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The effects of ibuprofen and indomethacin on renal function in the presence and absence of frusemide in healthy volunteers on a restricted sodium diet

A. P. PASSMORE, S. COPELAND & G. D. JOHNSTON
Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Belfast, Northern Ireland

1 Since salt depletion stimulates the renal prostaglandin system to maintain renal function, the effects of indomethacin and ibuprofen upon renal haemodynamics, electrolyte excretion and renin release were examined in eight healthy male volunteers on a salt restricted diet, before and after frusemide administration.

2 Neither indomethacin (50 mg) nor ibuprofen (400 mg and 800 mg) affected renal blood flow, glomerular filtration rate or electrolyte excretion before frusemide.

3 Renal blood flow and glomerular filtration rate were significantly increased in the first 20 min after frusemide. These changes were significantly attenuated by indomethacin compared with placebo and ibuprofen 400 mg. Frusemide-induced diuresis but not natriuresis was inhibited by all treatments.

4 Both nonsteroidal agents inhibited equally the rise in renin activity seen after frusemide.

5 In this group of healthy volunteers on a salt restricted diet, ibuprofen and indomethacin had no detrimental effects on renal function in the absence of frusemide. The changes in renal haemodynamics due to frusemide were suppressed more by indomethacin than by ibuprofen, probably reflecting the more potent nature of indomethacin as an inhibitor of prostaglandin synthesis.

Keywords frusemide ibuprofen indomethacin sodium restriction

Introduction

The renal prostaglandin system is implicated in the control of renal haemodynamics, electrolyte excretion and renin release, and may have an important role in frusemide-induced changes in these variables. The full modulatory effect of renal prostaglandins is most evident in situations of increased activity of the sympathetic nervous and renin-angiotensin systems. Examples of this include heart failure, cirrhosis and sodium deprived normal subjects, when vasodilatory prostaglandins offset these vasoconstrictor influences. The use of prostaglandin synthetase inhibitors in these circumstances may result in unopposed renal vasoconstriction (Clive & Stoff, 1984).

In a previous study we found that indomethacin and ibuprofen had little effect on renal haemodynamics or electrolyte excretion in a group of salt replete volunteers (Passmore *et al.*, 1989). In salt deplete humans, indomethacin has been reported to have little effect on basal renal haemodynamics (Donker *et al.*, 1976; Mackay *et al.*, 1984; Sedor *et al.*, 1984), but there are reports of a significant decrease (Kramer *et al.*, 1985). There is little information available on the renal haemodynamic effect of

Correspondence: Dr G. D. Johnston, Department of Therapeutics and Pharmacology, The Queen's University of Belfast, The Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland

ibuprofen. In humans, the majority of evidence suggests that prostaglandin inhibition is unlikely to result in reduced sodium excretion except in conditions of salt depletion (Raymond & Lifschitz, 1986).

Studies investigating the effects of prostaglandin synthetase inhibition on frusemide-induced diuresis and natriuresis show a blunting (Frolich *et al.*, 1976; Mackay *et al.*, 1984; Patak *et al.*, 1975) or no change (Bailie *et al.*, 1976; Riley *et al.*, 1985; Weber *et al.*, 1977). Prostaglandin synthetase inhibitors decrease renin activity in the basal state (Donker *et al.*, 1976; Frolich *et al.*, 1976; Riley *et al.*, 1985; Rumpf *et al.*, 1975) and after frusemide (Brater *et al.*, 1985; Mackay *et al.*, 1984; Patak *et al.*, 1975; Riley *et al.*, 1985; Rumpf *et al.*, 1975).

Sodium depletion results in activation of the renin-angiotensin system and produces an increased dependence of renal function upon prostaglandin systems (Clive & Stoff, 1984). We have described the effects of indomethacin and ibuprofen on renal haemodynamics, electrolyte excretion and frusemide-induced changes in these variables in a group of salt replete volunteers. The aim of this study was to examine the effects of indomethacin and ibuprofen on renal haemodynamics, electrolyte excretion and renin release, and on the frusemide-induced changes in these variables under conditions of moderate sodium depletion.

