Comparative effect of diuretics on renal water excretion in hyponatraemic oedematous disorders

V. L. SZATALOWICZ, P. D. MILLER, J. W. LACHER, J. A. GORDON AND R. W. SCHRIER
Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado U.S.A.

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Summary

1. The effects of intravenous chlorthiazide and frusemide on urinary osmolality were compared in 19 hyponatraemic oedematous patients.

2. Frusemide (1 mg/kg) caused production of a dilute urine (urine/plasma osmolality ratio, \( U_{\text{osm.}}/P_{\text{osm.}} \), \( 1.64-0.84 \), \( P < 0.01 \)) whereas chlorthiazide (10 mg/kg) did not (\( U_{\text{osm.}}/P_{\text{osm.}} \) 1.54-1.34, not significant).

3. The osmolar clearance (\( C_{\text{osm.}} \)) was higher after frusemide than after chlorthiazide (11.45 vs 4.99 ml/min, \( P < 0.01 \)). When the doses of frusemide (0.25-0.5 mg/kg) and chlorthiazide (20 mg/kg) were chosen to give a similar \( C_{\text{osm.}} \) (7.25 vs 7.48 ml/min, not significant), the \( U_{\text{osm.}}/P_{\text{osm.}} \) was still lower after frusemide (2.20-1.00, \( P < 0.001 \)) than after chlorthiazide (1.75-1.26, \( P < 0.01 \)).

4. Exogenous vasopressin did not increase the low \( U_{\text{osm.}}/P_{\text{osm.}} \) after frusemide (1.00-1.00, not significant) but increased the ratio after chlorthiazide (1.34-1.68, \( P < 0.001 \)).

5. These results indicate that frusemide, but not chlorthiazide, leads to the excretion of a dilute urine in hyponatraemic oedematous patients. This dilution is not due to a greater solution excretion but is associated with a resistance to the action of vasopressin.

Key words: chlorthiazide, diuretics, frusemide, hyponatraemia, oedema, sodium.

Introduction

Hyponatraemia associated with an impaired capacity to excrete a water load may occur in patients with sodium-retaining disorders including congestive heart failure, cirrhosis and nephrotic syndrome. The hyponatraemia may be of a degree to cause or worsen central nervous system symptoms. The infusion of isotonicmannitol solution has been shown to increase the excretion of solute-free water in some patients with cardiac failure [1] and cirrhosis [2]; such an approach, however, would be contraindicated in the patient with cardiac failure because of the associated expansion of intravascular volume. Demeclocycline increases solute-free water excretion in patients with the syndrome of inappropriate antidiuretic hormone secretion but it causes renal toxicity in patients with hepatic disease [3-5] and azotaemia in patients with congestive heart failure [6].

Diuretics which inhibit sodium chloride reabsorption in the diluting segment of the nephron diminish free water clearance, in normal subjects, and thus could worsen hyponatraemia in some oedematous patients. In a previous study, the loop diuretic, frusemide, increased solute-free water excretion in patients with hyponatraemic oedematous disorders and caused a resistance tovasopressin [7]. That study did not, however, demonstrate whether the effects were unique tofrusemide or could be observed with any diuretic which increased solute excretion rate to the same degree as frusemide. The present study was undertaken to compare at similar solute excretion rates the effects of frusemide and thiazide diuretics on urine osmolality and the response to

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p-aminohippurate in sufficient concentration to
between the four groups.

The patients remained supine except while voiding
characteristics of the patients in each of the four
groups are shown in Table 1. There was no
difference in non-diuretic drugs used
before or during the study. In eight of
three patients had congestive heart failure,
informed consent to participate in the study.

The patients were divided into four groups, and
they were given frusemide (Lasix, Hoechst-
Roussel Pharmaceuticals Inc., Sommerville, NJ,
U.S.A.), 1 mg/kg (group 2) or 0-25–0-5 mg/kg
(group 3), or chlorthiazide (Diuril, Merck Sharp
dohme, West Point, PA, U.S.A.), 10 mg/kg
(group 1) or 20 mg/kg (group 4). Some
characteristics of the patients in each of the four
groups are shown in Table 1; there were no
significant differences between the groups. There
was also no difference in non-diuretic drugs used
between the four groups.

