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The effects of naproxen and sulindac on renal function and their interaction with hydrochlorothiazide and piretanide in man

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1 We have studied the effect of a single dose challenge of naproxen (500 mg) and sulindac (200 mg) on renal function in five volunteers, and the effect of a single dose challenge of the thiazide, hydrochlorothiazide (100 mg), and loop diuretic, piretanide (6 mg) on renal function when the diuretics were given alone or when superimposed on chronic therapy of either naproxen or sulindac.
2 None of the nonsteroidal anti-inflammatory drug (NSAID) or diuretic exposures significantly influenced glomerular filtration rate, as measured by creatinine clearance.
3 Over the first 4 h of the study, both naproxen and sulindac reduced fractional excretion of sodium by approximately 50%. Sulindac also caused a significant uricosuria whilst naproxen promoted urate retention. Similar changes were observed over 8 h.
4 Superimposition of either hydrochlorothiazide or piretanide on top of chronic sulindac therapy resulted in a blunting of the natriuresis by approximately 30% compared to when these diuretics were given alone: the action of the diuretics was unchanged by naproxen.
5 Sulindac pretreatment did not alter the urinary excretion of either hydrochlorothiazide or piretanide; naproxen did not alter hydrochlorothiazide excretion.
6 On the basis of these findings, it is concluded that NSAIDs exert direct tubular effects that do not necessarily interfere with the delivery of diuretics to their sites of action within the nephron.

Keywords naproxen sulindac hydrochlorothiazide piretanide antinatriuresis uricosuria

Introduction

Salt and water retention is a well recognised unwanted effect of NSAID therapy (Carmichael & Shankel, 1985; Zipser & Henrich, 1986). NSAIDs, in turn, interfere with the action of diuretic drugs (Brater, 1986). Both these effects are of clinical importance, yet their mechanisms remain unclear. The present study was planned with two main objectives in mind. First, the renal action of two different NSAIDs have been investigated: sulindac (SUL) was chosen as an example of an agent which has been postulated to 'spare' the kidney (Ciabattoni *et al.*, 1980). It is an arylacetate derivative which undergoes extensive hepatic metabolism (Duggen *et al.*, 1977). SUL's action has been compared with naproxen (NAP), a propionate derivative excreted largely in the unchanged form in the urine (Thomson & Collins, 1973). Second, the effect of pretreatment with either of these drugs on the renal response to two different diuretics has

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been investigated. Hydrochlorothiazide (HCTZ) was selected as a well characterised thiazide compound, whilst piretanide (PIR), a sulphamoyl-benzoate derivative, was chosen both as a representative of loop diuretics, and as a drug that has been extensively studied in our laboratory (McNabb *et al.*, 1984). By employing diuretics with clearly defined loci of action within the nephron and by studying the ways in which their action is modified by two different types of NSAID, our aim was to throw light on the possible mechanisms whereby NSAIDs influence renal function and also interact with diuretics.

Subjects

Five male students, aged between 22 and 24 years old and weighing between 50 and 75 kg, volunteered to participate in the study. The protocol was approved by the Westminster Hospital Ethics Committee and all the subjects gave informed consent. Prior to the study the subjects underwent a complete physical examination which included blood analyses for routine haematology and biochemistry and also electrocardiography. All subjects completed each of the components of the study.

Diet

All subjects were counselled as to their normal dietary routine with view to ascertaining the approximate daily sodium and potassium intake. Once this was defined, subjects ate an individually tailored diet designed to maintain as stable sodium and potassium intake as possible throughout the study. The diet was supervised by our research dietitian. Caffeine, alcohol and cigarettes were not permitted.