Methods

Eight healthy male volunteers aged 21–31 years participated in the study which was approved by the local ethics committee. Each subject was randomly allocated to receive four treatments according to a double-blind four-way crossover design. The four treatment periods were each of 3 days duration, and were followed by the study day. There were at least 2 weeks between each treatment period. Subjects avoided any other nonsteroidal anti-inflammatory agent for 2 weeks before and throughout the study period.

For 7 days before each study day subjects consumed a fixed diet—60 mmol sodium (Na)/60 mmol potassium (K) 24 h^{-1}. A suitable dietary regime was advised by the hospital dietitian and diet sheets were given to each volunteer. After 4 days on the diet, subjects received 3 days treatment with either indomethacin 50 mg three times daily, ibuprofen 400 mg three times daily, ibuprofen 800 mg three times daily or matching placebo.

For the final 24 h of each treatment period subjects collected all urine for assessment of sodium and potassium excretion and creatinine clearance. Subjects who had sodium excretion over 70 mmol in 24 h were required to repeat the protocol for that period of the study. On the morning of the study days subjects had a light early breakfast without caffeine and presented early to the Department of Therapeutics.

Subjects assumed a semi-supine position for 30 min after which a blood sample was drawn for estimation of renin activity. Blood pressure was recorded using a Hawksley random zero sphygmomanometer. Subjects then received the final dose of study medication together with 500 ml water. At this time a bolus injection of inulin and para-aminohippurate (PAH) was given, followed by a sustaining infusion (Freestone *et al.*, 1986). Subjects received 150 ml water every 30 min throughout the study period. At 2 h after dosing subjects emptied their bladders. Between 2 and 3 h a urine collection was obtained for estimation of sodium, potassium and water excretion and inulin and PAH clearances. At the midpoint of the urine collection blood was drawn for the estimation of plasma inulin, PAH concentrations and plasma nonsteroidal anti-inflammatory drug concentration. At the end of the 1 h collection period, blood pressure was again recorded, a blood sample was taken for measurement of plasma renin activity and subjects emptied their bladders. The volume of urine was noted and aliquots reserved for subsequent assay of sodium, potassium, inulin and PAH. Frusemide (20 mg) was administered as a rapid intravenous bolus. This was followed by three 20 min urine collection periods for determination of sodium and potassium excretion, inulin and PAH clearances. Blood pressure was measured 10 min after frusemide. Blood was drawn at the midpoint of each collection period for estimation of plasma renin activity (PRA) and plasma inulin and PAH concentrations. The study continued for 60 min following frusemide administration.

Assay methods

For estimation of PRA 10 ml of blood was immediately placed in glass tubes at 0° C containing 0.3 ml of sodium ethylenediamine tetraacetate (EDTA), centrifuged at 4° C and plasma stored at −40° C. PRA was expressed as ng of angiotensin I (AI) generated h^{-1} ml^{-1} of plasma at pH 6 and 37° C. AI was measured by radioimmunoassay with a Gamma Coat Kit, Clinical Assays Travenol Laboratories Inc. (Haber *et al.*, 1969). PAH was measured as described by Smith *et al.* (1945) and inulin was measured as described by Heyrovsky (1956).

Statistics

The results obtained for the variables before the final dose of the study medication was administered (PRA, urine volume, urinary sodium and potassium excretion and creatinine clearance) were compared by an analysis of variance and the Neuman-Keuls multiple comparison. Following frusemide administration, measured variables were analysed by a repeated measures analysis of variance. The quadratic terms that resulted from the analysis were used to define a response profile to frusemide for PRA, urinary flow rate, sodium and potassium excretion, inulin and PAH clearances, and to test any differences between these profiles. The response profile is a reflection of overall change following frusemide. These variables were also analysed for each of the three 20 min time intervals, using an analysis of variance and the Neuman-Keuls multiple comparison test. PRA was measured both at the pre-dosing assessment and immediately prior to administering frusemide. The first of these values was analysed alone whilst the second was used in the repeated measures analysis.

