The interaction of paracetamol with frusemide

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Following the administration of paracetamol (1g 4 times per day) or placebo to 10 healthy female volunteers for 2 days, the pharmacological effects of intravenous frusemide (20 mg) were observed after a final dose of either paracetamol or placebo. Paracetamol pre-treatment had no effect on frusemide-induced diuresis or natriuresis. There was a significant reduction in the basal output of prostaglandin E2 (PGE2) with paracetamol pre-treatment (18.4 ± 15.4 vs 7.6 ± 5.0 ng h⁻¹, P < 0.05; 95% confidence interval of the difference 0.2 to 21.8). Frusemide induced a transient increase in the urinary excretion rate of PGE2 and although this effect was reduced by paracetamol (46.6 ± 50.9 vs 23.2 ± 13.8) the differences in the change of excretion rate from baseline were not statistically significant (95% confidence interval of the difference -17.8 to 15.7). The basal level of 6-keto prostaglandin Flα (PGFlα) was less with paracetamol pre-treatment (61.7 ± 41.1 vs 38.7 ± 26.1 ng h⁻¹, NS; 95% confidence interval of the difference -16.6 to 62.6) and the cumulative urinary output of PGFlα in the 6 h after frusemide administration was significantly reduced (305.9 ± 179.4 vs 181.8 ± 100.2 ng h⁻¹, P < 0.05; 95% confidence interval of the difference 32.2 to 216). The frusemide-induced rise in plasma renin activity was significantly less with paracetamol than placebo at 60 min (4.3 ± 2.9 vs 2.7 ± 1.9 ng ml⁻¹ h⁻¹, P < 0.01; 95% confidence interval of the difference 0.4 to 2.7).

Keywords paracetamol frusemide prostaglandins diuresis natriuresis renin

Introduction

Frusemide produces a marked increase in the excretion of renal prostaglandins which may mediate some of its pharmacological actions [1, 2]. Although the non-steroidal anti-inflammatory drugs which inhibit prostaglandin synthesis decrease the transient rise in plasma renin activity induced by frusemide [3-5] their effects on its natriuretic response are more controversial [6]. Some investigators have reported a reduced response [3-5] but others have not [7-9].

Paracetamol has been considered to be only a weak inhibitor of prostaglandin synthesis [10] but it caused a reduction in urinary PGE2 and sodium excretion in healthy female volunteers [11]. The present study investigates the effects of paracetamol on frusemide-induced diuresis, natriuresis, renal prostaglandin excretion and rise in plasma renin activity.

Methods

Volunteers

Ten healthy female volunteers of mean age 32 years (range 22–47) and weight 72 kg (range 46–101) were studied. They were taking no regular medication, they did not smoke and drank less than 5 units of alcohol per week. The results of routine biochemical and haematological screening tests were normal. The study was approved by the local Ethics Committee of Medical Research and all the subjects gave informed written consent.

Experimental design

Following the administration of placebo or paracetamol for 2 days the effects of intravenous frusemide
were studied on the third day after a final dose of either placebo or paracetamol. All subjects received both treatments which were given under single blind conditions in random order. Placebo (two lactose tablets) or 1 g paracetamol (two 0.5 g Panadol tablets) were taken at 08.30, 12.30, 16.30 and 20.30 h for 2 days. No food was taken for 2 h before and 2 h after dosing. To avoid problems with premenstrual fluid retention, the studies were carried out during the 18 days following the end of a normal menstrual period. At least 1 week separated both studies.

The volunteers were instructed by the hospital dietician how to restrict their intake of sodium to 75 mmol per day for 2 days before and during the study. They were asked to avoid sexual activity before the third study day on each occasion.

On the third study days an intravenous cannula was placed in a forearm vein and the fasting volunteers took 200 ml of water at 08.00 h. They remained recumbent for 30 min and venous blood was sampled for basal plasma renin activity (PRA activity). At 08.30 h the bladder was emptied and the final dose of either placebo or paracetamol 1 g was taken with 200 ml water. The subjects remained recumbent and 1 h later blood was again sampled for PRA activity and a urine sample collected.

