr>
<tr>
<td>Bile T 1/2</td>
<td></td>
<td></td>
<td>1.56 days</td>
</tr>
</tbody>
</table>

Total excretion, 7 days, in % of total dose administered

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile</td>
<td></td>
<td></td>
<td>8.1</td>
</tr>
<tr>
<td>Urine</td>
<td>33.99</td>
<td>73.5</td>
<td>58.5</td>
</tr>
<tr>
<td>Stool</td>
<td>15.16</td>
<td>11.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Number of patients.
†Data insufficient for calculation.

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Table 3

<table>
<thead>
<tr>
<th>Serum Digoxin Half-Time (h)</th>
<th>Cumulative urine excretion*</th>
<th>Urine T 1/2 (days)</th>
<th>Cumulative biliary excretion*</th>
<th>Total soil excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>Serum T 1/2 (h)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>24.57</td>
<td>3.94</td>
<td>3.94</td>
<td>3.94</td>
</tr>
<tr>
<td>4</td>
<td>24.57</td>
<td>3.94</td>
<td>3.94</td>
<td>3.94</td>
</tr>
</tbody>
</table>

*Expressed as percent of the total dose administered.

Data inadequate for calculation.

Abbreviations: sd = standard deviation; SEM = standard error of the mean.

heart failure whose renal and thyroid functions are normal.

Table 3 is a tabulation of all data collected on the serum half-times and excretion of "H digoxin. Individual studies are shown, and the data include the mean figures for cumulative and total excretions, half-times, etc., with the standard deviation (sd) and the standard error of the mean (SEM). Note that the individual serum half-times are near the mean normal of 34 hours, and the mean T % is 32.5 hours; however, individual variability of the serum T % of digoxin is again noted (range 26.7 to 36.7 hours). The excretion rates are similar but slightly reduced, the mean 7-day urinary excretion being 58.5% of the total administered dose compared to 73.5% recovered from patients given the drug intravenously during previous studies (table 2). The reduction in urinary excretion rate may be associated with the surgical procedure.

The stool excretion ranged from 0 to 2.7% of the total dose administered in a 7-day period. Biliary excretion was noted to be 4.3 to 12.7%. A surgically placed T-tube drain only rarely completely occludes the common bile duct, and this probably accounts for the variation noted in recovery of tritiated digoxin in stool and bile from different subjects. Total biliary and stool excretion was 9.37%, similar to total stool recovery of tritiated digoxin and its metabolites after parenteral administration as shown in table 2. Urine and bile half-times closely resemble the dominant serum half-time, demonstrating the relationship of this function to the excretion of the drug. Nasogastric tubes placed during surgery recovered only minute amounts of tritiated digoxin.

Figure 1 shows the composite serum turnover of tritiated digoxin obtained in these patients. The concentration of digoxin is shown on the vertical axis as digoxin radioactivity expressed as percentage of the 5-min specimen. Time in hours is indicated on the horizontal axis. Although the graph shown only includes points through 48 hours, the dominant T % (line B) was determined by these and additional points throughout the 7-day study period. A logarithmic plot was
Composite graph of serum turnover of tritiated digoxin in patients with surgically induced biliary fistula. Radioactivity is plotted on the vertical axis as percent of the 5-min specimen on a logarithmic scale; time is plotted on the horizontal. Line A represents the actual counting rate expressed in percent. Line B represents the plateau of the serum curve which is extrapolated to zero time and yields a dominant serum half-time of 32.3 hours. Line C is a representation of line A minus line B; thus eliminating metabolism and excretion of digoxin, the function of line B. This exponential function represents distribution and binding of the glycoside and has a half-time of 45 min, slightly longer than that observed after intravenous administration in patients with congestive heart failure and probably related to the recent surgical procedure.

Table 4

Recovery of Digoxin and Metabolites from Bile: Patient 5*

<table>
<thead>
<tr>
<th></th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4†</th>
<th>Day 5</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>1.6</td>
<td>BKG†</td>
<td>BKG</td>
<td>BKG</td>
<td>1.6</td>
</tr>
<tr>
<td>Trail</td>
<td>6.2</td>
<td>1.7</td>
<td>1.8</td>
<td>8.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Digoxin</td>
<td>80.3</td>
<td>91.1</td>
<td>66.8</td>
<td>71.9</td>
<td>77.5</td>
</tr>
<tr>
<td>Digoxigenin bis-digitoxiside</td>
<td>7.2</td>
<td>6.2</td>
<td>8.3</td>
<td>6.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Digoxigenin mono-digitoxiside</td>
<td>2.4</td>
<td>0.2</td>
<td>4.3</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Digoxigenin</td>
<td>1.6</td>
<td>0.8</td>
<td>3.1</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Solvent front</td>
<td>0.6</td>
<td>BKG</td>
<td>15.5</td>
<td>9.2</td>
<td>5.9</td>
</tr>
</tbody>
</table>

*Expressed as percent of total recovery from thin-layer chromatographic plate.
†Figure 2.
‡Background.

