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

Complete absorption 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.1-13

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 ³H digoxin intravenously. The ³H digoxin was 99.5% chemically pure by the manufacturer's statement,* and radiochromatographically pure. The specific activity was 25 μc/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-digitoxiside and digoxigenin) was extracted by a method of column chromatography previously described. Total recovery of radioactivity was verified by a modification of the Schoniger combustion technic. Metabolites were searched for by threedimensional 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 ³H digoxin intravenously², ⁶ and orally¹, ¹⁶ 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 ³H 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 (38*)</th>
<th>Intravenous bilary 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>
<tr>
<td>Total excretion, 7 days, in % of total dose administered</td>
<td></td>
<td></td>
<td></td>
</tr>
<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.

*Burroughs-Wellcome and Co. (USA), Inc., Tuckahoe, New York.
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 \(^3\)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\( \frac{1}{2}\) is 32.5 hours; however, individual variability of the serum T\( \frac{1}{2}\) 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\(^2\) 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. Naso-gastric 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\( \frac{1}{2}\) (line B) was determined by these and additional points throughout the 7-day study period. A logarithmic plot was
Figure 1

Composite graph of serum turnover of tritiated digoxin in patients with surgically induced biliary fistula. Radioactivity is plotted on the vertical axis as per cent of the 5-min specimen on a logarithmic scale; time is plotted on the horizontal. Line A represents the actual counting rate expressed in per cent. 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.

utilized so that line B (the best straight line after the serum plateau is reached) can be extrapolated to zero and a dominant half-time for disappearance of the drug determined. The dominant T½ in this graph is 32.3 hours. This portion of the serum turnover curve is determined to be a result of metabolism and excretion of the drug and can be eliminated from the early portion of the curve A by subtracting the figure obtained for line B from simultaneous points of curve A above. This maneuver yields another straight line function for which a T½ can be expressed. This line, designated as line C, represents distribution and binding of digoxin to tissue (metabolism and excretion having been eliminated as factors). Line C has a half-time in these patients of 45 min. These figures resemble

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.
TRITIATED DIGOXIN

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 per cent 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:
absolute%  
thus:  

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

It should be appreciated that refined pharmacokinetic studies are rarely obtainable for human subjects. We have chosen to base our calculations upon the data presented in this communication, as well as that obtained from six normal individuals who received digoxin by the oral route prior to nephrectomy as donors for renal transplant,10 12 patients with congestive heart failure,1 and 16 patients with thyroid disease6 whose excretion (but not their serum levels) approximates that of the other patients studied. These calculations reveal that the amount of absolute absorption of digoxin is 85% and the amount of enterohepatic circulation (recycling) is 6.5%. This figure can be compared to the estimate of Okita20 that 26% of an administered dose of digitoxin will participate in the enterohepatic circulation.

These data are in accord with the impression that polarity of the digitalis glycoside is of critical importance in determining excretion of the drug, its enterohepatic circulation, and thus the duration of therapeutic action in human subjects. Polar digoxin could be expected to be, and is, a short-acting glycoside (T ½, 34 hours), and nonpolar digitoxin, a long-acting glycoside (T ½, 105 hours).

A major reason for the short duration of action of digoxin, then, is the lack of recycling (or reabsorption) in the intestine. The polar characteristics of this glycoside also may account for its lack of degradation in the human body except by abnormal metabolic pathways.21 The nonpolar glycoside, digitoxin, on the other hand, appears to be extensively recycled during the process of its metabolism.20 The nonpolar characteristics of digitoxin thus contribute to its long duration of action and its properties of binding to serum protein.22, 23

A recent report by Caldwell and Greenberger24 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 T ½ as well as the serum turnover T ½ 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,20 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,25–27 which reveal similar half-times and excretion.

Acknowledgment

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

References

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