

A comparison of the effects of ibuprofen and indomethacin upon renal haemodynamics and electrolyte excretion in the presence and absence of frusemide

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1 This study has compared the effects of ibuprofen and indomethacin upon renal haemodynamics, electrolyte excretion and renin release in the presence and absence of frusemide under sodium replete conditions in eight healthy volunteers.

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

3 Frusemide had no effect on renal blood flow, but significantly increased glomerular filtration rate. This latter change was suppressed significantly only by ibuprofen 400 mg. Frusemide-induced diuresis was inhibited by all treatments, while natriuresis following frusemide was inhibited by indomethacin only.

4 Significant increments in plasma renin activity, which were suppressed by all treatments, were observed after frusemide. The degree of inhibition of the renin responses was significantly greater in the presence of indomethacin than with either dose of ibuprofen.

5 In a sodium replete setting in healthy volunteers, indomethacin and ibuprofen had no detrimental effects on basal renal function. In the presence of frusemide, indomethacin had more anti-natriuretic and renin-suppressing effect than ibuprofen. There was no evidence for a dose-related effect of ibuprofen.

Keywords ibuprofen indomethacin frusemide

Introduction

Prostaglandins are implicated in the control of renal haemodynamics, renin release and electrolyte excretion. Indomethacin is a prostaglandin synthetase inhibitor against which many nonsteroidal anti-inflammatory drugs are compared. Ibuprofen is a propionic acid derivative which is available without prescription as an 'over the counter' preparation. In a salt replete situation in humans, indomethacin has little effect on renal haemodynamics (Rumpf *et al.*, 1975; Donker *et al.*, 1976; Epstein *et al.*, 1979; Gullner *et al.*, 1980; Kramer *et al.*, 1985), but inhibits the acute

changes induced by intravenous frusemide (Williamson *et al.*, 1975; Mackay *et al.*, 1984). There is little information available on the renal haemodynamic effects of ibuprofen.

There is conflicting evidence on the effects of indomethacin on sodium excretion, with no change (Patak *et al.*, 1975; Mackay *et al.*, 1984), or sodium retention (Donker *et al.*, 1976; Brater, 1979) being found. In most cases, under salt replete circumstances, there is little change in sodium excretion. There is also some confusion over the effect of prostaglandin synthetase inhibition on frusemide induced nat-

riuresis and diuresis, with a blunting (Frolich *et al.*, 1975, 1976; Patak *et al.*, 1975; Mackay *et al.*, 1984) or no change (Williamson *et al.*, 1975; Bailie *et al.*, 1976; Weber *et al.*, 1977; Riley *et al.*, 1985) being reported. Data on the renal effects of ibuprofen are scarce. Riley *et al.* (1985) showed ibuprofen had no effect on frusemide induced natriuresis.

Prostaglandins have been reported to play an important role in renin secretion (Gerber *et al.*, 1981). Nonsteroidal anti-inflammatory drugs have usually been found to decrease plasma renin activity (PRA) in the basal state (Rumpf *et al.*, 1975; Donker *et al.*, 1976; Frolich *et al.*, 1976; Riley *et al.*, 1985) and after frusemide (Frolich *et al.*, 1975; Patak *et al.*, 1975; Rumpf *et al.*, 1975; Mackay *et al.*, 1984; Riley *et al.*, 1985). This has also been shown with ibuprofen (Riley *et al.*, 1985).

The aim of this study was to examine the effects of indomethacin and ibuprofen on renal haemodynamics, electrolyte excretion and renin release, and on frusemide induced changes in these variables under sodium replete conditions.

Methods

Eight healthy male volunteers aged 21–31 years gave full informed consent to 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—150 mmol Na/60 mmol K per 24 h. 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. These doses represent commonly prescribed treatment regimens for these drugs.

For the final 24 h of each treatment period subjects collected all urine for assessment of sodium and potassium excretion and creatinine clearance. 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 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 was drawn at the midpoint of each collection period for estimation of 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 10% sodium ethylenediamine tetra-acetate (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 7 and at 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 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 the shapes of these profiles. These profiles are essentially quadratic (upwards convex) and if any of the study medications blocked the action of frusemide, this would result in flattening of the corresponding response profile in comparison with that of placebo. These variables were also analysed for each of the three 20 min time intervals, using an analysis of variance and the Newman-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. 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 \pm s.e. mean, with significance accepted at the 5% level.

