Studies with Tritiated Digoxin in Anephric Human Subjects

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SUMMARY
Tritiated digoxin was given to 11 patients when anephric prior to renal transplant. These patients exhibited high digoxin serum levels, increased digoxin serum half-times, and reduced excretion of digoxin compared to those of patients with congestive heart failure and normal BUN and are similar in this respect to patients with severe compromise of renal function. The stool excretion of digoxin is increased in anephric patients, but this does not compensate for the lack of renal excretion of digoxin. These findings indicate the need for prudent administration of digoxin to anephric patients, as well as those with renal failure. Often the dose of digoxin may be reduced as much as one third to one half of the usual maintenance dose.

ADDITIONAL INDEXING WORDS:
Congestive heart failure
Renal failure

Digoxin is excreted by the kidney primarily as unchanged digoxin.\textsuperscript{1-3} Approximately 70 to 80\% can be recovered from the urine in a 7-day study after a single intravenous dose.\textsuperscript{2} Urinary excretion is reduced in patients with renal failure.\textsuperscript{4-6} Patients with severe renal failure excrete only about 25\% of an intravenous dose of digoxin in the urine in a 7-day study. A slight increase in the stool digoxin content is observed. A radiohydrogen digoxin turnover study of patients completely deprived of renal function should provide useful information regarding the serum levels and disposition of digoxin in these patients and lend new insight for the interpretation of previous metabolic studies of digoxin in patients with renal failure and those with normal renal function and congestive heart failure.

The purpose of this study was to document the serum levels and excretion of tritiated digoxin in subjects who were subjected to bilateral nephrectomy prior to renal transplant and to determine if the stool excretion assumed a more important role in these patients.

Methods
Tritiated digoxin was prepared by the Wilzbach hydrogen exchange method with specific activities of 66 to 125 microcuries per milligram. It was radiochromatographically pure, sterile and free of pyrogens.

Ten patients who were anephric prior to renal transplant were given 0.5 to 1.0 mg of tritiated digoxin intravenously; one received digoxin orally. One patient was given two doses of tritiated digoxin, one before bilateral nephrectomy, one after. All patients except numbers 5 and 8 were also subjected to splenectomy.

Frequent serum samples were obtained and all stools were saved for 7 days. Dialysate was collected from peritoneal or hemodialysis.
Clinical Information

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Race</th>
<th>BUN*</th>
<th>Dose of digoxin</th>
<th>Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&amp; sex</td>
<td></td>
<td></td>
<td>Mg</td>
<td>µc</td>
</tr>
<tr>
<td>1</td>
<td>38 M</td>
<td>W</td>
<td>85</td>
<td>0.5</td>
<td>30</td>
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<tr>
<td>2</td>
<td>29 M</td>
<td>W</td>
<td>104</td>
<td>1.0</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>21 F</td>
<td>N</td>
<td>64</td>
<td>1.0</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>31 F</td>
<td>W</td>
<td>90</td>
<td>1.0</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>28 M</td>
<td>W</td>
<td>25</td>
<td>0.5</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>25 M</td>
<td>W</td>
<td>112</td>
<td>1.0</td>
<td>125</td>
</tr>
<tr>
<td>7</td>
<td>47 M</td>
<td>W</td>
<td>69</td>
<td>0.5</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>65 F</td>
<td>N</td>
<td>195</td>
<td>1.0</td>
<td>125</td>
</tr>
<tr>
<td>9</td>
<td>49 M</td>
<td>N</td>
<td>114</td>
<td>1.0</td>
<td>125</td>
</tr>
<tr>
<td>10</td>
<td>35 F</td>
<td>W</td>
<td>138</td>
<td>1.0</td>
<td>125</td>
</tr>
<tr>
<td>11</td>
<td>17 F</td>
<td>W</td>
<td>120</td>
<td>1.0</td>
<td>125</td>
</tr>
</tbody>
</table>

*BUN = Blood urea nitrogen in mg per 100 ml.
†Pathological diagnosis on a large single kidney removed at another institution not available.

All specimens were extracted with chloroform, passed through an alumina column and eluted with a 2:1 chloroform-ethanol mixture. The specimens were then evaporated, counting solution was added,* and counting was done in a liquid scintillation counter.† All counting rates were corrected with an internal standard. This method will recover 95% of a known quantity of digoxin including the metabolites digoxigenin monodigitoxoside and di-digitoxoside, which are also cardioactive.

