Digoxin Metabolism in the Elderly

By Gordon A. Ewy, M.D., Geeta G. Kapadia, Ph.D., Linda Yao, Muriel Lullin, and Frank I. Marcus, M.D.

SUMMARY
Tritiated digoxin (0.5 mg) was given intravenously to five elderly men (mean age, 77 years) and nine young men (mean age, 27 years). The elderly were not in congestive heart failure. The serum creatinines of the old and young were not different. However, the creatinine clearance averaged 56 ml/min/1.73 m² in the old and 122 ml/min/1.73 m² in the young (P < 0.001). Digoxin clearance averaged 53 ml/min/1.73 m² in the old and 83 ml/min/1.73 m² in the young (P < 0.001). The blood concentrations of tritiated digoxin were significantly higher in the elderly throughout the study (P < 0.05). When blood digoxin concentrations were corrected for body surface area, there was no significant difference between the two groups during the first 24 hr, but thereafter the concentrations in the elderly were higher.

The same dose of digoxin resulted in higher blood concentrations and longer blood half-life in the elderly. This is due to the smaller body size and a diminished urinary excretion of digoxin in the elderly.

Additional Indexing Words:
Creatinine clearance Renal excretion of digoxin

The elderly patient may develop digitalis toxicity when given digoxin in amounts that are well tolerated by younger individuals.1-11 It is not known whether the apparent sensitivity in the elderly is related to an increased sensitivity of the aged myocardium to normal concentrations of digitalis or whether usual dosages of digitalis result in a higher myocardial concentration of the glycoside.

Since creatinine clearance is decreased in the elderly12-15 and since digoxin is predominantly excreted by the kidneys,16-19 it was postulated that the apparent sensitivity of the elderly patient to digitalis might be related in part to decreased renal excretion. To investigate this hypothesis, digoxin metabolism was studied in a group of elderly volunteers.

Methods
Five men, aged 73 to 81 years, were recruited from an old age social organization and hospitalized on the Clinical Study Unit at Georgetown University Hospital. Nine men between ages 20 and 33 years served as controls. The younger healthy volunteers were inmates of the District of Columbia Jail.

Each subject had a history taken and had a physical examination in addition to a chest roentgenogram, electrocardiogram, hemogram, urinalysis, blood urea nitrogen, and serum creatinine determinations. Serum electrolytes, calcium phosphorus, blood glucose, urine cultures, and intravenous pyelograms were obtained only on the elderly subjects.

The elderly subjects were not free of disease. Three had angina; two had glucose intolerance; one was hypertensive, had sustained a cerebral vascular occlusion 15 years previously, and had residual upper extremity paralysis. One had moderate obstructive pulmonary emphysema. However, none had evidence of congestive heart failure, none were taking digitalis, and none had a history of renal disease. The mean weight of the elderly patients was 143 pounds. Clinical evaluations of the younger subjects...
were within the limits of normal. All subjects were on regular diets with unrestricted intake of fluid and physical activity.

All subjects were given a single intravenous injection of 0.5 mg of tritiated digoxin as a 10% alcoholic solution over a 1-min period. Zero time was taken as the end of the injection. Specimens of venous cubital vein 3, 15, and 30 min, and 1, 2, 8, 12, and 24 hr after the injection, and daily thereafter for 8 days. All stool specimens were collected for 8 days.

Endogenous serum creatinine clearances were calculated for each patient from the third to the eighth day after digoxin was given. The creatinine clearances on each patient represent the average of five consecutive 24-hr creatinine clearances. Digoxin clearances were calculated by analyzing the 24-hr urine concentrations of digoxin on the second through the fifth day. The blood concentration on a given day was taken as the average between the blood levels obtained at the beginning and end of each 24-hr period. The digoxin and creatinine clearances were expressed in milliliters per minute per 1.73 square meters of body surface area (m² BSA).

