SHORT COMMUNICATION

The effect of frusemide on water and electrolyte absorption from the human jejunum

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Summary

1. Frusemide, in a dose of 120 nmol (40 mg) administered intravenously, significantly reduced the absorption of water and electrolytes from the human jejunum, a double-lumen perfusion system with proximal occluding balloons being used. Net secretion of water and electrolytes occurred in some subjects.

2. No significant change in water and electrolyte absorption was observed with 60 nmol (20 mg) of frusemide.

3. These findings may explain the diarrhoea which may be induced by frusemide in some patients.

Key words: electrolyte absorption, frusemide, small-intestinal perfusion, water absorption.

Introduction

The administration of frusemide is occasionally associated with diarrhoea as an unwanted side effect (Cooperman & Rubin, 1973; Kennedy, 1974). As frusemide is considered to be an inhibitor of renal transport mechanisms (Knox, Wright, Howards & Berliner, 1969), it is possible that intestinal transport mechanisms may also be altered by the drug. The principal action of frusemide on the kidney is similar to that of ethacrylic acid, namely inhibition of sodium reabsorption in the ascending loop of Henle (Cannon & Kilcoyne, 1969). Amongst other actions, ethacrylic acid has been shown to inhibit water absorption by hamster gut sacs, secretion occurring with higher dosage (Binder, Katz, Spencer & Spiro, 1966). A reduction of sodium absorption has also been noted in isolated rabbit ileum after mucosal application of ethacrylic acid (Al-Awquati, Field & Greenough, 1974). If frusemide were to alter the water absorption mechanism in this way in the human jejunum, a possible explanation of frusemide-induced diarrhoea would be found.

Methods and subjects

The study was performed by the technique of small-intestinal perfusion with a double-lumen tube with proximal occluding balloons and a mixing segment 30 cm long. Immediately proximal to this were two occluding balloons and above this was a further collection point for removal of the fluid collecting above the occluding balloons. The tube was passed under X-ray control, with an image intensifier, until the balloons were at the ligament of Treitz.

Lack of contamination by the perfusate of fluid aspirated above the balloons was demonstrated in the ensuing 10–15 min by measuring marker concentration.

The perfusing solution contained sodium (140 mmol/l), potassium (5 mmol/l), chloride (100 mmol/l), bicarbonate (45 mmol/l) and glucose (11.2 mmol/l). The osmolality was 300 mosmol/l.

Phenol Red (150 mg/l) was used as a non-absorbable, water-soluble marker. In some subjects, $^{14}$C-labelled polyethylene glycol 4000 (1 g/l) was used as a second marker.
The solution was infused at a rate of 15 ml/min at 37°C. An equilibration period of 50 or 60 min was allowed to develop 'steady-state' conditions. Three separate collections (10 min each) were taken before injection of frusemide and then for the ensuing 50 or 60 min.

The study was performed on twelve normal volunteer subjects, who gave informed consent for the procedure to be carried out. Five subjects received 60 nmol of frusemide and seven subjects received 120 nmol of frusemide.

Small-intestinal transmucosal electrical potential difference was measured in some subjects. The technique used was that described by Cochran, MacKenzie & Russell (1975). For this study, however, the probe electrode, containing saturated potassium chloride in agar, was incorporated into the double-lumen perfusion system with the distal end of the probe at the mid-point of the test segment. Throughout the investigation EPD(1) was recorded continuously.

Water, sodium, potassium and chloride absorption was calculated from the change in concentration of the non-absorbable marker, Phenol Red, and polyethylene glycol.

The statistical significance of the results was assessed by the paired t-test.

Results

There was no significant change in the absorption of water and electrolytes from the test segment after intravenous injection of 60 nmol of frusemide. A diuresis occurred in all five subjects.

The mean net water and electrolyte absorption after 120 nmol of frusemide is shown in Table 1. The reduction in net absorption of water is statistically significant at 20, 30, 40 and 50 min. The reduction in net sodium absorption is significant at 30, 40 and 50 min and the reduction in net potassium absorption significant at 40 and 50 min. There was a net secretion of chloride in some subjects and a rather low absorption (in relation to the sodium absorption) in the remainder—the effect of frusemide in a dose of 120 nmol is to increase the net secretion significantly at 40 and 50 min.

The mean urinary water excretion (±SEM) before and after 120 nmol of frusemide was 137.6 ± 28.5 ml/h and 1378 ± 176.1 ml/h respectively, and sodium excretion before and after the same dose of frusemide was 10.9 ± 3.1 mmol/h and 156.3 ± 21.2 mmol/h respectively.

The change in absorption after frusemide was statistically significant whether polyethylene glycol or the Phenol Red data were used to calculate the results. It was noted, however, that the water absorption calculated from polyethylene glycol data was consistently less than when Phenol Red data were used.

The mean EPD for the three subjects studied, recorded during the perfusion, was −2.35 mV (range −1.43 to −4.8 mV). After the administration of frusemide, the mean EPD was −2.84 mV (range −1.22 to −4.3 mV).

### Table 1. Water and electrolyte absorption before and after 120 nmol of frusemide

Mean values ± SEM are shown. Significance of results: * P < 0.05; ** P < 0.005.

<table>
<thead>
<tr>
<th>After frusemide</th>
<th>Before frusemide</th>
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<tr>
<td></td>
<td>10 min</td>
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<tr>
<td>Mean sodium absorption (mmol/h)</td>
<td>14.80 ± 4.83</td>
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<tr>
<td>Mean potassium absorption (mmol/h)</td>
<td>0.73 ± 0.23</td>
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<td>Mean chloride absorption (mmol/h)</td>
<td>−0.92 ± 4.63</td>
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<td>Mean water absorption (mmol/h)</td>
<td>140.41 ± 39.09</td>
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Discussion

It appears from this study that frusemide alters transport mechanisms in the human jejunum but the mechanism is not clear. It has been suggested that sodium/potassium-dependent adenosine triphosphatase may play a role in the active transport of sodium across the gut mucosa (Katz & Epstein, 1968), and both frusemide and ethacrynic acid are potent inhibitors of this enzyme system in vivo and in vitro (Knox et al., 1969; Duggan & Noll, 1965). It is possible that this effect may be responsible for inhibition of sodium transport by frusemide.

Measurement of water and electrolyte absorption in the jejunum by perfusion is a well-established technique (Schedl & Clifton, 1963; Phillips & Summerskill, 1966) and particularly lends itself to the present study in which each subject acted as his or her own control. Although we found a good correlation between the absorptive changes calculated from 14C-labelled polyethylene glycol results and from those with Phenol Red, it was noted that these specific figures obtained were consistently lower with the former results. This may be due to falsely high readings of absorbance obtained for Phenol Red solutions in the presence of mucoproteins (MacGregor & Meyer, 1974).

The recordings of the small-intestinal EPD measured during the basal rate in our subjects were similar to those found by Geall (1970). Loss of sodium into the bowel lumen and a normal EPD have been shown to occur in coeliac disease (Russell, Allan, Gerskowitch & Robertson, 1972; R.I. Russell & K.M. Cochran, unpublished work). Similar EPD values have been reported in the ileum of patients with cholera, where there is also sodium loss. In these two conditions the sodium loss is thought to be accompanied by an equivalent chloride loss; thus a change in EPD does not occur. Our results in this study suggest therefore that sodium loss after frusemide is accompanied by an equivalent loss of anions.

These results are of importance in relation to the mechanism of action of frusemide and its tendency to cause diarrhoea when given in high dosage.

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References


