The Effect of Altered Renal Perfusion Pressure on Clearance of Digoxin

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SUMMARY Controversy persists regarding the role of tubular reabsorption and secretion in the renal handling of digoxin. To determine the effect of reduction in renal perfusion pressure and blood flow on digoxin clearance during acute and chronic digitalis administration, renal clearances of digoxin and inulin were measured in pentobarbital-anesthetized dogs before and after repeated unilateral renal artery constriction. After reduction of renal arterial mean pressure to 67% of the control level, both inulin and digoxin clearances fell sharply, by 62–86% (p < 0.001). The digoxin-to-inulin clearance ratio in the arterially constricted kidney decreased only slightly, from 0.82 to 0.76 (p < 0.02) after unilateral renal artery constriction in the chronically digitalized group as determined by \(^{3} \text{H} \) counts in serum and urine of dogs given 12 \( \alpha-\text{[H]} \) digoxin. No significant change in the digoxin-to-inulin clearance ratio after renal arterial constriction was found by radioimmunoassay determination of digoxin in chronically dosed dogs. Digoxin-to-inulin clearance ratio also did not change significantly with renal artery constriction in the acutely digitalized group (0.72 vs 0.71). Slightly higher digoxin-to-inulin clearance ratios in chronically (mean 0.82) compared with acutely (mean 0.73; \( p = 0.038 \)) digitalized dogs may be accounted for by renal parenchymal digoxin binding under non-steady-state conditions of acute digitalis administration. These data support the concept that glomerular filtration is the principal mechanism of renal digoxin excretion. Reduction in renal arterial pressure, with consequent decrease in glomerular filtration and urine flow, produces a marked fall in digoxin clearance but no appreciable change in the digoxin-to-inulin clearance ratio in dogs given digoxin acutely or dosed chronically to attain a steady state. This is consistent with the absence of any important change in net tubular reabsorption of digoxin under these experimental circumstances. These experiments show that renal excretion of digoxin in the dog closely approximates the filtered load over a broad range of renal arterial perfusion pressures and urine flow rates.

THE KIDNEY is the chief pathway for digoxin excretion in normal man\(^{1-4} \) and in the dog, a species that closely resembles man in its handling of this drug.\(^{5,6} \) Three mechanisms have been reported to be of importance in the renal excretion of digoxin: glomerular filtration, tubular reabsorption and tubular secretion. Predominant patterns in man have been reported to be glomerular filtration alone,\(^{7,9} \) filtration combined with tubular reabsorption\(^{10} \) and filtration combined with tubular secretion of digoxin.\(^{11-14} \) Doherty and associates reported glomerular filtration with net tubular reabsorption of digoxin in dogs.\(^{6} \)

Clinical situations are commonly encountered in which acute or subacute changes in renal perfusion pressure occur in patients receiving digoxin, and an appreciable role has been suggested for tubular reabsorption in the renal handling of digoxin in patients with prerenal azotemia.\(^{11} \) Nevertheless, experimental studies exploring the effects of altered renal perfusion pressure and blood flow, with consequent changes in glomerular filtration and urine flow rates, have not been reported. Accordingly, we examined the effects of acute reductions in renal perfusion pressure by unilateral renal artery constriction on renal handling of digoxin in acutely and chronically digitalized dogs.

