The Excretion of Tritiated Digoxin in Normal Human Volunteers Before and After Unilateral Nephrectomy

By James E. Doherty, M.D., William J. Flanigan, M.D., Rodney M. Patterson, M.D., and Glenn V. Dalrymple, M.D.

With the technical assistance of Jacquelyn Gammill, B.S., M.T. (ASCP), and Joyce Sherwood, B.S., M.T. (ASCP)

SUMMARY

Six normal human volunteers as renal transplant donors were given $^3$H-digoxin before and again after unilateral nephrectomy. The serum digoxin concentration was modestly increased following nephrectomy, the serum digoxin half-time was slightly prolonged, and total digoxin excretion for the group was reduced by only 6.4% during a 7-day study. Four of the six patients studied before and after unilateral nephrectomy exhibited no important reduction in digoxin excretion after nephrectomy; two patients excreted only 66% and 64% as much of the administered dose of digoxin as they had excreted compared to the control study. The removal of one kidney from an individual whose remaining kidney is normal does not usually cause significant reduction in the excretion of tritiated digoxin, and one may conclude that in such instances nephrectomy should not in itself prompt a change in digoxin dosage provided the remaining kidney achieves its expected increased functional capacity. The adequacy of renal function determines digoxin excretion and the dosage of digoxin in these patients.

Additional Indexing Words:
Creatinine clearance    Digoxin clearance    Renal transplant donors
Tritiated digoxin turnover

digoxin by the transplanted human kidney is directly proportional to the functional status of the transplant.

TRITIATED DIGOXIN is excreted primarily as unchanged digoxin by the kidney.1-4 Prolongation of digoxin excretion has been noted in renal failure6-7 and in anephric subjects awaiting transplantation.8 It has been shown that quantitative excretion of digoxin by the transplanted human kidney is directly proportional to the functional status of the transplant.9 The purpose of this study was to determine the renal excretion, serum levels, and turnover rates of tritiated digoxin in normal subjects before and after unilateral nephrectomy, and thus provide additional clarifying data in regard to the apparent inter-relationship between existing renal function and urinary excretion of digoxin.

Methods

Six human subjects who were to undergo nephrectomy as donors for renal transplantation were studied before and after nephrectomy. Preoperative evaluation revealed these patients to be normal in every respect. Tritiated digoxin was prepared by the Wilzbach hydrogen exchange method; it possessed a specific activity of 125 μc/mg and was sterile and chemically and radio-
Table 1

