Acute Vasodilator Therapy Increases Renal Clearance of Digoxin in Patients with Congestive Heart Failure

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SUMMARY  We studied the effect of vasodilator therapy on renal digoxin clearance in patients with chronic congestive heart failure. Intravenous administration of nitroprusside or hydralazine to eight patients with severe heart failure produced the expected increase in cardiac output and a decrease in central circulatory pressure. Renal clearance of sodium para-aminohippurate and estimated renal blood flow increased without a change in glomerular filtration rate. Total renal clearance of digoxin increased by 50% during vasodilator therapy. Thus, acute administration of vasodilator increases renal digoxin clearance without changing glomerular filtration rate, suggesting an increase in tubular secretion of digoxin. Long-term vasodilator therapy may alter the maintenance dosage of digoxin required for optimal treatment of patients in congestive heart failure.

IN PATIENTS with congestive heart failure, renal excretion of digoxin occurs as a result of glomerular filtration and net tubular secretion of unchanged drug. Tubular reabsorption of digoxin may also be important in patients with low urinary flow rates. Patients with congestive heart failure often have substantially reduced renal blood flow (RBF) and may also have a decreased glomerular filtration rate (GFR). We recently showed that acute vasodilator therapy results in improved renal hemodynamics in such patients. Because vasodilator-induced improvements in renal function could influence renal digoxin clearance, we studied the effects of acute vasodilator therapy on the renal handling of digoxin.

Methods

Eight patients with congestive heart failure (New York Heart Association functional class III or IV) underwent hemodynamic and renal clearance studies. The mean age was 54 years. The clinical characteristics and laboratory evaluation of these patients have been presented. Of the nine subjects included in the original study, plasma and urine digoxin concentrations were measured in eight and the results are reported herein. No patient had a serum creatinine level greater than 1.5 mg/dl or a history of allergy to the study drugs. The protocol was approved by the University of California, San Francisco, Committee on Human Research. Each patient gave informed written consent.

All cardiac medications, including digoxin, diuretics and vasodilators, were discontinued 24 hours before the study. In the catheterization laboratory, catheters were placed in a femoral or radial artery and a forearm vein, and a Swan-Ganz thermocatheter was inserted into the pulmonary artery. In seven patients a Foley catheter was positioned in the bladder and connected to a gravity drainage apparatus; in the eighth patient urine was collected during spontaneous voiding. An i.v. loading dose of sodium para-aminomellitate (PAH) (Merck, Sharp & Dohme, Inc.) and iothalamate meglumine (Mallick and Dohme, Inc.) was followed by constant infusion of these compounds in isotonic dextrose in water at 1 ml/min for renal clearance measurements. Patients remained in bed for the entire study period and were allowed free access to drinking water.

The protocol consisted of four experimental periods. After initial measurement of hemodynamic variables and collection of blood and urine samples (period 1, control 1), sodium nitroprusside (Roche Laboratories) was administered intravenously at a starting dose of 5 \( \mu \)g/min. The infusion rate was gradually increased until repeat thermodilution...
measurements showed that a maximum increase in cardiac output had occurred (period 2). The mean final infusion rate was $131 \mu g/min$ (range $74-425 \mu g/min$). Hemodynamic measurements and urine and blood collections were repeated. Nitroprusside was then discontinued, and hemodynamic variables were allowed to return to control values for 30-90 minutes. Measurements were then repeated (period 3, control 2). Hydralazine (CIBA Pharmaceutical Co.) was then administered intravenously, 5 mg every 10-20 minutes. The mean total dose was $34 \mu g$ (range $10-60 \mu g$). Ninety to 120 minutes after the first dose of hydralazine, measurements were repeated (period 4). The duration of each experimental period was 60-90 minutes for periods 1, 2 and 3 and 90-120 minutes for period 4. The entire protocol lasted an average of 310 minutes.

During each of the four experimental periods, urine was collected for measurement of renal clearance of digoxin. In the seven patients with bladder catheters, three 10-20-minute samples of urine were collected within each of the four experimental periods, with blood samples obtained at the midpoint of the first and third collection periods. In the other patient, urine was obtained during spontaneous voiding during each period, with blood samples drawn at the beginning and the end of each period. Measurements during experimental periods were averaged to provide a single value for each patient under each condition. The techniques used to analyze iothalamate and PAH in plasma and urine and for renal and hemodynamic computations were reported previously. The GFR was calculated from the clearance of iothalamate, effective renal plasma flow (RPF) from the clearance of PAH and RBF from RPF/(1 – hematocrit). Arterial hematocrit was measured in heparinized glass capillary tubes in each period.

