Effect of Isoproterenol on Water Diuresis

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Within recent years there has accumulated increasing evidence that the adrenergic nervous system is involved in the control of water metabolism.

Rydin and Verney (1938) were the first to suggest this relationship, showing that the injection of adrenaline prevented the antidiuresis of emotional stress in dogs.

Some years later, Smythe et al (1952) demonstrated that the infusion of catecholamines in man increased free water clearance, and Lehr et al (1967) showed that the injection of isoproterenol (Isuprel\textsuperscript{R}) inhibited urine flow in water loaded rats.

The past few years have witnessed renewed interest in the possible relationship between these two systems. Fisher (1968) demonstrated that norepinephrine blocked the antidiuretic effect of ADH (Pitressin\textsuperscript{R}) during sustained water diuresis in man. Liberman et al (1970) confirmed Fisher's observation in rats, and demonstrated that an alpha-adrenergic blocking agent, Regitin\textsuperscript{R}, prevented the norepinephrine effect.

The precise manner in which isoproterenol can cause an ADH-like antidiuresis is unclear. Klein et al (1971) suggested that the antidiuresis produced in dogs by this agent was due to a direct effect on the renal tubules and that it was independent of ADH.

This question was further evaluated by Levi et al (1971) in congenital diabetes insipidus rats, animals completely lacking anti-diuretic hormone. An intravenous infusion of isoproterenol in these rats caused an ADH-like antidiuresis without a significant change in creatinine or solute excretion.

However, Schrier and his group (Schrier et al, 1972) concluded from their studies on dogs that the primary mechanism of the antidiuretic effect of beta-adrenergic stimulation involves the integrity of the hypothalamo-neurohypophysial system and the release of ADH.

The present study was undertaken to determine whether isoproterenol also inhibits water diuresis in man and to evaluate the role of hormonal (ADH) and non-hormonal factors in this inhibition.
RESULTS

The studies were performed on 7 normal young male volunteers and a representative experiment depicting the effect of the infusion of isoproterenol on one of these subjects is shown in Figure 1.

The effect of isoproterenol on urine volume, osmolar clearance, glomerular-filtration rate (GFR), renal plasma flow (RPF), blood pressure and heart rate, was observed. The study was conducted in three phases and the abscissa represents time in hours related to the beginning of water loading.

![Figure 1](image)

Following the establishment of this maximal steady state water diuresis, three control clearance periods were obtained. In phase II isoproterenol hydrochloride was infused over a 60–90 minute period at a rate of 0.04–0.06 μg/kg/min.

When a stable anti-diuresis was achieved in phase II, 30-45mg (0.5mg/kg body weight) of propranolol was added to the isoproterenol infusion and infused over a 30-60 minute period at a rate of 0.5-1.0 mg/min.

A striking anti-diuresis from 18ml to 2.0ml and a decrease in Cosm and free water clearance was observed in phase II. The marked anti-diuresis was accompanied by a fall in GFR and RPF in all patients, a fall in systolic and diastolic blood pressure, and a pronounced increase in heart rate (Table I).
Table I. The effect of intravenous isoproterenol and isoproterenol + propranolol on the systemic blood pressure and heart rate

<table>
<thead>
<tr>
<th>Subject</th>
<th>Isoproterenol infusion rate μg/kg/min</th>
<th>Water diuresis BP/HR/ADH μU/ml</th>
<th>Water diuresis + isoproterenol BP/HR/ADH μU/ml</th>
<th>Water diuresis + ISO + propranolol BP/HR/ADH μU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>0.04</td>
<td>132/83 78 ND</td>
<td>112/64 132 5.4</td>
<td>140/85 86 ND</td>
</tr>
<tr>
<td>TS</td>
<td>0.04</td>
<td>116/74 72 ND</td>
<td>94/66 126 7.6</td>
<td>124/80 84 ND</td>
</tr>
<tr>
<td>JM</td>
<td>0.04</td>
<td>138/80 90 ND</td>
<td>120/72 142 9.2</td>
<td>132/88 96 ND</td>
</tr>
<tr>
<td>BB</td>
<td>0.05</td>
<td>126/82 66 ND</td>
<td>96/66 124 8.6</td>
<td>138/88 72 ND</td>
</tr>
<tr>
<td>GB</td>
<td>0.05</td>
<td>118/72 78 ND</td>
<td>92/64 126 8.5</td>
<td>124/82 84 ND</td>
</tr>
<tr>
<td>BA</td>
<td>0.06</td>
<td>142/90 66 ND</td>
<td>115/58 96 5.7</td>
<td>132/82 72 ND</td>
</tr>
<tr>
<td>GA</td>
<td>0.06</td>
<td>135/88 84 ND</td>
<td>104/62 132 8.2</td>
<td>129/81 90 ND</td>
</tr>
</tbody>
</table>