The studies lasted 4–6 h, during which the
patients remained supine except while voiding
urine. No food or fluid was permitted for 8 h
before or during the study. In eight of 19 patients,
at 08.00 hours an infusion of inulin and
p-aminohippurate in sufficient concentration to
allow clearance measurements was started at 2
ml/min and continued throughout the study.

During the first and third hours of the study,
these patients also underwent a cardiac output
measurement, by injection of indocyanine green
dye. In the remaining 11 patients an infusion of
exogenous vasopressin in hyponatraemic patients
with oedematous disorders.

**Methods**

The 19 patients selected for this study had
clinically stable heart disease, liver disease or
nephrotic syndrome and peripheral oedema; they
excreted a concentrated urine (urine/plasma
osmolality ratio, \( U_{\text{o sm}}/P_{\text{o sm}} \), greater than 1-0),
had a creatinine clearance greater than 50 ml/min
and a serum sodium less than 135 mmol/l.

Three patients had congestive heart failure, 15
had cirrhosis and one patient had
nephrotic syndrome. The study was approved by
the Human Research Committee of the
University of Colorado Health Sciences Center, Denver,
Colorado, U.S.A., and patients gave their signed

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**Table 1. Characteristics of patients in the four study groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 4</td>
<td>48 ± 3</td>
<td>41 ± 6</td>
<td>43 ± 7</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>131 ± 4</td>
<td>131 ± 4</td>
<td>133 ± 2</td>
<td>137 ± 2</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>3.9 ± 0.3</td>
<td>3.9 ± 0.2</td>
<td>4.2 ± 0.4</td>
<td>4.1 ± 0.3</td>
</tr>
<tr>
<td>Urine/plasma osmolality ratio</td>
<td>1.68 ± 0.21</td>
<td>1.75 ± 0.28</td>
<td>2.2 ± 0.28</td>
<td>1.8 ± 0.25</td>
</tr>
</tbody>
</table>

Values are means ± SEM; none of the values was significantly different between
groups when tested by the unpaired Student's t-test. \( P < 0.05 \) was considered
significant. There were four males and one female in groups 1–3 and four
males in group 4. Serum calcium values were not available.

**Results**

All patients developed a significant natriuresis
after the parenteral diuretic therapy.

Chlorthiazide (10 mg/kg) had no effect on the
mean \( U_{\text{o sm}}/P_{\text{o sm}} \) (1.54 vs 1.34), but frusemide
(1 mg/kg) caused a fall in the mean ratio (1.64 to
0-84, \( P < 0.01 \)) and the urine became hypotonic
(ratio less than 1-0) in every patient. The osmolar
clearances \( (C_{\text{o sm}}) \) were significantly higher after
frusemide than after chlorthiazide (11.45 vs 4.99
ml/min, \( P < 0.01 \)) but there were no significant
changes in cardiac output or clearance of
p-aminohippurate.

In further studies five patients received intra-
venous frusemide, 0-25–0-5 mg/kg (group 3), and four patients received intravenous
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FIG. 1. Comparable increases in osmolar clearance with high-dose chlorthiazide (20 mg/kg; n = 4; ▲—▲) and low-dose frusemide (0.25–0.5 mg/kg; n = 5; ■—■). Values are means ± SEM.

Chlorthiazide, 20 mg/kg (group 4). As shown in Fig. 1, the osmolar clearances were not significantly different in these two groups. Nevertheless, in the patients receiving low-dose frusemide (group 3), the U_{osm}/P_{osm} diminished to a mean ratio which was significantly below that of those receiving chlorthiazide (group 4, 1.26 vs 1.00, P < 0.01), even though they started at a higher control ratio (Fig. 2). In fact, in two of the five patients the urine became hypotonic. The high dose of chlorthiazide (group 4) caused a small fall in the mean U_{osm}/P_{osm} (1.75–1.26, P < 0.01) but the urine did not become hypotonic in any of the patients.

The infusion of vasopressin increased the U_{osm}/P_{osm} in the patients receiving the low dose of chlorthiazide (group 1) from 1.34 to 1.68 (P < 0.01), whereas it had no effect in the group 2 patients given the high dose of frusemide (U_{osm}/P_{osm}, 0.84–0.93). Fig. 2 shows that this difference between the diuretics was also present in the two groups of patients with comparable solute excretion rates. Vasopressin increased U_{osm}/P_{osm} in the patients receiving the high dose of chlorthiazide (group 4) from 1.26 to 1.75 (P < 0.001), whereas it had no effect on the ratio in the group 4 patients given the low dose of frusemide (1.00–1.03).