Frusemide 20 mg ( Hoechst UK, Ltd) was then administered intravenously and blood was sampled at 15, 30 and 60 min for measurement of PRA activity. Urine was collected at 0.5, 1, 2, 4, 6 and 24 h. Fluid was replaced according to the volume of urine passed throughout the day. A light breakfast was served after the administration of frusemide and lunch was taken 3 h later.

Analytical methods

Plasma renin activity was measured by radioimmunoassay of angiotensin I generated under standard conditions [12]. Urinary sodium was measured by an ion selective electrode. Urinary PGE, and 6-keto PGF1α were measured by radioimmunoassay (Du Pont, UK, Ltd) and the method of Dray et al. [13], respectively. The inter- and intra-assay coefficients of variation were 7% and 14% for PGE and 7% and 19% for 6-keto PGF1α.

Statistics

Results are expressed as mean ± standard deviation (s.d.). The significance of differences between placebo or paracetamol pre-treatment on the responses to frusemide was assessed by the Student's t- or Wilcoxon tests for paired data. The level of significance was taken as P < 0.05 and the Bonferroni correction for multiple t-tests was used where appropriate.

Results

Frusemide induced diuresis and natriuresis

Intravenous frusemide caused a marked diuresis in the 30 min following its administration which was not altered by paracetamol pre-treatment (23.9 ± 2.5 vs. 23.0 ± 5.8 ml min⁻¹, 95% confidence interval of the difference −2.6 to 4.4). Similarly, the corresponding frusemide-induced natriuresis was not altered significantly by paracetamol at 30 (1998 ± 4.15 vs. 2192 ± 682 μmol min⁻¹, 95% confidence interval of the difference −805 to 417) or 60 min (1336± 375 vs. 1133 ± 356 μmol min⁻¹, 95% confidence interval of the difference −124 to 532, Table 1).

Urinary excretion of prostaglandin E₂ (PGE₂) and 6-keto prostaglandin F₁α (PGF₁α)

The mean basal urinary excretion rate of PGE₂ was significantly lower with paracetamol than with placebo pre-treatment (7.6 ± 5.0 compared with 18.5 ± 15.4 ng h⁻¹, P < 0.05, respectively; 95% confidence interval of the difference −21.8 to 0.2, Figure 1a). Following frusemide the rate of excretion of PGE increased in the first 30 min from 18.5 ± 15.4 to 46.6 ± 50.9 ng h⁻¹. With paracetamol pre-treatment the response was less (7.6 ± 5.0 to 23.2 ± 13.8 ng h⁻¹) but there were no significant differences in the rate of

![Figure 1](https://via.placeholder.com/150)
change of excretion of PGE2 from baseline on both study days (95% confidence interval of the difference −17.8 to 15.7) and the blunted response seemed to reflect the lower baseline excretion of PGE2. Although the rate of excretion of PGE2 was significantly lower from 30 to 60 min with paracetamol pre-treatment (22.3 ± 18.5 vs 10.43 ± 4.3, P < 0.01; 95% confidence interval for the mean difference 0.49 to 23.3), thereafter the excretion rates varied little between both study days (Figure 1a).

Similarly, the mean basal excretion rate of 6-keto PGF1α was lower with paracetamol than with placebo pre-treatment (38.7 ± 26.1 vs 61.7 ± 41.1 ng h⁻¹) but the differences were not significant (95% confidence interval of the difference −62.2 to 16.6, Figure 1b). In the 30 min following the administration of frusemide there was a transient increase in the urinary excretion rate of 6-keto PGF1α which was less with paracetamol pre-treatment (61.7 ± 41.1 to 91.2 ± 58.9 vs 38.7 ± 26.1 to 65.7 ± 31.9 ng h⁻¹). However, again the differences in the change of excretion rate from baseline were not statistically significant (95% confidence interval of the difference −33.4 to 58.1). At each subsequent collection point the mean excretion rate was always higher with placebo and the cumulative output over the 6 h after frusemide was significantly lower with paracetamol than with placebo pre-treatment (183.3 ± 100.6 vs 305.9 ± 179.7, P < 0.05; 95% confidence interval of the difference −216 to −32.2).

**Plasma renin activity**

With placebo pre-treatment, frusemide induced an increase in PRA activity up to 1 h (Table 1) and this was significantly reduced with paracetamol at 60 min (4.3 ± 2.9 vs 2.7 ± 1.9 ng ml⁻¹ h⁻¹, P < 0.01; 95% confidence interval 0.4 to 2.7).