Methods

General Methods

Experiments were performed on 15 mongrel dogs of either sex that weighed 20–30 kg. The dogs were anesthetized with pentobarbital 30 mg/kg i.v., intubated, and ventilated with room air using a Harvard respirator. Respiratory rates and tidal volumes were adjusted to maintain arterial blood pH, \( \text{PO}_{2} \) and \( \text{PCO}_{2} \) within normal limits for the dog. Body temperature was measured by means of a rectal thermometer and maintained between 36–37°C with a thermal blanket. Both femoral veins and one femoral artery were cannulated to infuse drugs and to monitor systemic arterial blood pressure. Both kidneys were exposed by a transabdominal approach. Each ureter was cannulated and the urine collected. A catheter was introduced into each renal artery to measure arterial pressure and to obtain blood samples. In 10 dogs, an adjustable constricting clamp was secured around one renal artery proximal to the catheter. Blood pressures in both renal arteries and in the femoral artery as well as a lead II ECG were recorded throughout each experiment. Pressures were measured using Statham P23Db transducers, signals from which were amplified and recorded with a physiologic recorder. All dogs were in normal circulatory condition and had constant urine flow from both kidneys at the beginning of each study. Normal saline infusion was maintained at 10
ml/kg/hr during the procedure. No diuretics were used.

Experimental Protocols

One group of five dogs received digoxin initially at the time of the study by a constant infusion of 0.03 mg/kg/hr. For this purpose, digoxin (Burroughs Wellcome) was suitably diluted in normal saline and tracer digoxin labeled with tritium at the 12α position (New England Nuclear, Boston, Massachusetts) was added to a final specific activity of 133 μCi/mg. Another group of five dogs received 0.03 mg/kg body weight of digoxin with the same content of 12α[3H]-digoxin intravenously each day for 5 days before the experiment and were studied on the sixth day. To maintain stable serum concentrations, the latter group of dogs received a constant infusion of 1/24 of the daily dosage of digoxin per hour during the experiment. To permit correlation of the renal excretion of digoxin with glomerular filtration rate (GFR), we infused 15 μCi of 14C-labeled inulin that had a specific activity of 2.16 μCi/g (New England Nuclear, Boston, Massachusetts) after an initial bolus injection of 0.5 μCi/kg.

After 1 hour of equilibration, urine was collected from each ureter and blood samples were obtained during four consecutive 15-minute periods for clearance measurements. Hematocrit values determined from the first blood sample obtained were similar in all dogs studied, averaging 39.9 ± 3.3% (SD) in the acute infusion group and 40.8 ± 2.2% in the group that received digoxin daily for 5 days. During the fifth 15-minute period, mean blood pressure was reduced in one renal artery to 67% of control by proximal constriction of the vessel.

In preliminary experiments, we determined the degree of reduction of renal arterial mean blood pressure that would decrease renal perfusion to an extent that still provided sufficient urine flow to permit accurate inulin and digoxin clearance measurements. We measured inulin and digoxin clearance after reducing renal arterial blood pressure 25%, 33% and 50%. The 25% reduction did not change the GFR appreciably. A 50% reduction led to cessation of urine flow in the majority of constriction periods studied. With a 33% reduction of renal arterial blood pressure, the GFR was reduced substantially but urine flow remained adequate for the purpose of clearance measurements.

After a recovery period of at least 15 minutes we again constricted the same renal artery to reduce mean blood pressure to 67% of control and this sequence was repeated a third time after urine flow had reached the new steady state. A total of 175 clearances for inulin and for digoxin were calculated from urine and serum radioactivity using double isotope counting in a liquid scintillation counting system. Serum or urine (0.1 ml) together with 0.8 ml of distilled water were added to 10 ml of Biofluor (New England Nuclear, Boston, Massachusetts) and radioactivity was measured in a Packard Model 3330 liquid scintillation counter.

To determine the influence of the constant infusion of 1/24 of the daily dosage per hour on clearance measurements, we also performed five experiments without this constant infusion of digoxin. We administered digoxin chronically to five dogs by injecting 0.03 mg/kg of 12α[3H]-digoxin daily for 5 days before the experiment. Clearances were measured as described above during four 15-minute periods. These results were compared with the inulin and digoxin clearances measured using a constant infusion of 1/24 of the daily digoxin dosage per hour.

To correlate measured tritium counts with an independent estimate of digoxin concentration in chronically treated dogs, we also measured serum and urine digoxin levels by radioimmunoassay as previously described.15, 16

Statistics

Data from groups of dogs given digoxin acutely or chronically were compared by means of a two-tailed t test to test the null hypothesis that no difference existed between the groups studied. A t test for paired data was used to compare results in dogs studied before and after renal arterial constriction.