Mean ± SEM 130±/-4 76        104±/-3 4 125 7.6        131±/-3 4 85

ISO = isoproterenol; BP = blood pressure; HR = heart rate

In this and the other experiment, extracted and concentrated samples of plasma were assayed for their ADH content in the water loaded ethanol anaesthetised rat. At the peak of the anti-diuresis ADH rose from undetectable levels in the control period to a mean of 7.6 μU/ml (Table I).

In phase III, upon adding propranolol to the infusate it rapidly reversed the cardiovascular and renal effects of isoproterenol. Although this was noted during the first period, it was only in the second and third period that the parameters of water diuresis returned to the control levels of phase I, with a fall in ADH to the undetectable levels observed in phase I.

CONCLUSION

In conclusion, this study clearly demonstrated that beta-adrenergic stimulation with intravenous isoproterenol (0.04-0.06 μg/kg/min) in man is associated with an anti-diuretic effect similar to that previously described in the dog, rat and cat. The anti-diuresis was associated with a decrease in systolic and mean arterial pressure, a decrease in GFR, RPF and solute excretion, and an increase in systemic venous ADH levels.

Therefore the anti-diuresis is the result of the combined effects of both hormonal, and non-hormonal factors acting on the kidney.

How can these studies in the human be reconciled with our earlier observations in dog and rat?
The best explanation is that unmeasured cardiovascular effects in both animals were able to cause an ADH like anti-diuresis. In the congenital diabetes insipidus rats this occurred despite the absence of circulating hormone, whereas in the normal dog a slight increase in circulating ADH contributed to the anti-diuresis. The anti-diuresis was found at hormonal levels below those detectable by our bioassay which would not cause anti-diuresis in the absence of the systemic and renal hemodynamic effects of isoproterenol. The results reflect the summation of the hormonal and non-hormonal effects of this beta-adrenergic agent on water diuresis.

REFERENCES

Lehr, D., Mallow, J. and Krukowski, M. (1967) Journal of Pharmacology and Experimental Therapeutics, 158, 150
Smythe, C. McC., Nickel, J. F. and Bradley, S. E. (1952) Journal of Clinical Investigation, 31, 499

OPEN DISCUSSION

T DRUEKE (Paris): If I understood your tables, you perfused 0.05μg/kg/min. We have never seen any increase or alteration in heart rate or in arterial pressure with such a small dose. Is this an error? My second question is, have you any evidence for thinking that the renin angiotensin system is implicated in this response?

LEVI: We tried to choose the dose which would cause the least cardiovascular effect. Above 0.03μg/kg/min we do see cardiovascular effects, with a drop of blood pressure, elevation of pulse rate and cardiovascular and haemodynamic changes in the kidney. In the cardiac literature 0.03μg/kg/min is a dose which is not associated with arrhythmias.

F BRUNNER (Basel): Would you care to speculate on the mechanism of the direct action on the renal tubule? Does isoproterenol increase permeability or has it an effect on transport somewhere?
LEVI: That work was evaluated well by Schreier and Giel. They injected isoprenolone directly into the renal artery and the effect was to increase delivery from the proximal to the distal tubule. This probably followed changes in the peritubular vessels due to changes in blood pressure. Most probably the effect is not directly on the tubules.

N JONES (London): In the slide you showed giving the course of a typical experiment, you were using 20 minute collection periods or thereabouts. I think it is very unusual not to see an artefactual fall in osmolar clearance when you first produce such a sharp antidiuresis. One possible explanation for not seeing this would be if there was a considerable increase in sodium excretion under the effect of isoproterenol, and I do not think that you gave any data on sodium excretion.

LEVI: I have a slide showing the sodium excretion: we have measured it but it did not change much at all. We did look at the question that you have raised.