Study protocol (Figure 1)

The study was divided into two major parts. In part I, the effects on renal function of acute challenges of NSAIDs and diuretics, when taken alone, were studied, and the subjects were exposed to each drug on two occasions. In part II, combination therapy was studied by superimposing a diuretic challenge on each subject who had been pretreated with either NAP or SUL. This meant that there were four possible combinations: NAP + HCTZ, SUL + HCTZ, NAP + PIR and SUL + PIR. The session designs and dosage schedules are illustrated in Figure 1. Each session was separated by at least 7 days and all drugs were given orally. Out of each 10 day session, fractional urine collections were carried out on 4 days, and on these study days, urine was collected over the periods: 0–4 h, 4–8 h, 8–24 h (fractional collection periods, Figure 1). On other days, urine was collected over 24 h. Drug dosing was undertaken at 09.00 h following a light breakfast 1 h before. A standard lunch was taken at 13.00 h following completion of the 0–4 h urine collection. Blood samples were collected at the beginning and end of each urine collection to enable clearance data to be calculated. Fluids were not restricted.

Analytical methods

Plasma electrolytes, creatinine and uric acid were measured by standard automated procedures

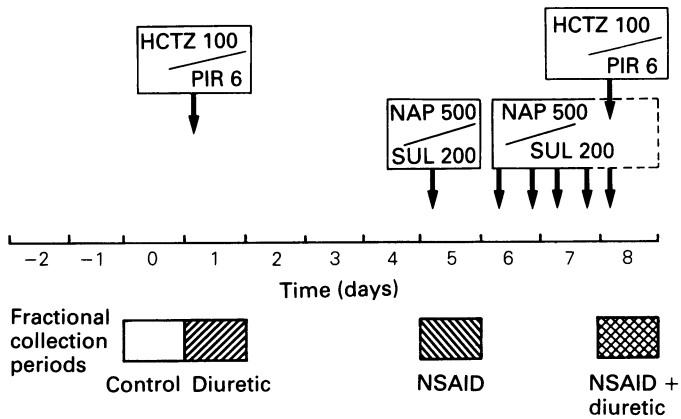

Figure 1 The study design and dosage schedule. The order of administration of diuretic or NSAID on its own was randomised, but once this was decided, each subject followed the sequence outlined. Fractional collection periods indicate urine collections over 0–4 h, 4–8 h and 8–24 h. HCTZ 100 = hydrochlorothiazide 100 mg, PIR 6 = piretanide 6 mg, NAP 500 = naproxen 500 mg, SUL 200 = sulindac 200 mg.

(Technicon). Urinary electrolytes were measured by atomic absorption spectroscopy (Perkin Elmer spectrophotometer model 603); chloride by a titratometric method (Buchler-Cotlove chloridometer); and urate by a uricase method (Boehringer 'Urica-quant'); urinary inorganic phosphate by a colorimetric method (Fiske & Subbarow, 1925); and creatinine by the alkaline picrate method (Bonsnes & Taussky, 1945).

HCTZ and PIR were analysed using two different h.p.l.c. methods: HCTZ by a method described previously (Koopmans *et al.*, 1984) and PIR by a spectroflurometric method developed in our laboratory. For the PIR assay, 500 ng of internal standard, bumetanide, was added to 1 ml of the urine sample, which was then mixed thoroughly and spun down to remove particulate matter. 10 μl of the resultant supernatant was then injected onto a 10 cm 3 μ Spherisorb ODS column. The mobile phase was prepared using a phosphate buffer (pH7), methanol and 2-propranol in the following proportions 55:45:1; flow rate was 1 ml min^{-1}. PIR and internal standard peaks were detected at 4.5 and 6.5 min respectively. Excitation wavelength was 220 nm and emission cut-off at 418 nm. The intra- and interassay coefficients of variation were 4 and 10% respectively.

Statistics

The data in this study are expressed both as mean ± s.e. mean or as means with their 95% confidence intervals (CI). Statistics were performed using a one way analysis of variance and where appropriate, changes were tested further for significance by using Student's two-tailed paired *t*-test.

Clearance values

Clearance values (CL_x) were calculated according to the formula: $CL_x = U_x \cdot V/P_x$ where U_x = urinary concentration of x (mmol l^{-1}), V = urine flow rate (ml min^{-1}), and P_x = plasma concentration of x (mmol l^{-1}). Fractional clearance values, E_x, were calculated by dividing CL_x by the simultaneous creatinine clearance (CL_{Cr}): $E_x = CL_x/CL_{Cr} \times 100\%$.

