Mechanism of Increased Sodium Reabsorption during Propranolol Administration

By Alan S. Nies, M.D., James S. McNeil, B.S., and Robert W. Schrier, M.D.

SUMMARY

The mechanism of diminished sodium excretion induced by propranolol was investigated in the dog. Propranolol (0.3 to 5 mg/kg) was given intravenously in a bolus to 16 dogs, eight of which had the renal perfusion pressure controlled by a suprarenal aortic clamp. In another group of six dogs propranolol (0.1 to 5 μg/kg/min) was infused into one renal artery for 45 min. Cardiac output (dye dilution), mean arterial and right atrial pressures, heart rate, renal clearances of inulin, creatinine, and para-aminohippurate, and sodium excretion were measured. Total peripheral resistance, central blood volume, stroke volume, renal plasma flow, renal blood flow, renal vascular resistance, glomerular filtration rate, and filtration fraction were calculated.

Intravenous propranolol resulted in significant decreases in cardiac output (−25%) and heart rate (−14%) and increases in total peripheral resistance (28%) and renal vascular resistance (37%). Renal blood flow decreased by 25% and filtration fraction increased 21% as urinary sodium excretion diminished 38%. Glomerular filtration did not change significantly. Infusions of propranolol into one renal artery resulted in either no change in sodium excretion or bilateral changes; thus an intrarenal effect of the drug was not demonstrable.

The data suggest that the changes in renal hemodynamics associated with propranolol administration are secondary to alterations in systemic hemodynamics, particularly a decrease in cardiac output. These alterations in renal hemodynamics, including an increase in renal vascular resistance and filtration fraction, most likely account for the decrease in sodium excretion rather than a direct effect of propranolol on sodium reabsorption.

Additional Indexing Words: Beta-adrenergic blockade Cardiac output Renal blood flow Renal vascular resistance Total peripheral resistance Filtration fraction Sodium excretion

PROPRANOLOL is being used in patients with heart disease for the therapy of cardiac arrhythmias, angina pectoris, and hypertension. However, propranolol is known to alter sodium metabolism in normal man and is potentially dangerous in patients with heart disease.1

An intact sympathetic nervous system is necessary for normal sodium metabolism. Phenoxybenzamine which blocks the alpha-adrenergic receptor, guanethidine which blocks the sympathetic nerve terminals, and renal denervation can cause a decrease in sodium reabsorption which is presumably due to direct effects of sympathetic blockade on the kidney and its circulation.2-4 However, sympathetic impairment secondary to spinal cord section5-6 and catecholamine depletion7 has in both instances been demonstrated to increase sodium reabsorption. Moreover, in patients with heart disease adrenergic blockade with guanethidine may precipitate overt...

From the Departments of Nephrology and Pharmacology, Walter Reed Army Institute of Research, Washington, District of Columbia 20012.

Address for reprints: Alan S. Nies, M.D., Department of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37203.

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heart failure and result in a net decrease in sodium excretion.\textsuperscript{8}

Since propranolol is now in widespread use, it is important to know whether the drug decreases sodium excretion by a direct intrarenal effect on sodium transport or alternatively by indirectly affecting renal hemodynamics and sodium reabsorption as a result of alterations in systemic hemodynamics.

**Methods**

Twenty-two experiments were performed in female mongrel dogs weighing 15 to 24 kg. The dogs were allowed water ad libitum and food was withdrawn 18 hours before the experiment, at which time 5 mg of deoxycorticosterone acetate (DOCA) was given intramuscularly. On the day of the experiment the animals were anesthetized with intravenous pentobarbital (30 mg/kg). At least 1 hour prior to the experiment an additional 10 mg DOCA and 2.5 units vasopressin-tannate in oil were injected intramuscularly.