*Individual Digoxin Excretion and Serum Turnover Rates*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Days after nephrectomy</th>
<th>Age (yr)/sex</th>
<th>Cumulative stool excretion*</th>
<th>Cumulative urine excretion*</th>
<th>Urine T 1/2</th>
<th>Total excretion</th>
<th>Serum T 1/2</th>
<th>CDig/CCr (eq/min)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 1   Day 3   Day 5   Day 7</td>
<td>Stool T 1/2</td>
<td>Day 1   Day 3   Day 5   Day 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (a)</td>
<td>50/W/F</td>
<td>1.28</td>
<td>11.01   13.26   13.99</td>
<td>1.4</td>
<td>18.82   34.03   39.36   41.59</td>
<td>1.4</td>
<td>55.58</td>
<td>34.3</td>
<td>62</td>
</tr>
<tr>
<td>(b) 25</td>
<td></td>
<td>2.41</td>
<td>8.77    15.75   16.54</td>
<td>1.4</td>
<td>18.21   31.86   38.55   41.52</td>
<td>1.6</td>
<td>58.06</td>
<td>42.7</td>
<td>62</td>
</tr>
<tr>
<td>2 (a)</td>
<td>35/W/M</td>
<td>0.02</td>
<td>1.73    1.73    1.73</td>
<td>NS</td>
<td>26.78   44.31   48.74   51.92</td>
<td>1.4</td>
<td>53.65</td>
<td>23.5</td>
<td>36</td>
</tr>
<tr>
<td>(b) 13</td>
<td></td>
<td>0.49</td>
<td>7.84    12.41   12.41</td>
<td>1.5</td>
<td>13.70   25.71   32.58   36.03</td>
<td>1.7</td>
<td>48.44</td>
<td>43.3</td>
<td>52</td>
</tr>
<tr>
<td>3 (a)</td>
<td>36/W/M</td>
<td>0.11</td>
<td>5.53    6.36    6.66</td>
<td>1.3</td>
<td>27.68   46.47   54.19   58.09</td>
<td>1.8</td>
<td>64.75</td>
<td>40.3</td>
<td>50</td>
</tr>
<tr>
<td>(b) 21</td>
<td></td>
<td>0.20</td>
<td>7.21    11.82   13.36</td>
<td>1.4</td>
<td>12.15   21.12   36.46   29.13</td>
<td>2.0</td>
<td>42.49</td>
<td>58.3</td>
<td>84</td>
</tr>
<tr>
<td>4 (a)</td>
<td>48/W/M</td>
<td>7.00</td>
<td>23.9    25.7    26.6</td>
<td>1.0</td>
<td>18.4    31.2    34.8    36.6</td>
<td>1.7</td>
<td>63.2</td>
<td>30.0</td>
<td>55</td>
</tr>
<tr>
<td>(b) 10</td>
<td></td>
<td>8.80</td>
<td>18.3    22.6    24.1</td>
<td>1.5</td>
<td>19.5    32.9    37.8    40.1</td>
<td>1.7</td>
<td>64.2</td>
<td>41.7</td>
<td>52</td>
</tr>
<tr>
<td>5 (a)</td>
<td>53/W/F</td>
<td>0.00</td>
<td>19.3    21.4    21.4</td>
<td>2.1</td>
<td>15.3    25.3    30.1    32.4</td>
<td>1.7</td>
<td>53.8</td>
<td>31.7</td>
<td>50</td>
</tr>
<tr>
<td>(b) 13</td>
<td></td>
<td>1.25</td>
<td>15.4    16.6    16.6</td>
<td>1.0</td>
<td>6.4     10.3    15.0    19.0</td>
<td>1.4</td>
<td>35.6</td>
<td>48.3</td>
<td>60</td>
</tr>
<tr>
<td>6 (a)</td>
<td>22/W/M</td>
<td>0.65</td>
<td>9.62    14.15   16.43</td>
<td>1.1</td>
<td>19.41   32.15   38.29   40.65</td>
<td>1.8</td>
<td>57.08</td>
<td>32.6</td>
<td>36</td>
</tr>
<tr>
<td>(b) 8</td>
<td></td>
<td>0†</td>
<td>5.58    6.61   ns</td>
<td>18.85</td>
<td>34.12    40.94   44.25</td>
<td>1.7</td>
<td>50.86</td>
<td>42.7</td>
<td>48</td>
</tr>
</tbody>
</table>

Mean:

|         | (a)                     | (b)          | (a)   Day 1 13.77   14.47 1.38   21.07   35.58   40.91   43.54   1.63 | 58.01  | 32.07   48   110.5/106.8 | 1.05 |
|         | (b)                     | 6.05         | 11.50   15.84   16.60 | 1.36  | 14.81   26.02   31.88   35.01 | 1.68   | 51.51           | 46.17 | 60              | 71.5/75.0 | 0.95 |

Abbreviations: (a) = before nephrectomy; (b) = after nephrectomy; B and C see text and figure 1; NS = specimens insufficient for calculation.

*Expressed as per cent of total administered dose.
† Determinations not done.
‡ Specimens lost.
EXCRETION OF TRITIATED DIGOXIN

Each subject received 1 mg of tritiated digoxin orally at the initiation of the study. During the following 7 days frequent serum samples were collected, and all urine and stools were saved for subsequent analysis. All samples were analyzed for radioactivity representing digoxin and its primary metabolites, digoxigenin mono-digitoxiside, bis-digitoxiside, and digoxigenin, by a method of extraction and alumina column chromatography previously described. Samples were counted in a liquid scintillation spectrometer and results were tabulated with an IBM 1620 computer.

