The interaction of paracetamol with frusemide

U. MARTIN & L. F. PRESCOTT

University Department of Clinical Pharmacology, The Royal Infirmary, Edinburgh EH3 9YW

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 E_2 (PGE_2) 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 PGE_2 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 $F_{1\alpha}$ ($PGF_{1\alpha}$) 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 $PGF_{1\alpha}$ 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 PGE_2 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 the 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_2 and 6-keto $\text{PGF}_{1\alpha}$ 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_2 and 7% and 19% for 6-keto $\text{PGF}_{1\alpha}$.

Statistics

Results are expressed as mean $\pm$ 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 $\mu\text{mol min}^{-1}$, 95% confidence interval of the difference -805 to 417) or 60 min (1336 ± 375 vs 1133 ± 356 $\mu\text{mol min}^{-1}$, 95% confidence interval of the difference -124 to 532, Table 1).

Urinary excretion of prostaglandin E_2 (PGE_2) and 6-keto prostaglandin $\text{F}_{1\alpha}$ ($\text{PGF}_{1\alpha}$)

The mean basal urinary excretion rate of PGE_2 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_2 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 The mean ($\pm$ s.e. mean) urinary excretion rates of a) prostaglandin E_2 and b) 6-keto prostaglandin $\text{F}_{1\alpha}$ (ng h⁻¹) following the administration of frusemide (20 mg) intravenously to 10 healthy female volunteers pre-treated with either placebo (○) or paracetamol (●).

change of excretion of PGE_2 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 PGE_2 . Although the rate of excretion of PGE_2 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 $\text{PGF}_{1\alpha}$ 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 $\text{PGF}_{1\alpha}$ 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 $\text{ng ml}^{-1} \text{h}^{-1}$, $P < 0.01$; 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 PGE_2 and 6-keto $\text{PGF}_{1\alpha}$. 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 II 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 PGE_2 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.*

Table 1 The diuresis (ml min^{-1}), natriuresis ($\mu\text{mol min}^{-1}$) and plasma renin activity ($\text{ng ml}^{-1} \text{h}^{-1}$) 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

	Time (h)						
	0	0.5	1	2	4	6	6–24
Volume (placebo)	2.9 ± 2.1	23.9 ± 2.5	18.6 ± 4.9	7.6 ± 3.3	2.7 ± 1.6	2.6 ± 1.4	1.0 ± 0.5
Volume (paracetamol)	3.8 ± 3.1	23.0 ± 5.8	16.6 ± 5.1	7.6 ± 2.6	3.0 ± 1.2	3.7 ± 1.2	0.9 ± 0.5
Sodium (placebo)	78 ± 43	1998 ± 415	1336 ± 375	329 ± 127	60 ± 47	61 ± 47	26 ± 10
Sodium (paracetamol)	109 ± 71	2192 ± 682	1133 ± 356	339 ± 134	73 ± 43	70 ± 24	34 ± 18
	Time (min)						
	-60	0	15	30	60		
PRA (placebo)	2.0 ± 1.4	1.7 ± 0.9	3.4 ± 2.7	3.5 ± 2.1	4.3 ± 2.9		
PRA (paracetamol)	1.5 ± 0.6	1.4 ± 0.5	2.4 ± 1.5	2.3 ± 1.4	2.7 ± 1.9		

[17] found reduced sodium and PGE₂ output in elderly volunteers but not young subjects and Bippi & Fröhlich [18] were unable to demonstrate a reduction in urinary PGE₂ excretion following para-

cetamol 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

- 1 Abe K, Yasujima M, Chiba S, Irokawa N, Ito T, Yoshinaga K. Effects of furosemide on urinary excretion of prostaglandin E in normal volunteers and patients with essential hypertension. *Prostaglandins* 1977; **14**: 513–521.
- 2 Scherer B, Weber PC. Time-dependent changes in prostaglandin excretion in response to frusemide in man. *Clin Sci* 1979; **56**: 77–81.
- 3 Patak RV, Mookerjee BK, Bentzel CJ, Hysert PE, Babej M, Lee JB. Antagonism of the effects of furosemide by indomethacin in normal and hypertensive man. *Prostaglandins* 1975; **10**: 649–659.
- 4 Fröhlich JC, Hollifield JW, Dormois JC, *et al.* Suppression of plasma renin activity by indomethacin in man. *Circ Res* 1976; **39**: 447–452.
- 5 Passmore AP, Copeland S, Johnston GD. A comparison of the effects of ibuprofen and indomethacin upon renal haemodynamics and electrolyte excretion in the presence and absence of frusemide. *Br J clin Pharmacol* 1989; **27**: 483–490.
- 6 Attallah A. Interaction of diuretics with prostaglandins. *Prostaglandins* 1979; **18**: 369–375.
- 7 Bailie MD, Crosslan K, Hook JB. Natriuretic effect of furosemide after inhibition of prostaglandin synthetase. *J Pharmacol exp Ther* 1976; **199**: 469–476.
- 8 Weber PC, Scherer B, Larsson C. Increase of free arachidonic acid by furosemide in man as the cause of prostaglandin and renin release. *Eur J Pharmacol* 1977; **41**: 329–332.
- 9 Riley L, Vlasses PH, Rotmensch HH, *et al.* Sulindac and ibuprofen inhibit furosemide-stimulated renin release but not natriuresis in men on a normal sodium diet. *Nephron* 1985; **41**: 283–288.
- 10 Brune, K. Prostaglandins and the mode of action of antipyretic analgesic drugs. *Am J Med* 1983; **75**: 19–23.
- 11 Prescott LF, Mattison P, Menzies DG, Manson LM. The comparative effects of paracetamol and indomethacin on renal function in healthy female volunteers. *Br J clin Pharmacol* 1990; **29**: 403–412.
- 12 Haber E, Koerner T, Page LB, Kliman B, Purnode A. Application of a radioimmunoassay for angiotensin I to the physiological measurement of plasma renin activity in normal human subjects. *J clin Endocrinol Metab* 1969; **29**: 1349–1355.
- 13 Dray F, Charbonnel B, Maclouf J. Radioimmunoassay of prostaglandins F_{1α}, E₁ and E₂ in human plasma. *Eur J clin Invest* 1983; **5**: 311–318.
- 14 Gerber JG, Nies AS, Olsen RD. Control of canine renin release: macula densa requires prostaglandin synthesis. *J Physiol* 1981; **319**: 419–429.
- 15 Haylor J. Prostaglandin synthesis and renal function in man. *J Physiol* 1980; **298**: 383–396.
- 16 Nusynowitz ML, Forsham PH. The antidiuretic effect of acetaminophen. *Am J med Sci* 1966; **252**: 429–435.
- 17 Berg KJ, Djøseland O, Gjellan A, *et al.* Acute effects of paracetamol on prostaglandin synthesis and renal function in normal man and in patients with renal failure. *Clin Nephrol* 1990; **34**: 255–262.
- 18 Bippi H, Fröhlich JC. Effects of acetylsalicylic acid alone and in combination on prostanoid synthesis in man. *Br J clin Pharmacol* 1990; **29**: 305–310.

(Received 12 July 1993,
accepted 24 January 1994)