In eight experiments, polyethylene catheters were placed retrograde through a suprapubic incision into the ureters, and through a flank incision into the renal or ovarian vein, and a modified Blalock clamp was placed around the aorta above both renal arteries. In another group of six animals a 25-gauge needle was also placed into one of the renal arteries. In the remaining eight experiments urine was collected from an indwelling urethral catheter. In all experiments, polyethylene catheters were inserted into the inferior vena cava, brachial artery, distal aorta, and right atrium. Pressures in the distal aorta, brachial artery, and right atrium were measured continuously by Sanborn 267 pressure transducers and a direct-writing Hewlett-Packard 7868 recorder.

After the surgical procedures, which required 30 to 60 min, the inulin (50 mg/kg) and/or creatinine prime (50 mg/kg) was administered intravenously and an intravenous infusion of isotonic saline begun at a rate of 0.5 to 1.0 ml/min. The saline infusion contained creatinine or inulin and para-aminohippurate (PAH) sufficient to maintain adequate blood levels for measurement of clearances. Aqueous vasopressin (25 mU/kg/hr) was also added to the maintenance infusion of saline. At least 60 min were allowed from completion of the surgery until the experiment was started.

During the experiment urine was collected at 15-min intervals. Arterial and renal venous blood samples were collected at the midpoint of alternate urine collections. Cardiac output (CO) and mean transit time from the right atrium to the distal aorta (MTT) were determined during each 15-min period by the dye-dilution technique using indocyanine green dye, a Gilford 103-IR densitometer, and a Gilford 104 computer. Total peripheral resistance was calculated by (mean brachial artery pressure minus mean right atrial pressure)/CO. Central blood volume was calculated by CO × MTT.

Analytical procedures have been described previously.\textsuperscript{9} Renal plasma flow (RPF) was calculated from the clearance of PAH divided by the renal venous extraction of PAH. Renal blood flow (RBF) was calculated as RPF/(1 − hematocrit); renal vascular resistance was calculated as mean arterial pressure/RBF; and filtration fraction was calculated as glomerular filtration rate (GFR)/RPF.

**Experiments with Intravenous Propranolol Administration**

Sixteen experiments were performed in which the effect of the intravenous administration of propranolol on sodium excretion and on renal and systemic hemodynamics was examined. The protocol of the experiments was as follows.

After at least three to five control periods in which the urinary flow rates were stable a dose of 0.3 to 5 mg/kg of propranolol was administered intravenously over 5 min: in two of the experiments the dose of propranolol was 3 mg/kg; in seven experiments the dose was 5 mg/kg; and in seven experiments the dose was 0.3 mg/kg. In four of the animals receiving 5 mg/kg and four of the animals receiving 0.3 mg/kg of propranolol the suprarenal aortic clamp was adjusted to maintain the renal perfusion pressure constant at 110 to 120 mm Hg throughout the experiment. After propranolol administration an additional three to five experimental periods were obtained. Renal venous extractions of PAH were measured in eight animals.

**Experiments during the Intrarenal Infusion of Propranolol**

In six animals, experiments were performed during the infusion of propranolol into one renal artery (0.1 to 5 μg/kg/min) in an effort to detect any direct intrarenal effect of the drug. The same protocol was used in this group of experiments as during the intravenous infusion of the drug, but the cardiac output and renal venous extractions of PAH were not measured.

**Results**

**Intravenous Propranolol Experiments**

The effect of intravenous injection of propranolol on systemic hemodynamics is shown in figure 1 and table 1. In the seven
experiments in which 0.3 mg/kg of propranolol was administered the mean cardiac output decreased significantly (−25%) as total peripheral resistance increased (30%). Arterial pressure was not significantly changed after this dose of propranolol, but the mean heart rate and stroke volume were significantly decreased (13% and 12%, respectively). These alterations in systemic hemodynamics were associated with several changes in renal hemodynamics and sodium excretion (table 2 and fig. 2). A decrease in renal blood flow (−18%) and an increase in renal vascular resistance (28%) and filtration fraction (16%) occurred and were accompanied by a significant decrease of −35% in urinary sodium excretion (UNaV), as glomerular filtration rate remained unchanged. A representative experiment is shown in table 3.