Results

Table 1 shows the stool and urine excretion and half-times, serum half-times, digoxin clearance, and digoxin-to-creatinine clearance ratios. It may be seen that urinary excretion of digoxin is only moderately reduced and stool digoxin excretion moderately increased after unilateral nephrectomy. Total digoxin excretion was reduced by less than 10%.

The composite serum turnover is graphically illustrated in figure 1. Digoxin concentration is plotted vertically, and time horizontally. Curve A represents the actual radioactive counts of tritiated digoxin, plotted as μg digoxin/kg × 10⁶. Line B represents the dominant serum half-time (the time required for one half of the radioactivity representing digoxin to disappear from the serum) and represents metabolism and excretion of digoxin. This exponential function has a half-time of 36 hours in these subjects before nephrectomy, and 47 hours after nephrectomy in this composite graph. Line C is a second exponential function and represents tissue distribution and binding of digoxin. It is derived by subtracting the points on line B from the points on curve A, thus excluding metabolism and excretion of digoxin from this portion of the curve. The half-time of line C was 50 minutes before nephrectomy, and 55 minutes after nephrectomy. Note that serum levels are only slightly higher after nephrectomy compared to before. These differences in the half-times and serum levels were determined by an IBM 1620 computer and are statistically significant. Individual curves for serum half-times are shown in figure 2. Note that there is some variability in the slope of the curves from patient to patient; however, comparison of the serum levels before and after nephrectomy demonstrates higher serum levels of digoxin after nephrectomy in every patient.
Figure 2
Individual serum digoxin turnover curves obtained on six normal subjects before (●) and after (○) unilateral nephrectomy. Serum digoxin levels are indicated on the vertical axis as µg of digoxin/kg × 10⁻⁶, and as time on the horizontal axis. Note some variation in the slope of the curves and the consistent elevation of serum digoxin levels following nephrectomy.

Figure 3 indicates the mean total excretion of tritiated digoxin before and after nephrectomy in these patients, for the 7-day study period. The excretion of tritiated digoxin in the stool is slightly increased and the urinary excretion is reduced in these patients after nephrectomy, when compared to a similar study before nephrectomy. Three patients excreted the same amount of tritiated digoxin in the urine as before operation or even more in 7 days. The remaining three patients excreted from 13 to 29% less of the total dose of tritiated digoxin following nephrectomy than they did before nephrectomy. The length of
time this study was performed after nephrectomy (shortest time, 8 days; longest time, 25 days) did not influence the amount of digoxin excreted (table 1).

All of these changes in excretion were related to the reduction observed in creatinine clearance, and no definite pattern could be related to time following transplant when the study was accomplished. The oldest donor (patient 5, table 1) was 53 years of age and had the lowest urinary excretion of digoxin before nephrectomy, as well as the lowest creatinine clearance. She experienced the largest reduction in excretion after nephrectomy (66% of the amount of the total dose excreted during control study). This patient’s CDig:CCr was 0.93 before nephrectomy and 0.90 afterward, demonstrating very well the relationship of creatinine clearance to digoxin excretion.

It is obvious that should this particular patient ever require digoxin therapeutically, a downward adjustment in the dosage will be necessary, probably in the order of 50% of the usual dosage. It is noteworthy that this reduction in digoxin excretion could be easily predicted from the patient’s reduced creatinine clearance.

Patient 3 (table 1) experienced a similar decrease in digoxin excretion (excreting 64% of the amount excreted in the control period).

Figure 4 illustrates the relationship of the creatinine clearance to the clearance of tritiated digoxin before and after nephrectomy. The ratio of creatinine clearance to digoxin clearance approaches unity in both studies, and the correlation coefficient is 0.832 for the regression line.