Discussion

The present results confirm the previous finding that parenteral frusemide, although an inhibitor of sodium chloride transport in the distal diluting segment of the nephron, increases solute-free water excretion in hyponatraemic patients with oedematous disorders [7]. The initial dose of the loop diuretic used to induce such an increase in free-water excretion was 1 mg/kg. In contrast, intravenous chlorthiazide (10 mg/kg) had no effect on the excretion of solute-free water. The increased excretion of solute-free water after frusemide may have been a consequence of its greater potency as a diuretic, as the mean solute excretion rate was much higher after frusemide than after chlorthiazide. An increase in solute excretion has been shown to decrease urinary osmolality in the presence of maximal exogenous doses of vasopressin [10]. The exact mechanism for this effect is not clear, but it may be due either to a decrease in medullary tonicity, owing to a rise in medullary blood flow, or to an increased rate of tubular fluid flow through the collecting duct with a failure of osmotic equilibration of water. Nevertheless, in normal human subjects [10], in contrast with monkey [11] and dog [12], an increase in solute excretion rate alone rarely makes the urine hypotonic. On the basis of previous results in normal subjects [10] the solute excretion rates induced by frusemide (1 mg/kg) would be expected to lower the U_{osm}/P_{osm} to only 1.3 and not the 0.84 which was observed. The concentrating mechanism in oedematous patients may, of course, respond differently to enhanced solute excretion, but these results suggested that frusemide might reduce urinary osmolality through mechanisms other than the increase in solute excretion.

To test this possibility studies were designed in which diuretic-induced solute excretion was comparable after frusemide and chlorthiazide. The frusemide dose was decreased to 0.25–0.50 mg/kg and the chlorthiazide dose was increased to 10 mg/kg; these doses produced comparable
osmolar excretion. A comparison of the effects of the different doses supported an effect of solute excretion rate in the $U_{osm}/P_{osm}$. The increase in the dose of chlorothiazide from 10 to 20 mg/kg increased solute excretion rate from 4.99 to 7.48 ml/min and reduced the $U_{osm}/P_{osm}$. (1.75–1.26, $P < 0.01$). The reduction in the dose of frusemide from 1 to 0.25–0.5 mg/kg caused an increase in the minimal $U_{osm}/P_{osm}$ from 0.84 to 1.0 and only two of five instead of five of five patients excreted a hypotonic urine. Nevertheless, frusemide lowered the ratio more than chlorothiazide did, even at comparable solute excretion rates (Fig. 2). Moreover, exogenous vasopressin increased the ratio during chlorothiazide administration but not during frusemide administration, and the differences persisted even when the doses of the two diuretics were adjusted to ensure comparable solute excretion rates.

A resistance to vasopressin has been demonstrated in vitro with another loop diuretic, ethacrynic acid, in both isolated perfused cortical collecting tubules [12] and the toad bladder [13]. Frusemide, however, had no effect in the toad bladder [13] or isolated collecting tubules [14]. Frusemide increases urinary prostaglandin excretion [15, 16], which could contribute to the resistance to vasopressin. However, because the inhibitors of prostaglandin synthesis cause sodium retention [17] and renal impairment [18] in oedematous patients, this possible contribution of prostaglandins to the resistance to vasopressin is probably best tested initially in vitro. The greater effect of frusemide compared with chlorothiazide on solute free water excretion in hypo-natraemic oedematous patients could be related to the different site of action of these diuretics in the nephron. Frusemide inhibits sodium and chloride transport in the medullary ascending limb and also may increase medullary blood flow, so that, like mannitol, it decreases the corticopapillary osmotic gradient. Chlorthiazide diuretics do not diminish the corticopapillary osmotic gradient [19]. However, mannitol, even at much higher solute excretion rates than those produced by frusemide in the present study, rarely causes production of hypotonic urine in human subjects [10], perhaps because the corticopapillary osmotic gradient does not become hypo-osmolar. The resistance of vasopressin after frusemide is, therefore, more likely to be the result of some direct inhibitory effect on the action of vasopressin to increase water permeability of the collecting duct epithelium.

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References