Control clearances are the mean of values obtained in each subject on four separate drug-free days. The responses to each of the drugs given alone are derived from the means of two exposures, whilst the drugs were given in combination to each subject on one occasion.

Results

CL_{Cr} was not altered by any drug or combination of drugs throughout this study.

Renal responses to single dose drug challenges

A. NSAID responses (a) NAP alone (Figure 2, Table 1) In comparison to control, treatment with NAP did not alter fractional urinary flow rate (E_V;%) over 0–8 h (Table 1) or 24 h. Fractional sodium clearance (E_{Na};%) was reduced within 4 h and 8 h of administration of NAP by a mean of 54% (95% CI: 27–80%) (Table 1 and Figure 2) and this fall was sustained so that over 0–24 h, E_{Na} still remained at only two thirds of control ($P < 0.05$, $n = 5$). The changes in fractional chloride clearance (E_{Cl};%) closely matched those of E_{Na}. NAP also reduced fractional potassium clearance (E_K;%) within the first 4 h by approximately one quarter (Figure 2) but this was not maintained for the remainder of the 24 h. Fractional urate clearance (E_{Urate};%) fell at 0–4 h with NAP treatment (7.85 ± 0.59 *vs* 4.51 ± 0.58, $P < 0.01$) with this reduction being maintained over 8 h; over 24 h however E_{Urate} was unchanged. Fractional phosphate clearance (E_{PO_4};%) was not influenced by NAP over 8 h (Table 1) or 24 h. NAP alone did not significantly alter any of the plasma parameters measured over the 24 h after administration.

(b) SUL alone (Figure 2, Table 1) In the presence of SUL, E_V was reduced from 0.82 ± 0.15 (mean ± s.e. mean) to 0.61 ± 0.16 ($P < 0.05$, $n = 5$) at 0–4 h in comparison to control (Figure 2), with E_V unchanged over 24 h. E_{Na} was reduced by a mean of 47% (95% CI: 26–80%) over 4 h and by 37% (95% CI: 16–58%) over 8 h by SUL (Table 1 and Figure 2) but, unlike NAP, this reduction was not sustained over 24 h. As before, E_{Cl} values closely matched those of E_{Na}. SUL did not influence E_K but, in contrast to NAP, SUL increased E_{Urate} from 7.85 ± 0.59 (mean ± s.e. mean) to 10.50 ± 1.23 ($P < 0.05$) at 0–4 h; the increase in E_{Urate} was still observed over 24 h (7.11 ± 0.62 *vs* 7.81 ± 0.69, $P < 0.05$). SUL did not cause significant changes in E_{PO_4} (Table 1) and, as with NAP before, did not alter any of the plasma parameters measured.

When the absolute 0–8 h responses to the two NSAIDs were compared, it was noted that, in the doses studied, NAP decreased sodium chloride excretion to a greater extent than did SUL. On the other hand, the amount of uric acid excretion with SUL was significantly greater than NAP (Table 1).