The nine experiments with the high dose of propranolol (3 to 5 mg/kg iv) showed nearly the same changes, with the exceptions that the increase in central blood volume (18%) was greater and reached the level of statistical

Figure 1

Systemic hemodynamic changes following intravenous propranolol administration. The mean values during the control periods are plotted on the abscissa. The values following propranolol are plotted on the ordinate. Values falling below the line of identity indicate a decrease after propranolol; values falling above the line of identity indicate an increase after propranolol. Triangles represent a propranolol dose of 0.3 mg/kg intravenously. Circles represent a propranolol dose of 3 to 5 mg/kg intravenously. Open symbols represent controlled renal perfusion pressure. Closed symbols represent uncontrolled renal perfusion pressure.
Table 1

Effect of Intravenous Propranolol on Systemic Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Cardiac output (liters/min)</th>
<th>Total peripheral resistance (mm Hg/liter/min)</th>
<th>Systemic arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Stroke volume (ml)</th>
<th>Central blood volume (ml)</th>
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</thead>
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<tr>
<td></td>
<td>Control</td>
<td>Propranolol</td>
<td>Control</td>
<td>Propranolol</td>
<td>Control</td>
<td>Propranolol</td>
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<td>&gt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>3 mg/kg iv (N = 9)</td>
<td>Mean</td>
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<td>1.95</td>
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<td>73.6</td>
<td>129</td>
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<tr>
<td>SEM</td>
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<td>0.20</td>
<td>9.1</td>
<td>12.0</td>
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<tr>
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<td>&lt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Controlled renal perfusion pressure (N = 8)</td>
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<td>1.79</td>
<td>72.2</td>
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<td>139</td>
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<tr>
<td>SEM</td>
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<td>0.25</td>
<td>10.0</td>
<td>15.1</td>
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<tr>
<td>All experiments (N = 18)</td>
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<td>57.0</td>
<td>73.0</td>
<td>129</td>
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<tr>
<td>SEM</td>
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<tr>
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*Statistical analysis by the paired Student t-test.
Table 2

<table>
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<tr>
<th>Glomerular filtration rate (ml/min)</th>
<th>Renal blood flow (ml/min)</th>
<th>Renal vascular resistance (mm Hg/ml/min)</th>
<th>Filtration fraction</th>
<th>Urinary sodium excretion (μEq/min)</th>
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</thead>
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<td>Propranolol</td>
<td>Control</td>
<td>Propranolol</td>
<td>Control</td>
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<tr>
<td>Mean</td>
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<td>&lt;0.01</td>
<td>&lt;0.05</td>
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</tbody>
</table>

0.3 mg/kg iv (N = 7)

| Mean     | 60          | 53        | 430        | 297        | 0.320  | 0.459       | 0.249  | 0.322       | 213     | 136        |
| SEM      | 6           | 5         | 42         | 30         | 0.050  | 0.087       | 0.014  | 0.019       | 41      | 38         |
| P value  | <0.05       | <0.01     | <0.05      | <0.05      | <0.01  | <0.01       | <0.01  | <0.01       |         |            |

3 mg/kg iv (N = 9)

Controlled renal perfusion pressure (N = 8)

| Mean     | 59          | 56        | 377        | 288        | 0.352  | 0.496       | 0.266  | 0.335       | 184     | 114        |
| SEM      | 7           | 8         | 44         | 43         | 0.052  | 0.097       | 0.017  | 0.011       | 40      | 27         |
| P value  | >0.05       | <0.01     | <0.05      | <0.05      | <0.01  | <0.01       | <0.01  | <0.01       |         |            |