In order to assess the adequacy of patient numbers, given the level of variation of results, each post-frusemide mean after placebo treatment was compared with the corresponding pre-frusemide mean by means of a *t*-test with the experimental error rate controlled to 5% using Sidak's adjustment (Sidak, 1967). The activity of frusemide after placebo treatment is beyond doubt, therefore a significant difference would be expected in the placebo profiles if the number of volunteers was adequate. This secondary test is not applicable for treatments other than placebo. All results are expressed as the mean ± s.e. mean, with significance accepted at the 5% level.

Results

Baseline values

At 150 min after dosing the plasma concentrations of ibuprofen 400 mg, 800 mg and indomethacin were 18.9 ± 1.5 μg ml^{-1}, 33 ± 2.8 μg ml^{-1} and 1.5 ± 0.3 μg ml^{-1} respectively. Although creatinine clearance was lower with indomethacin and ibuprofen than with placebo after 3 days treatment, these differences were not significant (Table 1). Twenty-four hour sodium and potassium excretion were not affected by ibuprofen or indomethacin compared with placebo (Table 1). Basal PRA following indomethacin (0.9 ± 0.2 ng AI ml^{-1} h^{-1}) was significantly lower than in the presence of placebo (2.2 ± 0.5 ng AI ml^{-1} h^{-1}, $P < 0.05$). Ibuprofen did not affect basal renin activity (Table 1). There were no differences in basal blood pressures for subjects on placebo (118 ± 1.2/83 ± 2.1 mm Hg), ibuprofen 400 mg (124 ± 4/86 ± 4.2 mm Hg), ibuprofen 800 mg (122 ± 1.9/83 ± 1.8 mm Hg) or indomethacin (119 ± 1.7/82 ± 0.8 mm Hg).

Water and electrolyte excretion

Frusemide significantly increased urine flow at all time periods in the presence of placebo ($P < 0.01$). The urine flow rate profiles after fruse-

Table 1 Plasma renin activity (PRA), creatinine clearance, urinary volume, sodium and potassium excretion over 24 h at the end of 3 days treatment with placebo (P), ibuprofen 400 mg three times daily (400), ibuprofen 800 mg three times daily (800) and indomethacin 50 mg three times daily in eight healthy male volunteers. Values are expressed as mean ± s.e. mean. DM = difference of means

	PRA (*ng AI ml^{-1} h^{-1}*)	*Urinary volume* (*ml*)	*Urinary excretion* (*mmol 24 h^{-1}*) *Sodium*	*Potassium*	*Creatinine clearance* (*ml min^{-1}*)
P	2.2 ± 0.5	1220 ± 110	54 ± 6	38 ± 6	92 ± 8
400	1.2 ± 0.3	1210 ± 180	48 ± 7	44 ± 10	73 ± 5
DM	−1.0	−10	−6	+6	−19
DM 95% CI	−0.44, 0.64	−281, 301	−10, 22	−10, 22	−39, 1
800	1.8 ± 0.5	1300 ± 120	44 ± 7	44 ± 7	81 ± 9
DM	−0.4	+80	−10	+6	−11
DM 95% CI	−0.19, 0.99	−227, 387	−3, 23	−7, 19	−25, 3
IND	0.9 ± 0.2*	1010 ± 150	37 ± 7	44 ± 8	79 ± 7
DM	+1.3	−190	−17	+6	−12
DM 95% CI	0.5, 2.1	−177, 557	−7, 27	−17, 29	−40, 16

*$P < 0.05$ compared with placebo

Table 2 Urine flow rate (ml min^{-1}) before and after frusemide 20 mg in the presence of placebo (P), ibuprofen 400 mg (400), 800 mg (800) and indomethacin (IND). Baseline (0), 0–20 min (F + 20), 20–40 min (F + 40) and 40–60 min (F + 60) after frusemide

