Renal Tubular Secretion of Digoxin

By Eva Steiness, M.D.

SUMMARY

To study the mechanism of the renal handling of digoxin, simultaneous measurements of digoxin and inulin clearances were performed in 13 digitalized patients with congestive heart disease. The renal digoxin clearances exceeded inulin clearances, indicating an active tubular secretion of digoxin. No evidence of tubular backward diffusion was disclosed. Treatment with spironolactone (Aldactone) decreased the digoxin clearances, suggesting an inhibition of the tubular secretion of digoxin in the distal segment of the renal tubulus. After blocking the tubular secretion, the calculated renal clearances of nonproteinbound digoxin in plasma were similar to that of inulin, suggesting a glomerular filtration of free plasma digoxin. Plasma digoxin level rose during treatment with spironolactone.

Additional Indexing Words:
Spironolactone
Cardiac glycosides

Digoxin is predominantly eliminated through the kidneys; excretion is greatly impaired in patients with advanced renal failure. It is primarily excreted both in normal individuals and in patients with congestive heart failure, as the unchanged glycoside.

Several authors have demonstrated that the renal clearance of digoxin calculated from the total plasma digoxin concentration is equal to the endogenous creatinine clearance, which, in man, approximates the glomerular filtration rate (GFR). However, about 25% of plasma digoxin is bound to protein and not available for filtration, suggesting that digoxin is subject to tubular secretion.

The present study was undertaken for a closer evaluation of the mechanism of the renal handling of digoxin in digitalized patients. Simultaneous determinations of digoxin and inulin clearance were performed since inulin is the accepted standard for measurement of the GFR. The observation of a significantly reduced digoxin clearance in a patient (not included in this series) who received spironolactone caused me to repeat the clearance determinations, when possible, after treatment with spironolactone.

Patients and Methods

Patients

Studies were performed on 13 hospitalized adult patients with chronic congestive heart disease. The pertinent clinical information is listed in table 1.

None of the patients gave a history of renal disease. Five had slightly elevated serum creatinine levels, but none had proteinuria, and the urinary sediments were normal.

All the patients had been on a stable oral maintenance digoxin dose (table 1) for more than one month prior to the study and presented no clinical or electrocardiographic evidence of digitalis toxicity. The bioavailability of the tablets was not studied; however, each patient received tablets from the same batch throughout the study. In addition to digoxin all the patients received only furosemide (40-160 mg daily) and supplemental potassium to maintain the serum concentration of potassium within normal limits. Medication was withheld 24 hours before the study. At the time of the investigation none of the patients had clinical signs of cardiac incompetence.

Simultaneous measurements of inulin and digoxin clearances were performed in all 13 patients. Nine of the patients were subsequently treated with 100 mg spironolactone (Aldactone) daily for ten days, and the measurements of inulin and digoxin clearances were repeated.

Inulin Clearance

Priming doses of 10% inulin solution of 100 mg per kg body weight were given followed by a constant infusion of 90 ml 10% inulin solution per hour. Sixty minutes were allowed for equilibration, and no clearance was used unless plasma inulin was 20-50 mg/100 ml and urine flow was about 1 ml per minute. Three periods of about 60 to 90 minutes voided urine were used.

Inulin was determined by the method of Heyrovsky; duplicate determinations varied 1.0 mg ± 2.5% for both plasma and urine. The inulin clearance was calculated as a mean of the three computed clearance rates. Patients whose separate clearance rates varied more than ± 5% of the mean were excluded.

Digoxin Clearance

Plasma digoxin was estimated by radioimmunoassay technique measuring both plasma proteinbound and free
digoxin. The sensitivity was 0.2 ng/ml and the precision ±0.05 ng/ml. Urinary digoxin was estimated by the same method, following extraction of digoxin by dichloromethane, evaporation to dryness, and redissolution first in 85% ethanol and then phosphate-buffered saline, pH 7.4, containing bovine albumin (1 g/L) to a concentration of ethanol of 1% and a total volume of 1000 ml. If the concentration of digoxin was high, the extraction was repeated and the redissolution diluted to insure that the digoxin concentration could be measured at the standard curve. Urine standards were extracted by the same method as described. All the assays, including the extraction by dichloromethane, were performed in duplicates. The recovery was 95 ± 6%. The sensitivity was 1.0 ng/ml and the precision ±0.5 ng/ml between 0 and 10 ng/ml and 1.0 ng/ml at concentrations higher than 10 ng/ml urine.