Results

Baseline values

The plasma concentrations of ibuprofen 400 mg, 800 mg and indomethacin were 16.1 ± 1.7

$\mu\text{g ml}^{-1}$, $34.1 \pm 3.8 \mu\text{g ml}^{-1}$ and $1.1 \pm 1.2 \mu\text{g ml}^{-1}$ respectively. Basal creatinine clearance was unaffected by either dose of ibuprofen or indomethacin (Table 1). The reductions in 24 h sodium excretion following indomethacin and both doses of ibuprofen were not significant (Table 1). Twenty-four hour urinary volume and potassium excretion were unchanged by any of the active treatments (Table 1). Following indomethacin basal plasma renin activity was significantly reduced in comparison with that following placebo administration ($0.7 \pm 0.3 \text{ ng AI ml}^{-1} \text{ h}^{-1}$ vs $1.7 \pm 0.3 \text{ ng AI ml}^{-1} \text{ h}^{-1}$, $P < 0.05$, Table 1). There were no significant differences in basal blood pressure between placebo ($123 \pm 2.8/81 \pm 2 \text{ mm Hg}$), ibuprofen 400 mg ($121 \pm 2.6/80 \pm 1.9 \text{ mm Hg}$), ibuprofen 800 mg ($125 \pm 2.4/85 \pm 2.2 \text{ mm Hg}$) or indomethacin ($125 \pm 2.5/85 \pm 2.3 \text{ mm Hg}$).

Water and electrolyte excretion

Frusemide elicited a significant increase in urine flow rate at all time periods in the presence of placebo ($P < 0.01$). Comparison of the profiles obtained for urine flow rate following frusemide showed that the profile was significantly lower with ibuprofen (400 mg and 800 mg, $P < 0.05$) and indomethacin ($P < 0.05$) than in the presence of placebo (Figure 1). There were no differences between the profiles obtained for each of the active treatments (Figure 1).

Sodium excretion rate was increased by frusemide in the presence of placebo at each time period ($P < 0.01$). A comparison of the profiles revealed that the sodium excretion rate following frusemide was significantly lowered by indomethacin ($P < 0.05$) when compared with placebo, ibuprofen 400 and 800 mg (Figure 2). The latter three profiles were not significantly different. The potassium excretion rate was significantly increased by frusemide at all three time periods ($P < 0.01$) when pre-

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 (IND) in eight healthy male volunteers. Values are expressed as mean \pm s.e. mean.

	PRA ($\text{ng AI ml}^{-1} \text{ h}^{-1}$)	Urinary volume (ml)	Urinary excretion ($\text{mmol } 24 \text{ h}^{-1}$)		Creatinine clearance (ml min^{-1})
			Sodium	Potassium	
P	1.7 ± 0.3	1420 ± 140	155 ± 15	45 ± 7	95 ± 6
400	1.0 ± 0.3	1520 ± 240	147 ± 13	46 ± 6	104 ± 5
800	1.2 ± 0.3	1660 ± 160	123 ± 8	58 ± 4	97 ± 6
IND	$0.7 \pm 0.3^*$	1210 ± 110	132 ± 12	51 ± 8	91 ± 10

* $P < 0.05$ compared with placebo

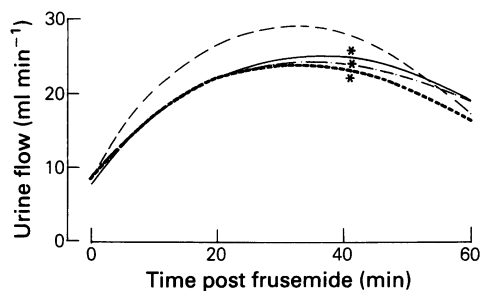


Figure 1 Urine flow rate profile (ml min^{-1}) following frusemide 20 mg i.v. in the presence of placebo (---), ibuprofen 400 mg (-.-), and 800 mg (—), and indomethacin 50 mg (---).
* $P < 0.05$ significant difference from placebo profile. Significance applies to the whole curve.

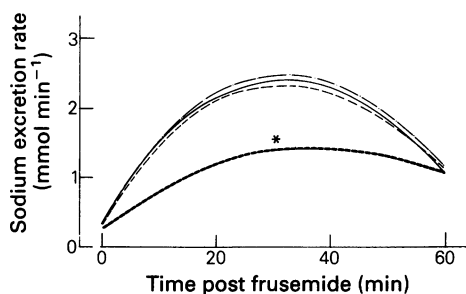


Figure 2 Sodium excretion rate profiles (mmol min^{-1}) following frusemide 20 mg i.v. in the presence of placebo (---), ibuprofen 400 mg (-.-), ibuprofen 800 mg (—) and indomethacin 50 mg (---).
* $P < 0.05$ significant difference from placebo profile and ibuprofen (400 mg and 800 mg) profile. Significance applies to the whole curve.

treated with placebo. The potassium excretion rate profile after frusemide was lower following indomethacin pretreatment ($P < 0.05$) than after ibuprofen (400 and 800 mg), while the profiles in the presence of placebo, ibuprofen 400 and ibuprofen 800 were not significantly different.