Digoxin concentration in plasma and urine was measured by radioimmunoassay in the Nuclear Medicine Laboratory at San Francisco General Hospital Medical Center. The coefficient of variation for this assay averaged 6% over a concentration range of 0.4–1.3 ng/ml. Additional studies showed that iothalamate did not interfere with the digoxin assay even when present in concentrations higher than those observed in this study. Renal clearance of digoxin was calculated using the urine/plasma digoxin concentration ratio and the urine flow rate. Clearance of digoxin by tubular secretion was estimated as clearance of digoxin – 0.75 GFR, assuming that 75% of digoxin is unbound in plasma. Data from the two control and two vasodilator periods were analyzed by repeated measures analysis of variance using a nested $2 \times 2$ design.

### Results

The hemodynamic data for the four experimental periods are summarized in table 1. Resting cardiac output was depressed and pulmonary capillary wedge pressure was elevated, confirming the diagnosis of low-output congestive heart failure in all patients. Administration of nitroprusside and hydralazine both substantially increased cardiac output. On cessation of nitroprusside, cardiac output returned to the control value and then increased after hydralazine administration. The changes after administration of both vaso-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period 1 (control 1)</th>
<th>Period 2 (nitroprusside)</th>
<th>Period 3 (control 2)</th>
<th>Period 4 (hydralazine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>$1.97 \pm 0.32$</td>
<td>$2.65 \pm 0.38^*$</td>
<td>$2.02 \pm 0.49$</td>
<td>$3.28 \pm 0.88^*$</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>$85 \pm 21$</td>
<td>$74 \pm 17^*$</td>
<td>$87 \pm 26$</td>
<td>$81 \pm 21^*$</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>$23 \pm 5$</td>
<td>$16 \pm 4^*$</td>
<td>$26 \pm 5$</td>
<td>$19 \pm 5^*$</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UF (ml/min)</td>
<td>$0.90 \pm 0.3$</td>
<td>$2.80 \pm 2.0$</td>
<td>$2.00 \pm 1.3^+$</td>
<td>$2.50 \pm 2.2$</td>
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<tr>
<td>GFR (ml/min)</td>
<td>$63 \pm 14$</td>
<td>$64 \pm 10$</td>
<td>$57 \pm 12$</td>
<td>$66 \pm 11$</td>
</tr>
<tr>
<td>CP Ah (ml/min)</td>
<td>$212 \pm 107$</td>
<td>$289 \pm 92^+$</td>
<td>$188 \pm 71$</td>
<td>$425 \pm 238^+$</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>$354 \pm 186$</td>
<td>$480 \pm 144^*$</td>
<td>$320 \pm 135$</td>
<td>$718 \pm 413^*$</td>
</tr>
<tr>
<td>Digoxin values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDC (ng/ml)</td>
<td>$0.76 \pm 0.25$</td>
<td>$0.61 \pm 0.21^*$</td>
<td>$0.63 \pm 0.25^+$</td>
<td>$0.56 \pm 0.17^*$</td>
</tr>
<tr>
<td>CDig (ml/min)</td>
<td>$102 \pm 56$</td>
<td>$152 \pm 77^+$</td>
<td>$106 \pm 69$</td>
<td>$147 \pm 115^+$</td>
</tr>
<tr>
<td>SDig (ml/min)</td>
<td>$55 \pm 34$</td>
<td>$104 \pm 64^+$</td>
<td>$62 \pm 49$</td>
<td>$97 \pm 96^+$</td>
</tr>
<tr>
<td>CDig, GFR (%)</td>
<td>$170 \pm 39$</td>
<td>$232 \pm 75^+$</td>
<td>$179 \pm 69$</td>
<td>$216 \pm 86^+$</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*p < 0.005.

†Significant interaction, control 2 period different from control 1 period.

‡p < 0.05.

Abbreviations: CI = cardiac index; MAP = mean arterial pressure; PCW = pulmonary capillary wedge pressure; UF = urine flow; GFR = glomerular filtration rate; CP AH = PAH clearance; RBF = renal blood flow; SDC = serum digoxin concentration; CDig = digoxin renal clearance; SDig = digoxin tubular secretory clearance.
dilator agents were associated with small but significant decreases in mean arterial pressure. Other details of the hemodynamic changes after drug administration in these patients have been published previously.8