The antibody used was made by the author according to the description of Butler and Chen.18 Cross-reaction with metabolites of digoxin, digoxigenin bisdigitoxoside, digoxigenin monodigitoxoside and digoxigenin was found at the same molar concentration. Physiological steroids at concentrations ordinarily encountered in normal or pathological human serum did not interfere with the antibody at the usual therapeutic levels of digoxin.

In order to investigate the cross-reaction with spironolactone or its metabolites in urine and plasma two healthy volunteers were treated with spironolactone 100 mg daily for eight days and two were treated with 200 mg daily for eight days. Both plasma and urine samples were analyzed for false positive digoxin concentration every second day during the investigation. All measurements gave less than 0.2 ng digoxin per ml, and it was concluded that no cross-reaction was found between the antibody used and spironolactone or its metabolites as demonstrated in a few other digoxin antibodies.17,18

Digoxin clearance was calculated as a mean of the three computed clearance rates. The maximal variation was ±8% of the mean.

Table 1

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Serum creatinine (mg %)</th>
<th>Maintenance digoxin dose (mg)</th>
<th>Diagnosis</th>
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<td>80.7</td>
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<td>57</td>
<td>63</td>
<td>F</td>
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<td>1.0</td>
<td>0.25</td>
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<td>75</td>
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<td>56</td>
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<td>65</td>
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<tr>
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<td>42</td>
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<td>Mitral insufficiency</td>
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<td>58.0</td>
<td>1.3</td>
<td>0.50</td>
<td>Arteriosclerosis</td>
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Statistical Analysis
The significance of the differences was determined by the Wilcoxon test for paired differences.

Results
The first part of the study was composed of 13 simultaneous inulin and digoxin clearances. Inulin clearances ranged from 25 to 110 ml/min, mean value 64 ml/min (fig. 1). The corresponding digoxin clearances were consistently higher, ranging from 47 to 205 ml/min, mean value 93 ml/min (P < 0.01) at plasma digoxin levels between 0.5 and 1.3 ng/ml. Digoxin clearances shown in figure 1 were calculated from the total plasma digoxin regardless of the amounts of protein-bound and free digoxin. If the clearances were calculated with the assumption of 25% albumin binding of digoxin, the digoxin/inulin clearance ratio increased from 1.46 to 1.94.

The urine flow of three patients varied considerably during the three consecutive periods (table 2). No correlation between the urine flow and digoxin clearance could be demonstrated.

The second part of the study was composed of nine simultaneous inulin and digoxin clearances in patients treated with spironolactone. Table 3 shows that no statistically significant differences in inulin clearances before and after treatment with spironolactone were observed. On the other hand, the corresponding
Table 2

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Urine flow ml/min</th>
<th>Digoxin clearance ml/min</th>
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<td>200</td>
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<td>206</td>
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</table>

Digoxin clearances were markedly decreased from those before treatment with spironolactone, and for all individuals except one, lower than the simultaneous inulin clearances (P < 0.02) (fig. 2). If the digoxin clearances were calculated from the free plasma digoxin, the digoxin/inulin clearance ratio increased from 0.84 to 1.12 (fig. 3). This close correlation was independent of the plasma digoxin concentration in ranges 0.6 to 3.5 ng/ml.

The plasma digoxin concentrations increased in all subjects (fig. 4). In one case, patient No. 91, plasma digoxin increased from 1.0 to 3.5 ng/ml. No explanation of this could be found. The renal function was unchanged (table 3), and the maintenance digoxin dose was the same throughout the study. Excluding the plasma levels of this patient, the mean concentration of plasma digoxin in the other patients increased from 0.8 ng/ml to 1.0 ng/ml (P < 0.01).

Discussion

The pharmacokinetics and metabolism of the digitalis glycosides differ considerably. Digoxin, a nonpolar compound, is largely metabolized and excreted in the urine as cardioinactive metabolites. In contrast, digoxin, a polar glycoside, is metabolized very little and primarily excreted in the urine as unchanged digoxin; the small amount of degradation products detected in the urine are composed of cardiovactive metabolites.