	Time			
Treatment	*0*	*F + 20*	*F + 40*	*F + 60*
P	7.5 ± 0.8	30.3 ± 1.3*	26.9 ± 1.5*	18.7 ± 1.7*
400	7.6 ± 0.8	26.8 ± 2.4†	22.4 ± 2.0†	17.9 ± 2.3†
800	7.4 ± 0.9	23.6 ± 1.8††	22.5 ± 1.4††	19.8 ± 1.5††
IND	7.9 ± 0.7	19.6 ± 1.9††	20.2 ± 2.0††	14.3 ± 1.3††

*Significantly different from pre-frusemide mean $P < 0.01$
†Profile different from placebo profile $P < 0.05$
††Profile different from placebo profile $P < 0.01$

Table 3 Sodium excretion rate (mmol min^{-1}) before and after frusemide 20 mg in the presence of placebo (P), ibuprofen 400 mg (400), ibuprofen 800 mg (800) and indomethacin (IND). Baseline (0), 0–20 min (F + 20), 20–40 min (F + 40) and 40–60 min (F + 60) after frusemide. DM = difference of means

	Time			
Treatment	*0*	*F + 20*	*F + 40*	*F + 60*
P	0.1 ± 0.0	2.2 ± 0.2*	1.8 ± 0.2*	1.1 ± 0.2*
400	0.1 ± 0.0	2.3 ± 0.3	2.3 ± 0.4	1.1 ± 0.2
DM	0	+0.1	+0.5	0
DM 95% CI	−0.05, 0.05	−0.2, 0.4	−0.5, 1.5	−0.4, 0.4
800	0.1 ± 0.0	1.9 ± 0.3	1.7 ± 0.3	1.2 ± 0.2
DM	0	−0.3	−0.1	+0.1
DM 95% CI	−0.02, 0.02	−0.4, 1.0	−0.3, 0.5	−0.4, 0.6
IND	0.1 ± 0.0	1.7 ± 0.2	1.4 ± 0.2	0.9 ± 0.1
DM	0	−0.5	−0.4	−0.2
DM 95% CI	−0.07, 0.07	−1.1, 0.1	−0.8, 0	−0.5, 0.1

*Significantly different from pre-frusemide mean $P < 0.01$

mide were significantly lower than placebo for all three active treatments, but with no inter-treatment differences (Table 2).

In the presence of placebo, sodium and potassium excretion rates were significantly augmented by frusemide at each time period ($P < 0.01$). Neither indomethacin nor ibuprofen had any effect on sodium or potassium excretion rates following frusemide (Tables 3 and 4). Analysis of the total sodium and potassium excreted in each period and over the 60 min after frusemide did not reveal significant differences between any treatment and placebo.

Blood pressure

There were no differences in the blood pressures recorded immediately before frusemide administration: Placebo (114 ± 2/81 ± 3 mm Hg), ibuprofen 400 mg (118 ± 3/84 ± 2 mm Hg); ibuprofen 800 mg (120 ± 3/85 ± 3 mm Hg); indomethacin (118 ± 3/85 ± 2 mm Hg). With placebo pretreatment, frusemide significantly increased both systolic (121 ± 2 *vs* 114 ± 2 mm Hg, $P < 0.01$) and diastolic (88 ± 2 *vs* 81 ± 3 mm Hg, $P < 0.01$) blood pressure. Treatment with nonsteroidals had no significant effect on the changes in blood pressure produced by frusemide: systolic pressure, ibuprofen 400 mg (120 ± 3 *vs* 118 ± 3 mm Hg); ibuprofen 800 mg (120 ± 3 *vs* 120 ± 3 mm Hg); indomethacin (118 ± 2 *vs* 118 ± 3 mmHg); diastolic pressure, ibuprofen 400 mg (87 ± 3 *vs* 84 ± 2 mm Hg); ibuprofen 800 mg (87 ± 2 *vs* 85 ± 3 mmHg); indomethacin (85 ± 3 *vs* 85 ± 2 mm Hg).