**Discussion**

Paracetamol has been considered to be only a weak inhibitor of prostaglandin biosynthesis. However paracetamol therapy reduced the urinary excretion of prostaglandins and consequently blunted the frusemide-induced increase in PGE2 and 6-keto PGF1α. Paracetamol also attenuated the rise in PRA activity following frusemide but had little effect on natriuresis or diuresis.

At least some of the pharmacological actions of frusemide in man are mediated by the prostaglandins and its administration is associated with an increase in urinary prostaglandin excretion [1, 2]. The acute rise in PRA activity following frusemide is prostaglandin-mediated [14] and this effect is consistently blocked by the non-steroidal anti-inflammatory drugs which inhibit the formation of prostaglandins [3–5]. A later rise is thought to be related to sodium and water depletion. In the present study paracetamol had most effect on PRA activity 60 min after frusemide administration suggesting that a small anti-natriuretic effect may have occurred which was not picked up by the methods used, possibly due to a Type 11 error. The relationship between prostaglandins and the natriuretic effect of frusemide is not clear [6]. Although non-steroidal anti-inflammatory drugs have been found in some cases to reduce the natriuretic response to frusemide [3–5] other reports showed no such interaction [7–9].

Paracetamol was previously shown to cause a reduction in PGE2 excretion in healthy female volunteers under conditions of controlled sodium intake associated with a reduction in sodium output [11]. Paracetamol reduced sodium and water output [15] and it has an antinatriuretic effect in patients with diabetes insipidus [16].

In contrast, Berg *et al.*

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**Table 1** The diuresis (ml min⁻¹), natriuresis (μmol min⁻¹) and plasma renin activity (ng ml⁻¹ h⁻¹) observed following the administration of 20 mg frusemide intravenously to 10 healthy female volunteers pre-treated with either placebo or paracetamol (1 g 4 times per day) for 2 days.

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<tbody>
<tr>
<td><strong>Volume</strong> (placebo)</td>
<td>2.9 ± 2.1</td>
<td>23.9 ± 2.5</td>
<td>18.6 ± 4.9</td>
<td>7.6 ± 3.3</td>
<td>2.7 ± 1.6</td>
<td>2.6 ± 1.4</td>
<td>1.0 ± 0.5</td>
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<tr>
<td><strong>Volume</strong> (paracetamol)</td>
<td>3.8 ± 3.1</td>
<td>23.0 ± 5.8</td>
<td>16.6 ± 5.1</td>
<td>7.6 ± 2.6</td>
<td>3.0 ± 1.2</td>
<td>3.7 ± 1.2</td>
<td>0.9 ± 0.5</td>
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<td><strong>Sodium</strong> (placebo)</td>
<td>78 ± 43</td>
<td>1998 ± 415</td>
<td>1336 ± 375</td>
<td>329 ± 127</td>
<td>60 ± 47</td>
<td>61 ± 47</td>
<td>26 ± 10</td>
</tr>
<tr>
<td><strong>Sodium</strong> (paracetamol)</td>
<td>109 ± 71</td>
<td>2192 ± 682</td>
<td>1133 ± 356</td>
<td>339 ± 134</td>
<td>73 ± 43</td>
<td>70 ± 24</td>
<td>34 ± 18</td>
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<tr>
<td><strong>PRA</strong> (placebo)</td>
<td>2.0 ± 1.4</td>
<td>1.7 ± 0.9</td>
<td>3.4 ± 2.7</td>
<td>3.5 ± 2.1</td>
<td>4.3 ± 2.9</td>
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<tr>
<td><strong>PRA</strong> (paracetamol)</td>
<td>1.5 ± 0.6</td>
<td>1.4 ± 0.5</td>
<td>2.4 ± 1.5</td>
<td>2.3 ± 1.4</td>
<td>2.7 ± 1.9</td>
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[17] found reduced sodium and PGE$_2$ output in elderly volunteers but not young subjects and Bippi & Fröhlich [18] were unable to demonstrate a reduction in urinary PGE$_2$ excretion following paracetamol in female volunteers. The present results confirm previous reports suggesting that paracetamol shares at least some of the renal properties of the non-steroidal anti-inflammatory drugs.

References


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