Renal function data are also summarized in table 1. Average control GFR and RBF were reduced below predicted normal values. The fraction of cardiac output as RBF was only 10% and filtration fraction (GFR/RPF) was 0.30, which were less than the 20% and greater than the 0.20, respectively, expected in normal subjects. These findings are characteristic of the renal hemodynamic abnormalities of congestive heart failure. After administration of vasodilators, no significant changes in GFR were noted (table 1), but clearance of PAH increased significantly. Renal clearance of digoxin increased after vasodilator therapy, rising in six of eight patients during nitroprusside and in seven of eight patients after hydralazine (table 1). Mean values (± sd) increased from 105 ± 15 ml/min (periods 1 and 3) during the control periods to 153 ± 24 ml/min (periods 2 and 4) after the administration of the vasodilators (p < 0.05). Renal clearance of digoxin exceeded the GFR during the control periods, and the ratio of digoxin clearance to GFR increased further after vasodilator administration, indicating that net tubular secretory clearance of digoxin was increased. Serum digoxin concentrations and urine output were the only variables that differed between the two control periods. Serum digoxin concentration decreased progressively during the course of study, whereas urine output increased from the control 1 to the control 2 period because of water ingestion.

Figure 1 shows the absolute changes that occurred in GFR, RBF, digoxin clearance and estimated digoxin tubular secretory clearance between control and treatment periods for nitroprusside and hydralazine.

Discussion

Acute administration of the vasodilator drugs nitroprusside and hydralazine increased the renal clearance of digoxin in our patients with low cardiac output congestive heart failure in conjunction with an increase in estimated RBF. Cessation of nitroprusside infusion restored PAH clearance, RBF and digoxin clearance to control values, whereas GFR was unchanged after administration of either drug.

The results permit the conclusion that vasodilators increase renal clearance of digoxin by stimulating tubular secretion of digoxin. Renal clearance of digoxin in these patients with congestive heart failure was considerably greater than the GFR, indicating a contribution of tubular secretion to total renal clearance. Vasodilator therapy had no effect on GFR but significantly increased renal clearance of digoxin. Assuming normal (25%) protein binding of digoxin in serum,9 tubular secretory clearance of digoxin increased by almost 100%. Even if we assume the unlikely circumstance that vasodilators totally displaced digoxin from serum proteins such that it was 100% unbound, the resultant increase in filtered digoxin clearance could not account for the observed increase in renal clearance of digoxin. These data support the hypothesis that vasodilator treatment increases the tubular secretion of digoxin.

The cause of this increased secretory clearance of digoxin is not established from these studies. Other compounds that are excreted by tubular secretion are known to be cleared at a rate proportional to RBF until the maximum secretory rate is reached.8 Thus, the increase in digoxin clearance after vasodilator treatment might be due to increased RBF. This conclusion is supported by the finding that the change in digoxin clearance correlated significantly with the change in RBF produced by the vasodilators in our patients (r = 0.77, p < 0.001). An increase in tubular secretion could also occur through a redistribution of blood flow from deep to superficial nephrons caused by the vasodilators.7 It has also been speculated that in humans,2 but not in dogs,8 tubular reabsorption of digoxin is an important determinant of renal clearance at low urine flow rates. In our patients, despite a significant increase in urine flow from the control 1 to the control 2 period, there was no change in digoxin clearance, suggesting that urine flow rate was not an important determinant of renal clearance of digoxin under these circumstances.

The decrease in serum digoxin concentration during vasodilator treatment periods was unexpected, but can
be explained in part by the time between samples. However, even after each value was corrected for the sampling interval by assuming a half-life of 36 hours, the decrease in serum digoxin concentration was still statistically significant. Several possibilities could explain this decrease. One is that renal clearance of digoxin increased sufficiently with vasodilator administration to cause the serum concentration of drug to fall. The constancy of the serum digoxin concentration from periods 2 to 3 (nitroprusside infusion to control 2) is consistent with this possibility. Alternatively, plasma volume could have increased, thereby diluting the serum digoxin concentration as has been observed during treatment with vasodilators, or the vasodilators could have increased tissue distribution of digoxin by increasing perfusion of uptake organs that had been previously poorly perfused.

Our findings raise important questions about the long-term management of patients with congestive heart failure with digoxin and vasodilators. If the improvement in renal hemodynamics observed in our acute studies is maintained during chronic treatment and is associated with a sustained increase in the renal clearance of digoxin, then maintenance digoxin doses would have to be increased to maintain therapeutic blood concentrations of drug. A prospective study to examine the effects of chronic vasodilator therapy on digoxin metabolism is necessary to clarify this point. In addition, these results suggest the need for future studies to investigate whether i.v. administration of vasodilators may be useful in the management of acute digitalis intoxication by effectively lowering serum levels of drug.

In summary, acute administration of nitroprusside and hydralazine was associated with improved renal hemodynamics and increased renal clearance of digoxin. The increase in digoxin clearance was probably due to an increase in tubular secretion of digoxin, which may be secondary to the increased renal blood flow produced by the vasodilators.

References
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