Plasma renin activity

Plasma renin responses are shown in Figure 1. The plasma renin activity immediately before frusemide was lowered by both doses of ibuprofen and indomethacin, but only the latter reduc-

Table 4 Potassium excretion rate (mmol min^{-1}) before and after frusemide 20 mg in the presence of placebo (P), ibuprofen 400 mg (400), ibuprofen 800 mg (800) and indomethacin (IND). Baseline (0), 0–20 min (F + 20), 20–40 min (F + 40) and 40–60 min (F + 60) after frusemide. DM = difference of means

	Time			
Treatment	*0*	*F + 20*	*F + 40*	*F + 60*
P	0.07 ± 0.01	0.2 ± 0.03*	0.21 ± 0.03*	0.15 ± 0.02*
400	0.13 ± 0.06	0.23 ± 0.03	0.25 ± 0.04	0.15 ± 0.04
DM	+0.06	+0.03	+0.04	0
DM 95% CI	0.04, 0.08	−0.04, 0.1	−0.08, 0.16	−0.05, 0.05
800	0.09 ± 0.01	0.22 ± 0.02	0.21 ± 0.05	0.18 ± 0.03
DM	+0.02	+0.02	0	+0.03
DM 95% CI	0, 0.04	−0.05, 0.09	−0.05, 0.05	−0.04, 0.1
IND	0.09 ± 0.02	0.19 ± 0.02	0.26 ± 0.09	0.14 ± 0.03
DM	+0.02	−0.01	+0.05	−0.01
DM 95% CI	0, 0.04	−0.1, 0.08	−0.02, 0.12	−0.06, 0.04

*Significantly different from pre-frusemide mean $P < 0.01$

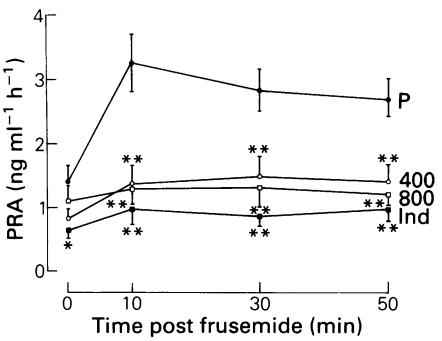

Figure 1 Plasma renin activity (PRA) before and after frusemide (20 mg i.v.) in eight volunteers pretreated with placebo (●), ibuprofen 400 mg (○), ibuprofen 800 mg (□) and indomethacin (■). *$P < 0.05$; **$P < 0.01$ compared with placebo. Mean ± s.e. mean, $n = 8$.

tion was significant ($P < 0.05$). There were no differences between the nonsteroidal treatments. In the presence of placebo, frusemide caused an increment in plasma renin activity at 10, 30 and 50 min (Figure 1). This response was significantly attenuated at all three time periods by both doses of ibuprofen ($P < 0.01$) and by indomethacin ($P < 0.01$). There were no significant differences between active treatments at any time point (Figure 1). This was reflected in the analysis of the plasma renin response profiles after frusemide, where all three active treatments reduced plasma renin activity significantly compared to placebo ($P < 0.01$), but with no differences between active treatments.

Renal haemodynamics

Values for PAH clearance are shown in Figure 2. There were no differences between treatments when baseline values were compared. In the presence of placebo, frusemide produced a significant increase in PAH clearance only at the first time period (Δ = 203 ± 39 ml min^{-1}/1.73 m^2, $P < 0.01$). Values reverted to baseline over the hour following frusemide. The early increment was significantly attenuated by indomethacin (Δ = 22 ± 25 ml min^{-1}/1.73 m^2, $P < 0.01$), but was unaffected by ibuprofen 400 mg or 800 mg. The change in PAH clearance in the first time period following frusemide was significantly lower in the presence of indomethacin than ibuprofen 400 mg ($P < 0.05$), but the responses at this time period with ibuprofen 400 mg and 800 mg were not different, nor were there any differences between the responses with ibuprofen 800 mg and indomethacin. These findings were corroborated by the analysis of the frusemide response profiles for PAH clearance. The profile for indomethacin was significantly lower than both the placebo ($P < 0.05$) and ibuprofen 400 mg ($P < 0.05$) profile (Figure 2).