All experiments (N = 18)

| Mean     | 61          | 56        | 410        | 306        | 0.315  | 0.431       | 0.266  | 0.323       | 166     | 107        |
| SEM      | 4           | 5         | 28         | 25         | 0.029  | 0.052       | 0.010  | 0.011       | 28      | 24         |
| P value  | >0.05       | <0.01     | <0.01      | <0.01      | <0.01  | <0.01       | <0.01  | <0.01       |         |            |

Table 3

Representative Experiment of the Effect of Propranolol on Renal Hemodynamics and Sodium Excretion

<table>
<thead>
<tr>
<th>Cardiac output (liters/min)</th>
<th>Total peripheral resistance (mm Hg/liter/min)</th>
<th>Systemic arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Stroke volume (ml)</th>
<th>Central blood volume (ml)</th>
<th>Renal arterial pressure (mm Hg)</th>
<th>GFR (ml/min)</th>
<th>PAH extraction (ml/min)</th>
<th>RBF (ml/min)</th>
<th>Renal vascular resistance (mm Hg/ml/min)</th>
<th>Filtration fraction</th>
<th>UnNaV (μEq/min)</th>
<th>Urinary flow (ml/min)</th>
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</thead>
<tbody>
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<td></td>
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<td>598</td>
<td>115</td>
<td>85.6</td>
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<td>150</td>
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<td>140</td>
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<td>483</td>
<td>0.239</td>
<td>0.36</td>
<td>91.3</td>
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</table>

Propranolol (0.3 mg/kg iv)

Abbreviations: GFR = glomerular filtration rate; PAH = para-aminohippurate; RBF = renal blood flow; UnNaV = urinary sodium excretion.
PROPRANOLOL AND SODIUM METABOLISM

With Propronolol

GLOMERULAR FilTRATION RATE (CC/MIN)

RENAI ARTERY PRESSURE (mm Hg)
RENAI BLOOD FLOW (ml/MIN)

FILTRATION FRACTION
RENAL PLASMA FLOW
[GLOMERULAR FILTRATION RATE]

Figure 2

Intrarenal hemodynamic changes following intravenous propranolol administration. The figure is the same format as figure 1. UNaV = urinary sodium excretion.

significance (P < 0.05); the decrease in stroke volume was not statistically significant; and the decrease of −12% in glomerular filtration rate was significant at P < 0.05 (tables 1 and 2, figs. 1 and 2).

In the eight experiments with controlled renal perfusion pressure there was no change in central blood volume or in glomerular filtration rate (table 1). The statistically significant decreases in cardiac output (−20%), stroke volume (−10%), and heart rate (−10%) and an increase in total peripheral resistance (26%) were associated with significant increases in renal vascular resistance (41%) and filtration fraction (26%) and decreases in renal blood flow (−24%) and urinary sodium excretion (−38%) (tables 1 and 2). No changes in renal extraction of PAH occurred at any dose of propranolol, and the mean was 0.82 ± 0.02 (SE) in eight animals. This mean renal extraction was used to calculate renal plasma flow in the other eight animals.

Intrarenal Propranolol Experiments

Infusion of small quantities of propranolol (0.1 to 5 μg/kg/min) for 45 minutes into one renal artery failed to show any unilateral effect on sodium excretion in six animals (fig. 3). No effects were seen in two animals receiving 0.1 and 0.5 μg/kg/min. In four animals receiving 0.5 to 5 μg/kg/min the effects were bilateral, involving both kidneys equally. The mean inulin clearance in the experimental kidney changed −2.7 ± 1.6 (SEM) ml/min, and that in the control kidney −2.8 ± 1.6 ml/min during propranolol infusion. The mean PAH clearance of the experimental kidney changed −16.8 ± 6.6
Sodium excretion during propranolol infusion into one renal artery. The experimental kidney received an intrarenal propranolol infusion while the contralateral kidney served as the control kidney. The ordinate represents the ratio in the experimental kidney of the sodium excretion during propranolol infusion divided by the control sodium excretion. The abscissa represents the same ratio in the control kidney. Points that fall below the 45° line (or line of no change) indicate that during propranolol administration larger decreases in sodium excretion occurred in the experimental kidney than in the control kidney. The failure of most of the points to fall below the line indicates that such a unilateral effect of propranolol in the experimental kidney was not observed.

ml/min, and that of the control kidney changed −16.7 ± 7.4 ml/min during propranolol infusion.