Results

Acute Administration of Digoxin

The time course of serum digoxin concentrations in dogs given digoxin acutely is shown in figure 1. Serum levels increased linearly, from a mean of 27.4 ± 4.0 ng/ml (SD) at 15 minutes to 48.2 ± 8.5 ng/ml after 150 minutes of infusion of 0.03 mg/kg/hr.

Unilateral renal arterial constriction in these dogs decreased mean pressure distal to the clamp from an average of 94 mm Hg to 62 mm Hg (table 1). Urine flow in the arterially constricted kidney fell markedly, from a mean of 0.9 to 0.1 ml/min (table 1), while urine flow rate from the contralateral control kidney did not change significantly (0.8 ± 0.2 ml/min to 1.2 ± 0.4 ml/min). The reduction in arterial blood pressure resulted in a decrease of the GFR as determined by inulin clearance from a mean of 23.0 ml/min to 3.3 ml/min. The digoxin clearance was simultaneously reduced from 16.6 ml/min to 2.5 ml/min (table 1).

Chronic Administration of Digoxin

In the chronically digitalized dogs (fig. 1), serum digoxin concentration remained essentially constant in the 3.2–3.5 ng/ml range during experimental observation. Renal arterial pressure before constriction averaged 91 mm Hg (table 1) and decreased to a mean of 59 mm Hg distal to the clamp after constriction. This resulted in a marked fall in mean urine flow rate from the arterially constricted kidney, from a mean of 1.3 ml/min to 0.2 ml/min (table 1). In the contralateral control kidney, urine flow rate did not change significantly (1.3 ± 0.7 ml/min to 0.9 ± 0.2 ml/min).

In the chronically digitalized dogs, reducing renal arterial perfusion pressure to 67% of control resulted in a decrease in inulin clearance, from a mean of 23.7
ml/min to 9.1 ml/min. Digoxin clearance decreased from 19.6 ml/min to 6.4 ml/min in the arterially constricted kidney as measured by \(^3\)H activities in serum and urine (table 1). Similar mean values of 18.6 ml/min and 6.9 ml/min, respectively, were determined by digoxin radioimmunoassay.

**Mechanism of Renal Excretion of Digoxin**

Data were then analyzed to determine the effect of reduction in renal arterial perfusion pressure on the mechanism of digoxin excretion. The mean digoxin-to-inulin clearance ratio in the acutely digitalized dogs was 0.72 and remained unchanged after renal arterial constriction (table 2). In the contralateral non-constricted kidney, the mean digoxin-to-inulin clearance ratio was similar at 0.75. In chronically digitalized dogs, the mean baseline digoxin-to-inulin clearance ratio was slightly higher at 0.82 and decreased to 0.76 after arterial constriction (\(p = 0.011\) by paired \(t\) test). The digoxin-to-inulin clearance ratio in the contralateral control kidney remained unchanged at 0.82. Digoxin determination by radioimmunoassay yielded an initial digoxin-to-inulin clearance ratio of 0.81, which did not change significantly (0.79) after renal artery constriction. Radioimmunoassay data also confirmed a similar mean digoxin-to-inulin clearance ratio for the non-constricted contralateral kidney of 0.80. The digoxin-to-inulin clearance ratio in the five dogs chronically digitalized but receiving no digoxin infusion on the day of the experiment was 0.81 ± 0.09 (sd) and was not different from that in the group receiving an infusion of 1/24 of the daily dosage per hour.

Pooling the data from all chronically dosed dogs without renal arterial constriction and comparing the mean value of 0.82 ± 0.08 (sd) thus obtained with the mean of 0.73 ± 0.09 for all studies in dogs given digoxin acutely, the relatively small difference observed proved to be statistically significant (\(p = 0.038\)).