Inulin clearances are shown in Figure 3. There were no differences between treatments when baseline values were compared. With placebo pretreatment, frusemide significantly increased inulin clearance at the first time period only ($P < 0.01$). This was followed by a gradual return to baseline values over the 1 h period. The frusemide-induced increases at 0–20 min were unaffected by ibuprofen 400 mg and 800

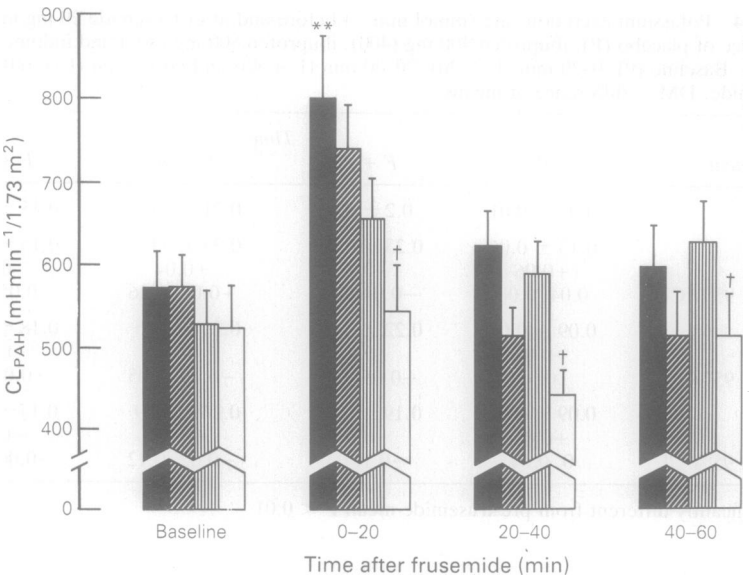

Figure 2 Para-aminohippurate clearances (CL_{PAH}) before and after frusemide (20 mg i.v.) in volunteers pretreated with placebo (■), ibuprofen (400 mg (▩), 800 mg (▥)) or indomethacin (□) (mean ± s.e. mean, $n = 8$). **$P < 0.01$ compared with baseline.

†Profile in the presence of indomethacin significantly lower than placebo and ibuprofen 400 mg ($P < 0.05$).

0–20 min value suppressed significantly by indomethacin compared with placebo ($P < 0.01$) and ibuprofen 400 mg ($P < 0.05$).

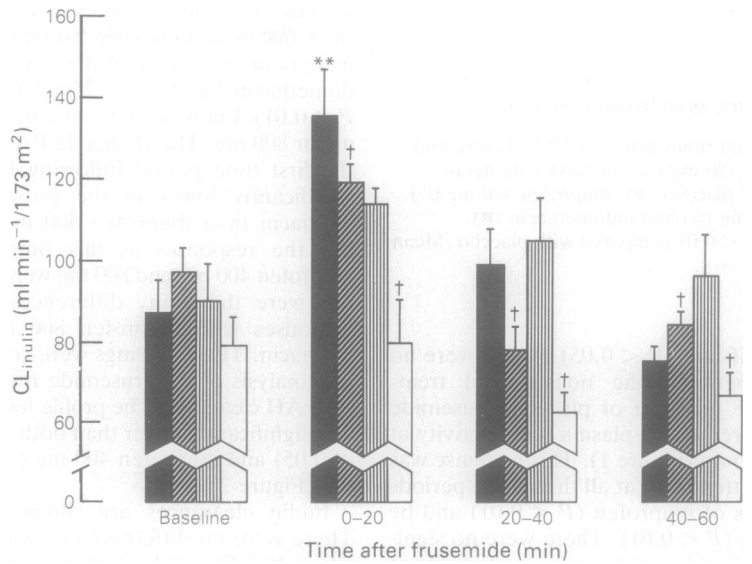

Figure 3 Inulin clearances (CL_{inulin}) before and after frusemide (20 mg i.v.) in volunteers pretreated with placebo (■), ibuprofen (400 mg ▩, 800 mg ▥) or indomethacin (□) (mean ± s.e. mean, $n = 8$). **$P < 0.01$ compared with baseline.