The concentration of digoxin was measured by methods previously reported in this laboratory. Briefly, blood samples were extracted with 20% ethanol in chloroform. The solvent was evaporated and an aliquot was counted directly. The recovery of tritiated digoxin added to blood prior to extraction was 98.6 ± 4.5% (mean ± 1 SD). The radioactivity in each sample of urine was determined in triplicate by pipetting a 0.2-ml aliquot of urine into vials containing naphthalene-dioxane counting solution. Stools were homogenized in a blender, and aliquots of known weights were dried and combusted by a modification of the Schoniger combustion technic. The recovery of tritiated digoxin added to biologic samples and combusted was 86.4 ± 2.9%. The radioactivity of each specimen was counted in a Model 314 EX Packard Tricarb Liquid Scintillation Counter. The counts were corrected for quenching by adding tritiated toluene of known activity and recounting. Differences in radioactivity between the two groups were analyzed using the two-tailed Student t-test.

**Results**

Following a single intravenous dose of tritiated digoxin, concentrations of digoxin and metabolites were found to be almost twice as high in the elderly as in the younger subjects (fig. 1). This higher blood concentration was sustained throughout the period of measurement. When blood concentrations were related to body weight by calculating the digoxin concentration in micrograms (µg) per liter per 70 kg of body weight, the differences were not significant during the first 24 hr (fig. 2). Thereafter, the blood concentrations in the elderly subjects were again significantly higher ($P<0.01$). The metabolites. The concentration of digoxin in the blood is usually too small for satisfactory fractionation. However, extraction and partition chromatography of urine in patients previously studied indicate that nearly 90% of the radioactivity migrates with unchanged digoxin and the remainder with the cardio-active metabolites digoxigenin-mono-digitoxoside and digoxigenin-bis-digitoxoside. Studies of the metabolism of tritiated digoxin in renal insufficiency in dogs and man indicate that the drug is likewise excreted primarily unchanged.

---

*Hereafter, digoxin will refer to digoxin and meta-*

---

![Figure 1](http://circ.ahajournals.org/)

Concentration of digoxin in micrograms (µg) per liter of blood at intervals after the injection of tritiated digoxin. P values are all less than 0.005 except for the 1 and 2 hr samples which are less than 0.025 and 0.05 respectively.
mean blood half-life of digoxin was prolonged to 73 hr in the elderly compared to 51 hr in the normals.

Although the average blood urea nitrogen (BUN) concentration of the elderly subjects was only 10 mg% higher than the mean value in the normals and the serum creatinine levels were not significantly different in the two groups, the measured creatinine clearances of the elderly were less than half the clearances of the normals (table 1). The 24-hr creatinine clearance averaged 56 ml/

\[ \text{min/1.73 m}^2 \text{ BSA} \] in the elderly compared to a value of 122 in the young. The digoxin clearance was also significantly lower in the elderly (table 1).

**Discussion**

There is a general clinical impression that digitalis intoxication is more likely to occur in the elderly, \(^1\)-\(^11\) and that this complication is potentially serious, even fatal.\(^{25}\) Accordingly, it is common practice to decrease the initial and maintenance doses of digitalis when treating the aged. However, the reason for the sensitivity has not been hitherto established. It has, therefore, not been possible to judge the amount by which a given dose should be reduced.

Our studies indicate that the same dose of digoxin given to elderly and young adult subjects results in blood concentrations nearly twice as high in the elderly (fig. 1). The relatively high blood concentrations of digoxin in our elderly subjects probably have clinical significance, since it has been shown that plasma concentrations of digitoxin are directly correlated with the daily administered dose\(^{26}\) (correlation coefficient, \(r = 0.91\)); furthermore, patients with electrocardiographic evidence of digitalis toxicity were found to have the highest plasma concentrations. Marcus and associates\(^{24}\) have shown that nephrectomized dogs have higher blood concentrations and higher myocardial tissue concentrations of tritiated digoxin than control dogs. These observations suggest that higher blood concentrations of digoxin in man may result in higher myocardial tissue concentrations.