**Discussion**

The renal elimination of cardiac glycosides depends on several important variables. There is general agreement that glomerular filtration is the predominant mechanism for digoxin elimination, and that serum protein binding limits the amount of drug that undergoes glomerular filtration.\(^{17-19}\) The mechanisms of renal excretion of digoxin at the renal tubular level are

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**TABLE 1. Effect of Unilateral Renal Arterial Constriction on Perfusion Pressure and Renal Function**

<table>
<thead>
<tr>
<th></th>
<th>Before constriction (n = 5)</th>
<th>p</th>
<th>After constriction (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Digitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>94 ± 21</td>
<td>&lt;0.01</td>
<td>62 ± 21</td>
</tr>
<tr>
<td>Inulin clearance (ml/min)</td>
<td>23.0 ± 2.4</td>
<td>&lt;0.001</td>
<td>3.3 ± 2.0</td>
</tr>
<tr>
<td>Digoxin clearance (ml/min)</td>
<td>16.6 ± 2.0</td>
<td>&lt;0.001</td>
<td>2.5 ± 1.6</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>0.9 ± 0.2</td>
<td>&lt;0.001</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>Chronic digitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>91 ± 22</td>
<td>&lt;0.01</td>
<td>59 ± 13</td>
</tr>
<tr>
<td>Inulin clearance (ml/min)</td>
<td>23.7 ± 2.2</td>
<td>&lt;0.001</td>
<td>9.1 ± 5.4</td>
</tr>
<tr>
<td>Digoxin clearance (ml/min)</td>
<td>19.6 ± 2.0</td>
<td>&lt;0.001</td>
<td>6.4 ± 3.8</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>1.3 ± 0.4</td>
<td>&lt;0.001</td>
<td>0.2 ± 0.4</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± sd; \(p\) value for comparison of paired values before and after renal arterial constriction.
Table 2. Effect of Unilateral Renal Arterial Constriction on the Digoxin-to-Inulin Clearance Ratio

<table>
<thead>
<tr>
<th></th>
<th>Digoxin-to-inulin clearance ratio</th>
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<tbody>
<tr>
<td></td>
<td>Acute digoxin administration*</td>
</tr>
<tr>
<td></td>
<td>12 α - 3H label</td>
</tr>
<tr>
<td>Before arterial constriction</td>
<td>0.72 ± 0.12</td>
</tr>
<tr>
<td>During arterial constriction</td>
<td></td>
</tr>
<tr>
<td>Constricted kidney</td>
<td>0.71 ± 0.10</td>
</tr>
<tr>
<td>Nonconstricted kidney</td>
<td>0.75 ± 0.08</td>
</tr>
</tbody>
</table>

Values are mean ± SD (n = 5).
*Values determined by direct measurement of 3H counts in serum and urine of dogs given 12 α [3H]-digoxin.

less fully understood. In humans, tubular secretion in addition to glomerular filtration has been reported by some investigators; others found tubular reabsorption in addition to glomerular filtration.

Comparison of experimental studies has been complicated by methodologic differences, including differences in the species studied. Using the stop-flow technique, Doherty et al. demonstrated net tubular reabsorption in addition to glomerular filtration in dogs. Rasmussen et al. reported net tubular reabsorption of digoxin in swine and tubular secretion in goats. Roman and Kauker used the micropuncture technique in experiments in rats that indicated glomerular filtration followed by tubular reabsorption.

Other differences in methods also appear to be important. Both acute and chronic digoxin administration have been used in experimental studies, presumably resulting in differences in tissue distribution and plasma-tissue equilibration of the drug. Although clearance by glomerular filtration per se should be independent (in terms of mechanism) of free plasma concentration, tubular secretion or reabsorption mechanisms might well be influenced by differing plasma concentrations produced by acute and chronic administration.

GFR has been estimated by inulin clearance in some studies and by endogenous creatinine clearance in others. The latter approach is complicated by tubular secretion of creatinine under circumstances of markedly reduced glomerular filtration.