†Profile in the presence of indomethacin and ibuprofen 400 mg significantly lower than placebo ($P < 0.05$).

0–20 min value suppressed significantly by indomethacin compared with placebo ($P < 0.01$), ibuprofen 400 mg ($P < 0.01$) and ibuprofen 800 mg ($P < 0.05$).

mg. However the change in the presence of indomethacin was significantly lower than placebo (1 ± 4 ml $min^{-1}/1.73$ m^2 *vs* 48 ± 9 ml $min^{-1}/1.73$ m^2, $P < 0.01$), ibuprofen 400 mg (22 ± 7 ml $min^{-1}/1.73$ m^2, $P < 0.01$) and ibuprofen 800 mg (24 ± 14 ml $min^{-1}/1.73$ m^2, $P < 0.05$). The frusemide response profiles for inulin clearance were lower in the presence of ibuprofen 400 mg ($P < 0.05$) and indomethacin ($P < 0.05$) than with placebo (Figure 3).

Discussion

Nonsteroidal anti-inflammatory drugs are presumed to act chiefly through inhibition of prostaglandin systems. Renal prostaglandins are important in the control of renal haemodynamics and electrolyte excretion, particularly in conditions of impaired renal function, where maintenance of normal renal capability may be critically dependent on vasodilator prostaglandin systems (Clive & Stoff, 1984). In conditions of salt depletion the kidney is in a salt retaining state, where prostaglandin systems may have a more important role, and the situation of renal impairment is mimicked. Thus interruption of prostaglandin pathways by nonsteroidal anti-inflammatory drugs may result in unopposed renal vasoconstriction and impair haemodynamic and electrolyte responses. Although prostaglandin excretion was not measured, the lowest level of indomethacin in plasma was 0.65 μg ml^{-1}, which has been shown to suppress prostaglandin release by 90–100% (Rane *et al.*, 1978). There are no equivalent data for ibuprofen effects on prostaglandin release.

In sodium restricted volunteers, glomerular filtration rate has been reduced (Donker *et al.*, 1976) or unchanged (Roberts *et al.*, 1985; Sedor *et al.*, 1984) by indomethacin, which may also reduce (Kramer *et al.*, 1985) or have no effect (Donker *et al.*, 1976; Roberts *et al.*, 1985; Sedor *et al.*, 1984) on renal blood flow. In salt deplete volunteers indomethacin causes transient sodium retention (Donker *et al.*, 1976; Roberts *et al.*, 1985; Sedor *et al.*, 1984). Ibuprofen has been reported as having no effect on renal haemodynamics or sodium excretion in salt restricted subjects (Brater *et al.*, 1985). In the present study, neither indomethacin nor ibuprofen changed basal renal haemodynamics, water or electrolyte excretion. This was also the case in our previous study in salt replete volunteers (Passmore *et al.*, 1989). The basal results in the present study cannot support a significant modulatory role for renal prostaglandins in conditions of mild sodium deletion. The absence of effect of the prostaglandin inhibitors on basal renal haemodynamics would also be consistent with an unchanged basal electrolyte excretion. It may be that it requires conditions of more severe sodium restriction (e.g. 10 mmol $24\ h^{-1}$) to produce a situation where prostaglandins have a significant modulatory role, and where prostaglandin inhibition is likely to result in renal deterioration.