Discussion

The mechanism whereby beta-adrenergic blockade with propranolol may be associated with sodium retention was examined. The results demonstrated that intravenous administration of propranolol (0.3 to 5 mg/kg) consistently decreased cardiac output, heart rate, renal blood flow, and urinary sodium excretion and increased total peripheral resistance, renal vascular resistance, and filtration fraction. The decrease in cardiac output during propranolol administration in animals and man has been shown to be related to the blocking of the inotropic and chronotropic effects of catecholamines (beta-adrenergic blockade). In large doses propranolol also causes cardiac depression. The results of the present study demonstrate that when cardiac output is primarily reduced by propranolol, the arterial pressure remains relatively constant because of an increase in total peripheral resistance. The mechanism of this increase in total peripheral resistance seems likely to be of a reflex nature since the direct effect of propranolol on the peripheral vasculature is minimal. A baroreceptor-initiated increase in sympathetic outflow to the peripheral vasculature is a potential mediator of this increase in total peripheral resistance following propranolol infusion.

An important vascular bed sharing in the peripheral vasoconstriction was the renal vasculature, in which a consistent increase in renal vascular resistance (mean of 37%) and decrease in renal blood flow (mean of −25%) occurred. The glomerular filtration rate decreased in some experiments, but was not significantly altered when the renal arterial pressure was maintained constant. The increase of 21% in filtration fraction which occurred during propranolol administration indicated a postglomerular site of vasoconstriction. An accompaniment of these renal hemodynamic changes was a decrease of −36% in sodium excretion which occurred in spite of the administration of large doses of mineralocorticoid or antidiuretic hormone. Other investigators have suggested that alterations in Starling’s forces may enhance sodium reabsorption by facilitating the peritubular capillary removal of reabsorbate. In the present study, the increase in renal vascular resistance and filtration fraction which occurred during the administration of propranolol would be expected to decrease hydrostatic and increase oncotic pressures in the peritubular circulation and thereby enhance reabsorption. These alterations in renal hemodynamics may thus be the mechanism whereby propranolol increases sodium reabsorption and decreases

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sodium excretion. This indirect effect of propranolol on sodium excretion by alterations in systemic and renal hemodynamics seemed most tenable since a unilateral effect on sodium excretion was not demonstrated during the intrarenal infusion of the drug. Although unilateral stimulation of renal beta-adrenergic receptors with isoproterenol has been reported to decrease proximal tubular sodium reabsorption unilaterally, our results indicate that under the circumstances of this study renal beta-receptor blockade does not affect sodium excretion. An effect of beta-blockade on proximal sodium reabsorption (which does not alter sodium excretion because of adjustments in distal reabsorption) cannot, however, be excluded.

Chronic oral administration as well as acute intravenous administration of propranolol to man decreases cardiac output and increases total peripheral resistance. Chronic propranolol administration, particularly in patients with heart disease, has also been shown to result in abnormalities of urinary sodium excretion. The results of the present study suggest that this effect of propranolol on sodium excretion may be related to the systemic effect of the drug, with reflex renal hemodynamic alterations which enhance sodium reabsorption.

The present results indicate that propranolol increases renal vascular resistance and filtration fraction as part of a systemic adjustment to a decrease in cardiac output. These intrarenal hemodynamic alterations may increase sodium reabsorption and decrease urinary sodium excretion by altering the Starling's forces in the peritubular circulation. These findings also suggest that the same mechanism may be responsible for the sodium retention associated with propranolol administration in patients with heart failure.

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