The present study was designed to investigate the influence of changes in renal perfusion pressure, GFR and urine flow rate on the mechanism of digoxin excretion in dogs. Two groups of dogs, one digitalized chronically and the other acutely, were used in an experimental design in which each dog served as its own control. In all dogs, reduction in renal arterial perfusion pressure to 67% of control had profound effects on GFR and urine flow, which decreased by averages of 62% and 85%, respectively. In each instance, the decrease in digoxin clearance was quantitatively similar to the decrease in GFR as determined by inulin clearance. This predominant dependence of renal excretion of digoxin on GFR is consistent with the studies of Bisset et al., who reported that digoxin clearances in patients with diabetes insipidus were not significantly different from those in normal patients with comparable GFRs and with studies of the influence of diuretics on digoxin excretion.

We used the digoxin-to-inulin clearance ratio in the present studies as an indicator of the renal excretion mechanism. Digoxin is about 20% bound to serum protein both in man and in the dog, in contrast to inulin, which is not protein-bound at all. Because only the non-protein-bound fraction would be expected to undergo glomerular filtration, a digoxin-to-inulin clearance ratio of 0.8 would be compatible with the concept that digoxin undergoes glomerular filtration without net tubular reabsorption or secretion. A digoxin-to-inulin clearance ratio above 0.8 suggests net tubular secretion and a ratio below 0.8 suggests net tubular reabsorption of digoxin. In the present experiments, the digoxin-to-inulin clearance ratio observed in acutely digitalized dogs was 0.72 before any intervention, consistent with a small amount of net tubular reabsorption of digoxin. In chronically digitalized dogs, however, the corresponding value was 0.82 when determined by 3H counts in serum and urine and 0.76 by radioimmunoassay determination of digoxin concentration. The latter method was used in addition to direct determination of 3H counts to exclude the possibility of substantial biotransformation giving misleading results in dogs given 12 α [3H]-digoxin chronically.

Comparison of data obtained by direct counting of 3H activity in serum and urine of dogs given 12 α [3H]-digoxin shows slightly but significantly higher ratios of digoxin-to-inulin clearance in chronically digitalized dogs compared with dogs given the drug acutely at the time of clearance measurements. A possible explanation of this finding is that an appreciable uptake of digoxin by renal parenchyma occurs during acute infusion, resulting in decreased appearance of digoxin in the urine compared with steady-state conditions of chronic drug administration.

Reduction in renal perfusion pressure to 67% of control was accompanied by marked decreases in urine flow rate, creatinine clearance, and digoxin clearance (Table 1). The small decrease in mean digoxin-to-inulin clearance ratio from 0.82 to 0.76 measured by 12 α [3H]-digoxin content of serum and urine from chronically dosed dogs was statistically significant, but of minor quantitative importance (Table 2). No significant change in the digoxin-to-
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inulin clearance ratio occurred either in acutely digitalized dogs or in dogs given digoxin chronically followed by radioimmunoassay determination of the clearance ratio. Our findings are in general agreement with those of Gierke et al., 25 who found a mean digoxin-to-creatinine clearance ratio of 0.82 (calculated from their data) in dogs with normal renal function, with no significant change after surgical removal of sufficient renal tissue to produce a decrease to 36% of control in creatinine clearance. A linear relationship of digoxin-to-creatinine clearance was also found by Okada and colleagues in human subjects over a wide range of renal functional states, 26 but the pathophysiology of stable chronic renal failure differs considerably from the acutely induced reduction in renal perfusion pressure brought about in the experiments reported here. Our findings might be expected to have greater relevance to clinical states of acute hypotension or low cardiac output.

Although caution is in order in extrapolating these findings to the clinical setting, our data suggest that marked changes in renal perfusion pressure profoundly affect the magnitude of digoxin excretion by reducing GFR, but have remarkably little effect on the renal mechanism of digoxin excretion.

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