As anticipated, frusemide significantly increased water and electrolyte excretion in the presence of placebo. In salt replete conditions, indomethacin has been reported to inhibit (Frolich *et al.*, 1976; Mackay *et al.*, 1984; Passmore *et al.*, 1989) or have no effect (Weber *et al.*, 1977; Williamson *et al.*, 1975) on frusemide-induced natriuresis and diuresis. Ibuprofen has also had little effect (Passmore *et al.*, 1989; Riley *et al.*, 1985). In salt deplete volunteers diuresis and natriuresis following frusemide were unaffected by indomethacin (Roberts *et al.*, 1985), but reduced by ibuprofen (Brater *et al.*, 1985). The present study shows that both doses of ibuprofen and indomethacin reduced diuresis but had no effect on natriuresis after frusemide, and that there were no differences between the nonsteroidal agents. This suggests a mediatory role for renal prostaglandins in frusemide-induced diuresis, but not natriuresis. The results in our previous study also showed this and suggest that prostaglandins consistently have a mediatory role in frusemide induced diuresis whatever the sodium balance of the individual.

The significant increment in renal plasma flow and glomerular filtration rate seen after frusemide in the present study is consistent with previous reports of renovascular responses to frusemide in man (Mackay *et al.*, 1984; Roberts *et al.*, 1985), although it is at variance with the lack of effect reported by Brater *et al.* (1985). In our previous study in salt replete volunteers there was a significant increment in glomerular filtration rate but not renal plasma flow (Passmore *et al.*, 1989). This could suggest that the renal haemodynamic responses to frusemide are dependent on the salt balance of the individual. This was found to be the case in the dog model (Nies *et al.*, 1983). Frusemide is associated with an increased urinary excretion of prostaglandins (Ciabattoni *et al.*, 1979; Mackay *et al.*, 1984; Patrono *et al.*, 1982; Roberts *et al.*, 1985; Scherer & Weber, 1979; Sedor *et al.*, 1984), suggesting an increased renal prostanoid synthesis, which has been purported to be the mediator of the renal haemodynamic changes. In support of this is the evidence that indomethacin has reduced the prostaglandin excretion after frusemide (Mackay *et al.*, 1984;

Roberts *et al.*, 1985) and also inhibited the increases in renal blood flow (Mackay *et al.*, 1984) and glomerular filtration rate (Mackay *et al.*, 1984; Roberts *et al.*, 1985) which follow frusemide although Roberts *et al.* (1985) found that indomethacin did not inhibit renal blood flow changes after frusemide. Neither glomerular filtration rate nor renal plasma flow following frusemide were affected by ibuprofen (Brater *et al.*, 1985). Only indomethacin significantly reduced the renal haemodynamic changes of frusemide in the present study, compared to both placebo and ibuprofen.

The early rise in renin activity, seen in the present study 10 min after frusemide, has been widely reported (Brater *et al.*, 1985; Frolich *et al.*, 1976; Johnston *et al.*, 1985, 1986; Mackay *et al.*, 1984; Passmore *et al.*, 1989; Riley *et al.*, 1985) and is not related to natriuresis but may coincide in some way with the increment in renal blood flow. While the nature of this response is not clear, most of the available evidence suggests that prostaglandins act as mediators, since the rise in renin activity following frusemide is consistently blocked by indomethacin (Frolich *et al.*, 1976; Mackay *et al.*, 1984; Passmore *et al.*, 1989) and ibuprofen (Brater *et al.*, 1985; Passmore *et al.*, 1989; Riley *et al.*, 1985). The effects seen in the present study, where plasma renin activity is consistently reduced, both in the basal and frusemide-stimulated state by both nonsteroidal agents, lend further support to this theory.

This study provides further evidence for the acute renal haemodynamic effects of frusemide in humans and suggests that such effects may be more apparent in salt deplete conditions. In this group of moderately salt restricted volunteers neither indomethacin nor ibuprofen adversely affected basal levels of renal haemodynamics or electrolyte excretion. Frusemide-induced diuresis and renin increase were inhibited by both agents, implying that these responses are principally mediated through prostaglandin-related mechanisms. The difference between indomethacin and ibuprofen in their effects upon frusemide-induced renovascular change is most likely due to the more potent nature of indomethacin as a prostaglandin synthesis inhibitor. This study provides no evidence of a dose-related effect of ibuprofen nor of an adverse effect on renal function before or after frusemide under the study conditions.

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