Plasma renin activity

Plasma renin activity responses are shown on Figure 3. Immediately before frusemide, plasma renin activity was significantly reduced in the presence of ibuprofen 400 mg ($P < 0.01$), ibuprofen 800 mg ($P < 0.05$) and indomethacin ($P < 0.01$). Ibuprofen 400 mg reduced plasma renin activity significantly compared with ibuprofen 800 mg ($P < 0.05$), but was not different from indomethacin whereas indomethacin suppressed plasma renin activity significantly compared with ibuprofen 800 mg ($P < 0.05$).

With placebo pretreatment there was a sig-

nificant increase ($P < 0.01$) in plasma renin activity at 10, 30 and 50 min following frusemide. This response was significantly attenuated at 10 min by ibuprofen 400 mg ($P < 0.01$), ibuprofen 800 mg ($P < 0.01$) and indomethacin ($P < 0.01$). Plasma renin activity values for both doses of ibuprofen were not different at this time, but indomethacin had a significantly greater depressant effect than either dose of ibuprofen ($P < 0.01$). At 30 min post-frusemide plasma renin activity was significantly suppressed compared with placebo pretreatment by ibuprofen 400 mg ($P < 0.05$) and indomethacin ($P < 0.01$). Comparison between nonsteroidal treatments at 30 min showed that values for ibuprofen 400 mg were not different from ibuprofen 800 mg nor indomethacin but that indomethacin reduced PRA significantly more than ibuprofen 800 mg ($P < 0.05$). At 50 min after frusemide plasma renin activity was significantly depressed compared with placebo by ibuprofen 400 mg ($P < 0.01$); ibuprofen 800 mg ($P < 0.01$) and indomethacin ($P < 0.01$). Values for ibuprofen 400 mg and 800 mg were not significantly different, but both were significantly higher than indomethacin ($P < 0.01$, Figure 3).

Renal haemodynamics

PAH clearance values are shown on Figure 4. Baseline levels in the hour before frusemide were unaffected by nonsteroidal treatment. In the presence of placebo, although the clearance value in the first time period was increased from the baseline value by frusemide ($\Delta = 151 \pm 38 \text{ ml min}^{-1}$), this was not statistically significant. There were no significant differences between treatments when the frusemide response profiles were analysed.

Baseline inulin clearances were unaffected by any of the active treatments compared with placebo (Figure 5). Following placebo mean inulin clearance was significantly increased at the first time period (0–20 min) after frusemide ($\Delta = 33 \pm 10 \text{ ml min}^{-1}$, $P < 0.05$). Clearance values returned to normal over the next 40 min. When the profiles for inulin clearance were compared with placebo, the attenuation produced by ibuprofen 800 mg and indomethacin ($0.05 < P < 0.10$) just failed to achieve significance while the suppression produced by ibuprofen 400 was statistically significant ($P < 0.05$).

Discussion

Nonsteroidal anti-inflammatory drugs do not usually affect renal haemodynamics (Rumpf *et*

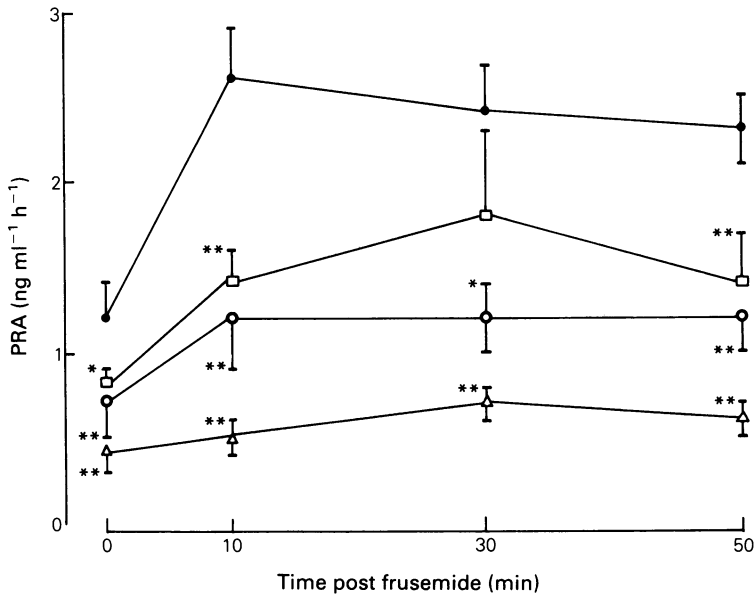


Figure 3 Plasma renin activity (PRA ngA1 ml⁻¹ h⁻¹) before and after frusemide 20 mg i.v. (mean \pm s.e. mean, $n=8$) in the presence of placebo (●), ibuprofen 400 mg (○), ibuprofen 800 mg (◻) and indomethacin (△). * $P < 0.05$, ** $P < 0.01$ significant difference from placebo pretreated group.