Results

The clinical information and renal diagnosis on the 11 patients selected for study is shown in table 1. The concentration of blood urea nitrogen (BUN) is shown as this can be inversely correlated with the excretion of digoxin in patients with renal failure; the higher the BUN values, the less digoxin is excreted.4

Figure 1 illustrates the composite serum turnover for all anephric patients and shows the derived exponential functions. Counts per minute per milliliter are plotted on a semilogarithmic scale on the vertical axis, time on the horizontal. Although time is only extended through 60 hours for better demonstration of the exponential functions, the study continued 7 days. Curve A represents the actual counting rates. Line B is the best straight line that can be drawn after the serum plateau is reached, extrapolated to zero time, and is the dominant serum half-time; it should represent the metabolism and excretion of digoxin. Line C is curve A minus line B, thus eliminating the function of metabolism and excretion and represents tissue distribution and binding of

*Counting solution: 4.0 g 2,5-diphenyloxazole, 0.1 g p-bis 2-(5-phenyloxazolyl)-benzene, 1.0 g hyamine 10-X; 3.5 ml methanol. Volume brought to 1 L with toluene.
†Packard Instrument Company, LaGrange, Illinois.

Figure 1

Composite serum digoxin curve on all anephric patients. Serum concentration is plotted on a semilogarithmic scale on the vertical axis as percentage of the 15-minute counting rate, time in hours on the horizontal axis. Derivation of the exponential functions is given in the text. The dominant serum half-time is 93 hours (line B). The half-time of line C is 46 minutes.
### Table 2

**Digoxin Serum Half-Time and Excretion**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stool excretion of digoxin</th>
<th>% of total dose administered</th>
<th>Dialysis time (hr)</th>
<th>Stool T 1/2 (days)</th>
<th>Serum digoxin T 1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
<td>Day 5</td>
<td>Day 7</td>
<td>Urine 7 day</td>
</tr>
<tr>
<td>1</td>
<td>8.11</td>
<td>23.13</td>
<td>32.13</td>
<td>38.22</td>
<td>2.48</td>
</tr>
<tr>
<td>2</td>
<td>0.14</td>
<td>8.88</td>
<td>16.47</td>
<td>21.42</td>
<td>0.90</td>
</tr>
<tr>
<td>3a*</td>
<td>3.68</td>
<td>19.27</td>
<td>32.05</td>
<td>32.84</td>
<td>0.138</td>
</tr>
<tr>
<td>b</td>
<td>3.71</td>
<td>20.31</td>
<td>30.84</td>
<td>36.97</td>
<td>0.66</td>
</tr>
<tr>
<td>4</td>
<td>9.83</td>
<td>29.36</td>
<td>36.89</td>
<td>40.00</td>
<td>2.03</td>
</tr>
<tr>
<td>5</td>
<td>15.62</td>
<td>17.13</td>
<td>25.69</td>
<td>27.58</td>
<td>0.29</td>
</tr>
<tr>
<td>6</td>
<td>5.27</td>
<td>14.34</td>
<td>26.59</td>
<td>33.98</td>
<td>1.70</td>
</tr>
<tr>
<td>7</td>
<td>10.36</td>
<td>16.72</td>
<td>24.87</td>
<td>37.43</td>
<td>2.73</td>
</tr>
<tr>
<td>8†</td>
<td>8.86</td>
<td>10.63</td>
<td>30.40</td>
<td>34.69</td>
<td>2.00</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>23.21</td>
<td>30.40</td>
<td>34.69</td>
<td>2.85</td>
</tr>
<tr>
<td>10</td>
<td>1.78</td>
<td>12.07</td>
<td>16.09</td>
<td>19.44</td>
<td>1.75</td>
</tr>
<tr>
<td>11</td>
<td>2.81</td>
<td>19.28</td>
<td>25.36</td>
<td>30.54</td>
<td>1.81</td>
</tr>
<tr>
<td>Mean</td>
<td>5.25</td>
<td>18.59</td>
<td>26.63</td>
<td>32.56</td>
<td>1.75</td>
</tr>
</tbody>
</table>

| Congestive heart failure | 8.7 | 9.7 | 11.8 | 80.0 | — | 91.8 | 33.6 | 30.4 |
| With renal failure | — | 6.89 | 13.40 | 16.54 | 23.30 | — | 39.84 | 83.3 | 66.1 |

*a, study performed before nephrectomy; b, study performed after nephrectomy.
†Not included in mean.
‡Excretion through 32 hours only.
§Data insufficient for calculation.
the glycoside. An additional exponential could be derived if more frequent early serum samples were obtained, representing serum distribution.

Table 2 shows the individual serum half-times and excretions obtained on the 11 anephric patients.

Two patients expired during the course of observation and postmortem tissue studies were carried out for tritiated digoxin. The data on the tissue analyses from these patients is shown in figures 2 and 3.

**Discussion**

The data obtained from anephric patients are similar to that obtained from patients with renal failure and are related to the prolongation of renal excretion. The effect on the serum concentration of tritiated digoxin is shown in figure 4. The composite serum turnover curves in anephric patients, patients with renal failure, and patients with congestive heart failure and normal renal function are shown. Highest serum levels are seen in anephric patients with no renal function; intermediate in renal failure; and the lowest serum levels in patients with uncomplicated heart failure. Serum half-times are also appropriately increased in anephric patients and patients with renal failure.