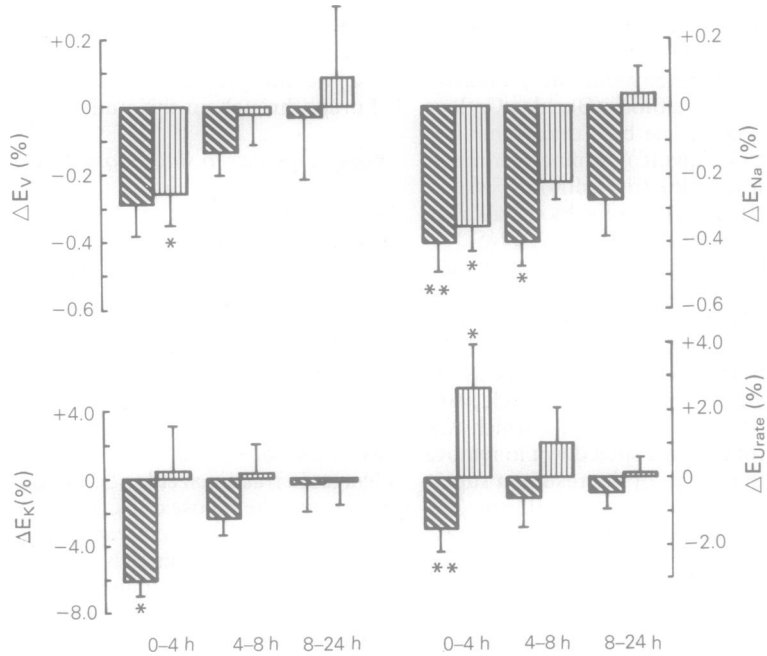

Figure 2 Effect of single dose challenge of naproxen 500 mg (▨) and sulindac 200 mg (▥) on the changes from control of E_V, E_{Na}, E_K and E_{Urate} in five subjects (E_V = fractional urinary flow rate (%), E_{Na} = fractional sodium clearance (%), E_K = fractional potassium clearance (%), and E_{Urate} = fractional urate clearance (%). * = $P < 0.05$, ** = $P < 0.01$).

Table 1 Effect of single dose challenge of naproxen (500 mg) and sulindac (200 mg) *vs* control on CL_{Cr}, E_V, E_{Na}, E_{Cl}, E_K, E_{Urate} plus E_{PO_4} over 0–8 h in five subjects (95% confidence intervals given in brackets).

	Control	*0–8 h Naproxen*	*Sulindac*
CL_{Cr} (ml min^{-1})	102.96 ± 6.96 (85.60 – 120.31)	102.84 ± 8.09 (80.36 – 125.32)	106.79 ± 6.83 (87.81 – 125.77)
E_V (%)	0.79 ± 0.09 (0.54 – 1.03)	0.61 ± 0.11 (0.30 – 0.92)	0.65 ± 0.08 (0.41 – 0.88)
E_{Na} (%)	0.75 ± 0.04) (0.63 – 0.87)	0.35 ± 0.07** (0.15 – 0.55)	0.46 ± 0.05* (0.32 – 0.60)
E_{Cl} (%)	1.27 ± 0.10 (0.99 – 1.55)	0.51 ± 0.09** (0.27 – 0.76)	0.88 ± 0.06*‡ (0.70 – 1.05)
E_K (%)	19.62 ± 1.22 (16.24 – 23.00)	15.18 ± 0.87* (12.76 – 17.60)	19.82 ± 2.06 (14.14 – 25.60)
E_{Urate} (%)	7.51 ± 0.56 (5.95 – 9.08)	6.54 ± 0.73* (4.51 – 8.76)	9.41 ± 1.10*† (6.34 – 12.48)
E_{PO_4} (%)	7.89 ± 1.23 (4.47 – 11.31)	7.61 ± 1.64 (3.05 – 12.13)	6.99 ± 0.76 (4.88 – 9.10)

CL_{Cr} = creatinine clearance (ml min^{-1}), E_V = fractional urinary flow rate (%), E_{Na} = fractional sodium clearance (%), E_{Cl} = fractional chloride clearance (%), E_K = fractional potassium clearance (%), E_{Urate} = fractional urate clearance (%), E_{PO_4} = fractional phosphate clearance (%). * = $P < 0.05$, ** $P < 0.01$ refer to comparison with control; † = $P < 0.05$, ‡ = $P < 0.01$ refer to NAP *vs* SUL.