The renal digoxin clearance has been studied by means of tritium-labeled digoxin7-10 and the rubidium-86 inhibition technique.11 Using tritium-labeled digoxin, the total radioactivity of the urine and plasma has been used for the calculation of the renal clearance. Chromatography of the urine has demonstrated that nearly all the radioactivity is present as digoxin and only a little as the metabolite digoxigenin bisdigitoxoside.19 Using the rubidium-86 method, Kaufman and Belpaire20 have demonstrated that the metabolites of digoxin are measured as digoxin at the same molar concentration. The clearance values in these studies were calculated from the total urinary content of digoxin and metabolites. As the antibody used in the present study reacted with the digoxin metabolites, the results should be comparable.

The suggestion of Jelliffe and Blankenhorn21 that a linear relation exists between creatinine and digoxin clearances was confirmed later by clearance studies which revealed a close relationship between creatinine and digoxin clearance in many patients. Creatinine clearance was not determined in the present study. The relationship between creatinine and inulin clearance at different levels of GFR was studied by Lavender, Hilton, and Jones.22 If the digoxin clearance values obtained in the present study were calculated from the total urinary content of digoxin and metabolites. As the antibody used in the present study reacted with the digoxin metabolites, the results should be comparable.

In advanced renal failure Marcus23 observed an increase in the digoxin/creatinine clearance ratio. This may be due to the fact that creatinine/inulin clearance ratio approximates 1 in patients with low GFR (fig. 5).23, 24

Table 3

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Inulin clearance (ml/min) Before Treatment with spironolactone</th>
<th>Inulin clearance (ml/min) After Treatment with spironolactone</th>
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</thead>
<tbody>
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<td>61</td>
<td>75</td>
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In evaluating renal excretion, three main processes should be considered: passive glomerular filtration, active tubular secretion, and passive tubular backward diffusion. The finding that the renal clearance of digoxin exceeded the simultaneous GFR (i.e., inulin clearance) demonstrated that digoxin is subjected to active tubular secretion. The tubular transport of a substance is limited by a maximum rate ($T_m$). An analysis of the digoxin/inulin clearance ratio to total plasma concentration of digoxin demonstrated that the $T_m$-digoxin was not reached within the range of plasma digoxin levels observed in this study.

In vitro experiments have shown that about 25% of plasma digoxin is proteinbound. Subsequent studies performed on plasma samples from patients similar to those in this series gave corresponding results (Steiness E, Rasmussen F, unpublished data.). When allowance was made for protein binding, calculations showed that about 50% of the urinary digoxin content was excreted by tubular secretion. The clearance of substances subjected to tubular backward diffusion will tend to increase with rising urine flow. In three patients considerable variations in flow rate occurred without alterations in the digoxin clearance (table 3). Thus evidence for backward diffusion was not revealed.

Treatment with spironolactone resulted in a significant decrease of the renal digoxin clearance (fig. 2). The clearance approached the GFR of the free unbound fraction in plasma suggesting a strong inhibition of the tubular secretion. This inhibition of the tubular secretion might be caused by passive competition due to the close structural similarity. However, in the few patients investigated until now, triamterene was also found to inhibit the tubular secretion (Steiness E, unpublished data.). The inhibition might therefore be explained by a nonspecific inhibition of a tubular digoxin-carrier system.

Plasma digoxin concentrations increased significantly during treatment with spironolactone. The mean increase in the plasma level corresponds to a calculated increase of the total body digoxin content of about 0.20 mg. The mean cumulative retention of digoxin in this period calculated from the decrease of the renal excretion of digoxin was of the same magnitude, 0.18 mg.

A protective effect of spironolactone on digitoxin toxicity has been demonstrated in rats. This is presumably due to increased metabolism resulting in increased biliary excretion. However, in humans digoxin is only slightly metabolized. The agreement between the amount of digoxin retained and the increase in plasma digoxin concentration suggests that spironolactone does not influence the metabolism of digoxin.

In one patient plasma digoxin concentration increased to a higher level than the decrease of renal digoxin excretion would warrant. No obvious explanation of this could be found. However, even small changes in the tissue binding of digoxin during treatment with spironolactone would change the digoxin...
The decreased renal excretion of digoxin during treatment with spironolactone might allow a reduction of the daily maintenance dose. However, interaction between spironolactone and digoxin in cardiac tissue is also possible, and further investigations are needed.

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References

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