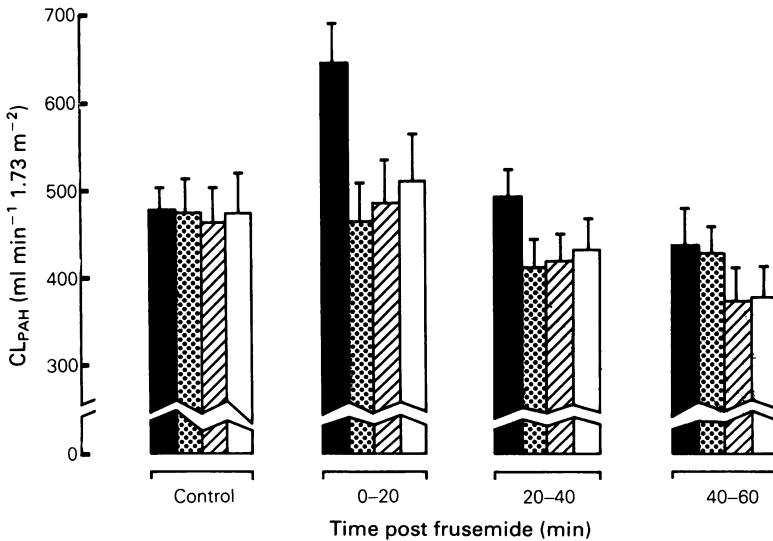


Figure 4 *p*-aminohippurate clearances (CL_{PAH}) before and after frusemide 20 mg i.v. in the presence of placebo (■), ibuprofen 400 mg (◻) and 800 mg (◻), and indomethacin 50 mg (□). Results are shown as mean \pm s.e. mean, $n=8$.

al., 1975; Donker *et al.*, 1976; Gullner *et al.*, 1980; Clive & Stoff, 1984; Di Bona, 1986) or electrolyte excretion (Rumpf *et al.*, 1975; Kramer, 1978; Gullner *et al.*, 1980) under salt replete conditions. These drugs are presumed

to act chiefly through inhibition of prostaglandin systems. Renal prostaglandins are important in the control of renal haemodynamics and electrolyte excretion but in the setting of normal renal function these variables

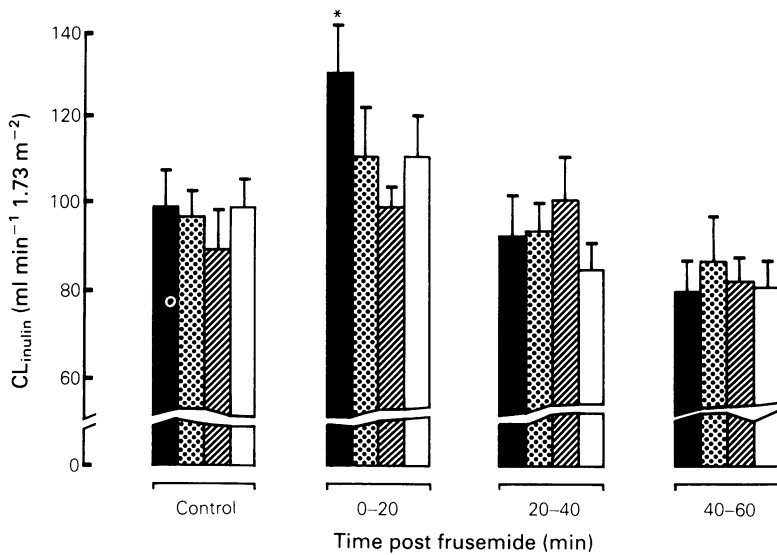


Figure 5 Inulin clearances (CL_{inulin}) before and after frusemide (20 mg i.v.) in the presence of placebo (■), ibuprofen 400 mg (▨) and 800 mg (▩), and indomethacin 50 mg (□). Results are mean \pm s.e. mean, $n=8$.