B. Diuretic responses (a) HCTZ alone (Figure 3) HCTZ increased E_V throughout the 24 h period when compared to control; the maximum increase of almost threefold occurred at 4–8 h. Similarly there was a threefold rise in E_{Na} over the first 8 h with HCTZ and a significant natriuresis persisted over 24 h (0.76 ± 0.04 *vs* 1.52 ± 0.08, $P < 0.01$). The rise in E_{Cl} followed a similar pattern to that of E_{Na}. HCTZ was also significantly kaliuretic over 24 h with the maximum urinary potassium loss within the first 4 h (20.70 ± 2.12 *vs* 28.66 ± 3.89, $P < 0.05$) (Figure 3). E_{Urate} remained unchanged between 0–8 h, but was significantly reduced thereafter [(8–24 h: 6.91 ± 0.73 *vs* 4.84 ± 0.51, $P < 0.05$); (0–24 h: 7.11 ± 0.62 *vs* 5.63 ± 0.48, $P < 0.05$)]. HCTZ did not alter any of the plasma parameters measured.

(b) PIR alone (Figure 3) The diuretic response to PIR was completed within 4 h with a rise in E_V from 0.82 ± 0.15 (mean ± s.e. mean) to 4.82 ± 0.35 ($P < 0.01$, $n = 5$) (Figure 3): over 24 h the cumulative total diuresis induced by PIR was similar to that of HCTZ. At 0–4 h, PIR caused a sixfold rise in E_{Na} which was followed over the 4–8 and 8–24 h periods by a significant antinatriuresis (Figure 3) so that over 0–24 h E_{Na} was not significantly different from control. E_{Cl} once again matched the changes in E_{Na}. Despite a significant kaliuresis during 0–4 h (20.70 ± 2.12 *vs* 29.77 ± 1.06, $P < 0.05$), and 0–8 h (19.62 ± 1.22 *vs* 23.92 ± 0.96), PIR caused no significant change in potassium clearance over 0–24 h. PIR reduced E_{Urate} consistently throughout the 24 h period (Figure 3) with the maximum reduction at 0–4 h (7.85 ± 0.59 *vs* 5.44 ± 0.82, $P < 0.05$).

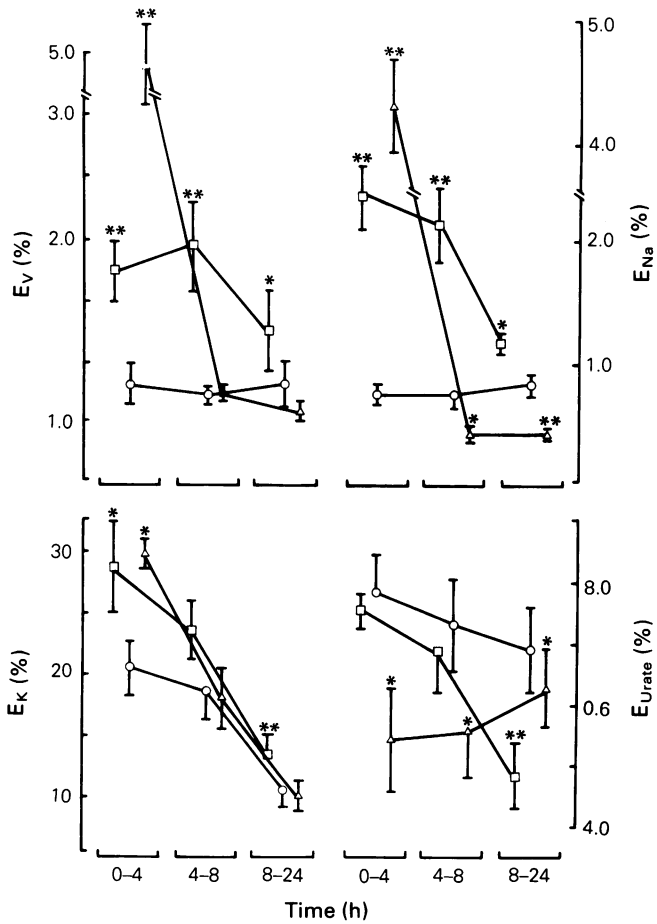

Figure 3 Effect of hydrochlorothiazide 100 mg (□——□) and piretanide 6 mg (△——△) versus control (○——○) on E_V, E_{Na}, E_K and E_{Urate} in five subjects (E_V = fractional urinary flow rate (%), E_{Na} = fractional sodium clearance (%), E_K = fractional potassium clearance (%), and E_{Urate} = fractional urate clearance (%). * = $P < 0.05$, ** = $P < 0.01$).