**Table 1**

**Comparison of Laboratory Data in Young and Elderly Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>BUN (mg%)</th>
<th>Serum creatinine (mg%)</th>
<th>Creatinine clearance (ml/min/1.73 m(^2))</th>
<th>Digoxin clearance (ml/min/1.73 m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>27</td>
<td>14 ± 5</td>
<td>1.00 ± 0.16</td>
<td>122 ± 19</td>
<td>83 ± 17</td>
</tr>
<tr>
<td>Mean ±1 sd</td>
<td>±4</td>
<td>±4</td>
<td>1.00 ± 0.16</td>
<td>122 ± 19</td>
<td>83 ± 17</td>
</tr>
<tr>
<td>Old</td>
<td>77</td>
<td>24 ± 3</td>
<td>1.24 ± 0.11</td>
<td>56 ± 17</td>
<td>53 ± 9</td>
</tr>
<tr>
<td>Mean ±1 sd</td>
<td>±4</td>
<td>±4</td>
<td>1.24 ± 0.11</td>
<td>56 ± 17</td>
<td>53 ± 9</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Circulation, Volume XXXIX, April 1969*
CREATININE CLEARANCE (ml/min/1.73 M²)

Relation between the clearance of creatinine and digoxin.

The elevated blood digoxin concentrations found in this study appear to be related to the smaller body size and the diminished renal function of elderly patients. Our elderly subjects were on the average smaller than the younger controls, and when the blood concentrations of digoxin were corrected for these differences in body weight, there was no significant difference between the two groups during the first 24 hr.

In the one elderly patient (J. R.) whose body weight of 83 kg was greater than the mean weight of the younger controls, the blood concentrations of digoxin uncorrected for weight during the first 2 hr were lower than the mean concentrations of the elderly patients and nearer the mean concentration of the controls. Thus, one factor contributing to the elevated blood concentration of digoxin in the elderly is body weight.

Even when the concentrations of blood digoxin were corrected for body weight, there was a significant and a progressively greater difference in concentrations between the elderly and the young subjects after the first day (fig. 2). The blood half-life of digoxin in elderly subjects was prolonged to 73 hr compared to 51 hr in the young subjects. These differences can be explained by the lower digoxin clearance in the elderly (table 1). Since the major route of digoxin excretion is the kidneys with little drug inactivation by biotransformation, it is understandable that digoxin excretion would be reduced in patients with decreased renal function. Our findings (fig. 3) support those of Bloom and associates in which there was a direct correlation between digoxin clearance and creatinine clearance. Several investigators have found creatinine clearance in the elderly to be only one half normal. Since creatinine clearance can decrease over 50% before there is a significant rise in the serum creatinine concentration, it is not surprising that we observed a decreased digoxin clearance in the elderly patients with normal or near normal concentrations of serum creatinine (table 1). In the azotemic patient, the digoxin clearance would be further decreased. Thus, a decrease in the renal excretion of digoxin in the elderly is a second factor that may account for digitalis sensitivity in this age group.

We cannot exclude the possibility that there may be increased sensitivity of the aged heart to digitalis. Another factor that has to be taken into account is hypokalemia from diuretic therapy or laxative abuse. However, in this study, the decreased body size and the diminished renal function generally found in the elderly were sufficient to alter digoxin metabolism and for recommending an appropriate decrease in dosage of digitalis.

Acknowledgment

We are indebted to Dr. Joseph Perloff and Dr. W. Proctor Harvey for critical review of the manuscript; to Dr. Stanley Bloomfield, Burroughs Wellcome and Company, Tuckahoe, New York, for the supply of tritiated digoxin; and to the secretarial assistance of Mrs. Roslyn Appel and Mrs. M. Yvonne McIlwain.

References

DIGOXIN METABOLISM IN THE ELDERLY

Digoxin Metabolism in the Elderly
GORDON A. EWY, GEETA G. KAPADIA, LINDA YAO, MURIEL LULLIN and FRANK I. MARCUS

Circulation. 1969;39:449-453
doi: 10.1161/01.CIR.39.4.449

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/39/4/449