These data are supported by the digoxin excretory studies summarized as a bar graph in figure 5. The excretory rates of digoxin are lowest in anephric patients, intermediate in renal failure, and highest in congestive heart failure without renal failure after comparable doses of the glycoside.
Seven-day digoxin excretion in congestive heart failure with normal BUN (CHF), renal failure, and in the anephric state. Digoxin excretion is plotted as percentage of the total dose administered on the vertical axis; the total excretion is shown below each column. Urine excretion is indicated by the solid bar, stool excretion by the cross-hatched bar, and dialysate excretion by the stippled bar.

Much larger amounts of digoxin are recovered from the stool of patients with renal failure, partially compensating for the lack of renal function in these patients. Even greater increases in stool digoxin excretion are seen in the anephric patient, often as much as two to three times that found in patients with normal renal function, partially compensating for the complete lack of urinary excretion. Similar results were demonstrated in anephric dogs by Marcus and co-workers\(^5\) following administration of tritiated digoxin.

Patient 3 (table 2) was studied before and after bilateral nephrectomy. Renal function was minimal during the first study; stool excretion of digoxin increased slightly after bilateral nephrectomy.

The tissue studies on the two anephric patients who expired during the course of hospitalization, shown in figures 2 and 3, indicate higher tissue concentrations in these patients when compared to patients with renal failure and patients with congestive heart failure.\(^7\) The digoxin concentration in heart muscle is particularly increased. Marcus and associates\(^5\) demonstrated increased tissue digoxin in anephric dogs and dogs with renal failure, which supports these observations and which is consistent with the reduction in digoxin excretion and increased digoxin sensitivity of these patients.

It is of interest that peritoneal dialysis and hemodialysis removed only very small amounts of digoxin in spite of the readily dialyzable properties of digoxin.\(^6, \ 8\) This is explained by the low blood level of digoxin compared to that present in tissue which is not readily available for dialysis.

The clinical importance of these findings is evident when one considers the number of patients whose congestive heart failure is accompanied by renal failure. Renal failure is often accompanied by potassium retention and overt digitalis toxicity may be absent or unrecognized; however, it may be readily precipitated by peritoneal or hemodialysis when potassium levels are reduced without an appreciable fall in the total body digoxin, particularly that present in the cardiac muscle.

The stool excretion of digoxin is increased in renal failure and even more so in the anephric subject. This probably accounts for many patients who appear to tolerate average digoxin dosage with renal failure or when in the anephric state without digitalis toxicity.

The dose of digoxin for anephric patients and in cases of renal failure should be critically determined. In our experience these patients may be maintained on one half to two thirds of the usual dose of digoxin. Although overt digitalis intoxication is not present, toxicity is evident with peritoneal dialysis or hemodialysis even before normal serum potassium levels are achieved, thus confirming the presence of increased total body and cardiac muscle digoxin.

**Acknowledgment**

The authors wish to acknowledge the help of the nursing staff of the Clinical Study Section of the University of Arkansas Medical Center in Little Rock for clinical care and assistance in collection of specimens from the patients included in this study. The tritiated digoxin was supplied by Drs. Donald S. Searle, Stanley Bloomfield, and C. W. Ferry, and by Mr. James Murphy of the Burroughs-Wellcome & Co. (USA) Inc., Tuckahoe, New York.

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TRITIATED DIGOXIN

References

Hope and Prognosis

Many think that the expectation of effecting an improvement in the treatment of diseases of the heart, is chimerical: and they think so because, not being accustomed to recognize the diseases in question before they have attained an advanced stage, they are preoccupied with the old and popular idea of their incurability. To such it might, perhaps, be a sufficiently philosophical answer to reply, that an improved knowledge of the nature and causes of a disease must alone necessarily lead to an improvement in the treatment; and that therapeutic weapons are dangerous when wielded in the dark. But here we may go much farther: we may say that, by the improved means of diagnosis, the maladies under consideration may be recognized, not only in their advanced but in their incipient stages, and even when so slight as to constitute little more than a tendency. We may say, on the grounds of incontestable experience, that, in their early stages, they are, in a large proportion of instances, susceptible of a perfect cure; and that, when not, they may in general, be so far counteracted as not materially, and sometimes not at all to curtail the existence of the patient. We may, accordingly, predict that the term "disease of the heart," which at present sounds like a death knell when uttered by the physician, will hereafter become by familiarity not more alarming than the term asthma, under which it is frequently disguised. James Hope: A Treatise on the Diseases of the Heart and Great Vessels, ed. 1 American. Philadelphia, Haswell & Johnson, 1842, p. 22.
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