* $P < 0.05$ significant difference from baseline.

are not completely dependent on an intact renal prostaglandin system (Clive & Stoff, 1984), and therefore interruption of renal prostaglandins may be expected to produce little effect. In our study, the subjects had normal renal function and the kidneys were in an unstressed situation because sodium balance was normal. Therefore, treatment with prostaglandin inhibitors would not be expected to have a significant effect. In the present study pre-frusemide electrolyte excretion, creatinine clearance and renal haemodynamics were unchanged following treatment with either nonsteroidal agent, and are thus in support of the above theory. The lack of effect of the prostaglandin inhibitors on basal renal haemodynamics would also be consistent with an unchanged basal electrolyte excretion.

Frusemide, as expected, enhanced water and electrolyte excretion acutely in the presence of placebo. Under salt replete conditions indomethacin has been reported to inhibit (Frolich *et al.*, 1976; Mackay *et al.*, 1984) or have no effect (Williamson *et al.*, 1975; Bailie *et al.*, 1976; Weber *et al.*, 1977) on frusemide induced natriuresis and diuresis. Ibuprofen had no effect on frusemide induced natriuresis (Riley *et al.*, 1985). Therefore the evidence for prostaglandin mediation in the water and electrolyte excretion following frusemide is conflicting. In the present study, both doses of ibuprofen and indomethacin reduced water excretion follow-

ing frusemide. This finding supports a role for prostaglandins in frusemide induced water excretion. Only indomethacin inhibited frusemide induced natriuresis, suggesting that either this is due to a non-prostaglandin effect (Koopmans, 1985) or that it merely reflects that indomethacin is a more potent inhibitor of prostaglandin systems than ibuprofen. Nonsteroidal anti-inflammatory drugs tend to produce potassium retention (Clive & Stoff, 1984) which is more likely if renal function is impaired. Any lack of effect of these agents on potassium in the present study reflects the normal renal function of the volunteers and is not unexpected.

Although frusemide generally increases renal blood flow in animals, there is less evidence for the acute renovascular effects in man. Mackay *et al.* (1984) found an acute increase in renal blood flow and glomerular filtration rate after frusemide, changes which were accompanied by increased prostaglandin excretion, and were blocked by indomethacin. Frusemide is associated with increased urinary secretion of prostaglandins (Ciabattini *et al.*, 1979; Scherer & Weber, 1979; Patrono *et al.*, 1982), suggesting an increase in renal prostanoid synthesis, which in turn has been proposed as a mediator of renal haemodynamic changes (Mackay *et al.*, 1984). In the present study, while the increment in renal blood flow after frusemide was not significant, frusemide did result in an increase in glomerular filtration rate consistent with that

reported by Mackay *et al.* (1984). The non-steroidal agents had no effect on renal blood flow, while only ibuprofen 400 mg was seen to impair the glomerular filtration change after frusemide. This suggests that prostanoid inhibition in a salt replete setting has little adverse effect on frusemide induced changes in renal haemodynamics.

An early increase in renin activity, which was evident from 10 min after frusemide, has been seen in many studies (Frolich *et al.*, 1976; Mackay *et al.*, 1984; Johnston *et al.*, 1985, 1986; Riley *et al.*, 1985) and is unrelated to natriuresis. The exact nature of this response remains unclear, but a weight of evidence suggests that prostaglandins are involved, since the increase in renin activity following frusemide is consistently blocked by the prostaglandin inhibitors indomethacin (Frolich *et al.*, 1976; Weber *et al.*, 1977; Mackay *et al.*, 1984) and ibuprofen (Riley *et al.*, 1985). Our results show that renin activity is consistently inhibited, both in the basal state and when stimulated by frusemide, by both nonsteroidal agents. This is consistent with other studies, and lends further

weight to the suggestion that prostaglandins are important mediators of renin release.

In a situation where the kidneys are unstressed, there is little evidence for a deleterious effect of nonsteroidal agents on basal renal function. The consistent reduction of frusemide induced diuresis and renin increase by both indomethacin and ibuprofen would suggest that these changes are mainly mediated through a prostaglandin related mechanism and that even in a salt replete setting prostaglandin inhibition can have adverse effects on these variables. Conversely renal haemodynamic changes following frusemide in sodium replete individuals are largely unaffected by prostaglandin inhibitors. The possibility of a Type II error cannot be completely dismissed in a study involving eight volunteers.

Under the present experimental conditions, indomethacin has more anti-natriuretic effect than ibuprofen, but apart from this and its greater suppression of renin activity, there is little difference between the two drugs. There is no evidence for a dose related effect of ibuprofen.

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