Discussion

That digoxin turnover and excretion are closely related to renal function has been consistently shown by previous studies.5-9 The removal of a normal kidney from an individual with normal bilateral renal function offered an opportunity to determine the reserve ability of the remaining normal kidney to excrete tritiated digoxin. The adaptive increase in glomerular filtration rate which occurs in the remaining kidney after unilateral nephrectomy is well established.10 The functional ability of the single kidney to increase digoxin excretion is demonstrated in this study. Only a 6% mean reduction in the total 7-day excretion was observed after unilateral nephrectomy in these
patients. The reduction in renal excretion roughly parallels the decrease in glomerular filtration rate, the ratio of $C_{\text{dig}}$ to $C_r$ being 0.95, compared to a ratio of 1.05 before nephrectomy.

Inspection of the dominant digoxin serum half-times (time required for one half of the dose originally determined to be present at zero time to be excreted or metabolized) reveals considerable variation during the control study (24 to 40 hours). There was a consistent increase in the serum half-time following nephrectomy. Serum digoxin levels were consistently higher following nephrectomy. These changes were accompanied by reductions in digoxin excretion which can be measured with much greater accuracy and are felt to be a more reliable index for evaluation of digoxin requirement than serum levels. Patients with severe reduction in renal function and renal insufficiency have much more greatly prolonged serum half-times and higher serum levels of digoxin$^6$-$^7$ than those observed in this group of postnephrectomized normal individuals.

Because excretion of digoxin is prolonged by renal insufficiency, it is customary to administer smaller than usual doses of digoxin to such patients. One might therefore expect a similar impairment of digoxin excretion following unilateral nephrectomy. The compensatory increase in glomerular filtration rate after nephrectomy in normal subjects is of sufficient magnitude to compensate for the reduction in renal mass, thus permitting cumulative digoxin excretion comparable to that observed in normals. Although these studies were accomplished in "normal" subjects, Marcus and associates$^4$ have shown that there is no significant difference in digoxin turnover and excretion in normal subjects compared to those with congestive heart failure. Our studies confirm this observation and support the concept that there is no alteration in digoxin serum levels, metabolism, or excretion in the "normal" state compared to that in patients with congestive heart failure.

The clinical implication of our study appears clear; namely, that renal functional capacity, whether by one kidney or two, determines digoxin excretion. Should digoxin administration be required in a unilaterally nephrectomized patient, ordinary doses of digoxin will usually suffice to achieve and maintain adequate digitalization. Dosage of digoxin might be appropriately based upon a scheme such as that proposed by Jelliffe$^{11}$ which bases dosage requirement and body stores of digoxin upon knowledge of creatinine clearance. In general, no alteration in digoxin dosage is recommended until creatinine clearance approaches 50 ml/min, because there is an increase in nonurinary digoxin excretion in renal failure. Any downward adjustment in the dose of digoxin should be judged on the basis of observed reduction of creatinine clearance,$^5$ or increase in the blood urea nitrogen.$^5$

Acknowledgment

The authors wish to acknowledge the assistance of the nursing staff of the Clinical Research Center of the University of Arkansas Medical Center, and the encouragement of the medical staff of the University of Arkansas Medical Center. The help of Drs. Donald S. Searle and Stanley T. Bloomfield, and Mr. James Murphy of Burroughs Wellcome & Company (USA), Inc., in providing the tritiated digoxin used in these studies was invaluable. The secretarial assistance of Mrs. Sondra Stone is greatly appreciated, as is the photographic work of Mr. Fred Jungkind. The encouragement of Dr. Eugene Towbin, Dr. Joseph Bates, and Dr. Robert Abernathy is gratefully acknowledged.

References


Circulation, Volume XL, October 1969
EXCRETION OF TRITIATED DIGOXIN


The Excretion of Tritiated Digoxin in Normal Human Volunteers Before and After Unilateral Nephrectomy

JAMES E. DOHERTY, WILLIAM J. FLANIGAN, RODNEY M. PATTERSON, GLENN V. DALRYMPLE, Jacquelyn Gammill and Joyce Sherwood

Circulation. 1969;40:555-561
doi: 10.1161/01.CIR.40.4.555

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1969 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/40/4/555

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/