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Figure 2

Thin-layer chromatogram of bile obtained after administration of tritiated digoxin. Markers of the specific glycosides (10 μg) were added to the sample for purposes of identification. This sample represents an extract of 10 ml of bile. The origin, glycosides, and solvent front are easily identified in this photograph in ultraviolet light. The percent of radioactivity representing the actual amounts of digoxin and its metabolites is shown for this patient in Table 4 (day 4). The major product of biliary secretion is pure digoxin.

those obtained through similar analysis of data obtained from patients with congestive failure but without renal failure: Line B = 33 hours, and line C = 30 min. The data described are determined by the "peel-off" method, commonly employed in this type of study.

Table 2 compares the findings obtained in these studies to those previously reported after intravenous administration in subjects with congestive heart failure, and hyperthyroidism, hypothyroidism and normal human sub-
jects. These data are utilized to compute absolute absorption and the percent of enterohepatic circulation in the next section.

Figure 2 is a thin-layer chromatogram of bile obtained from patient 5 on day 4. Note the identity peaks of digoxin, digoxigenin mono-digitoxiside, bis-digitoxiside, and digoxigenin in the figure.

Table 4 documents the distribution of digoxin and its metabolites by thin-layer chromatography on this patient. The figures shown in the table quantify the amounts of digoxin and its major metabolites in the bile on days 2, 3, 4, and 5 of the study on patient 5 and are representative of studies of bile from other patients. Digoxin is the major excretory product with small amounts of metabolites being identified. Chromatograms of urine reveal that 95 to 98% of the radioactivity present in the urine is unchanged digoxin.

These findings again are nearly identical to those obtained from patients with congestive heart failure.

Discussion

These studies demonstrate that the major portion of digoxin excreted in the stool is a product of biliary secretion. The total amount of digoxin recovered from stool and bile in this study suggests that the bile may be the only significant source of excretion of digoxin from the bowel, as the amount in the bile and the stool closely resembles total stool recovery by previously reported studies. Application of the formula proposed by Okita appears to show that recycling of digoxin in the bowel is of minor importance in its pharmacokinetic behavior.

The formula proposed by Okita for estimation of the enterohepatic circulation is of interest and deserves comment. He calculates the biliary excretion as:

Biliary excretion = Amount excreted via biliary fistula after intravenous dose of drug.

and:

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% absolute absorption = \frac{\text{oral dose} - \text{amount in GI tract} \times 100}{\text{oral dose}}

Enterohepatic circulation = \text{biliary excretion} \times \% \text{ absolute absorption},

thus:

% enterohepatic circulation = \frac{\text{enterohepatic circulation}}{\text{intravenous dose}} \times 100

A recent report by Caldwell and Greenberger reveals that the enterohepatic recycling of digitoxin may be partially interrupted by orally administered cholestyramine, thus shortening its metabolic half-life and duration of action. This experimental drug, studied primarily as a hypocholesterolemic agent, would appear to bind digitoxin similarly and interrupt its relatively large enterohepatic circulation. The physiologic T½ as well as the serum turnover T½ of digitoxin was shortened in patients given cholestyramine. A lesser effect was seen with digoxin as enterohepatic recycling plays only a minor role in its metabolism.

Digoxin is polar, virtually nonprotein bound, and excreted largely as unchanged glycoside. These properties all contribute to its short duration of action in human subjects in a clinical setting.

This study is in agreement with the mathematical evaluations of digoxin kinetics by Jelliffe, which reveal similar half-times and excretion.

Acknowledgment

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Drs. D. S. Searle, Stanley Bloomfield and C. C. Ferry, and Mr. James Murphy of Burroughs-Wellcome

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and Co. (USA), Inc., Tuckahoe, New York, provided and purified the tritiated digoxin.

References


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