Plasma measurements taken through the first 24 h after PIR were unchanged; a trend towards increased plasma urate did not attain significance.

Renal responses after diuretic challenge in the presence of NSAID

In these combination studies, all parameters measured with the drugs alone were followed again. No significant changes were noted in CL_{Cr}. There was a significant reduction in the HCTZ-induced kaliuresis over 0–8 h by NAP, (26.10 ± 2.90 *vs* 21.07 ± 2.77, $P < 0.05$). Plasma measurements did not alter significantly with the single exception of those of urate where a consistent reduction was observed in the case of SUL pretreatment irrespective of challenge with either HCTZ or PIR (Figure 4).

The renal excretions of HCTZ and PIR over 24 h are given in Table 2. These measurements relate to studies where the diuretics were given both alone and in the presence of either NAP or SUL. The values for the PIR challenge in the presence of NAP are not reported as NAP was found to interfere with the analytical method for PIR. Pretreatment with either NAP or SUL did not significantly influence the absolute excretion of the HCTZ over this period. The excretion of PIR in the presence of SUL was reduced from (mean ± s.e. mean, $n = 5$) 1.81 ± 0.21 mg to 1.64 ± 0.21 mg over 0–4 h, but this difference was not statistically significant.

(a) HCTZ challenge with NAP pretreatment (Table 3) Overall, the renal effects of HCTZ were little influenced by pretreatment with NAP. E_V was unchanged as were HCTZ-induced rises in E_{Na} (Table 3) and E_{Cl}. With respect to E_{Urate}, the only significant change noted was a reduction in urate clearance over 0–4 h (7.55 ± 0.29 *vs* 6.02 ± 0.45, $P < 0.05$ (Table 3). Plasma urate was not altered by this combination.

Table 2 Effect of chronic naproxen (NAP) and sulindac (SUL) treatment on the urinary excretion (mg/period) of diuretic following acute challenge with hydrochlorothiazide (HCTZ; 100 mg) and piretanide (PIR; 6 mg) compared to when the diuretics were given alone. The values for piretanide challenge in the presence of naproxen are not given as naproxen was found to interfere with the analytical method for piretanide.

	Drug excretion (mg/period) Time interval (h)		
	0–4	*4–8*	*8–24*
HCTZ	24.93 ± 5.45	15.59 ± 2.55	8.70 ± 1.40
NAP + HCTZ	24.90 ± 6.30	13.00 ± 1.50	13.50 ± 1.00
SUL + HCTZ	22.80 ± 5.40	18.50 ± 2.10	9.40 ± 2.20
PIR	1.81 ± 0.21	0.29 ± 0.05	0.03 ± 0.02
SUL + PIR	1.64 ± 0.21	0.30 ± 0.06	0.01 ± 0.01

(b) HCTZ challenge with SUL pretreatment (Figures 4 and 5) At 0–4 h, SUL reduced the HCTZ-evoked rise of E_V (from 1.75 ± 0.26 (mean ± s.e. mean) to 1.13 ± 0.20: $P < 0.01$, $n = 5$) and of E_{Na} (2.34 ± 0.26 *vs* 1.65 ± 0.31, $P < 0.05$ (Figure 5). Beyond 4 h, SUL pretreatment did not affect these HCTZ responses. With respect to E_{Urate}, combined treatment resulted in an increased urate clearance when compared to HCTZ alone at 0–4 h (7.55 ± 0.29 *vs* 9.92 ± 0.85,

Table 3 Effect of superimposition of hydrochlorothiazide (HCTZ) and piretanide (PIR) on top of chronic naproxen (NAP) therapy on E_{Na} and E_{Urate} compared to when the diuretics were given alone.

	HCTZ vs *(NAP + HCTZ)*				*PIR* vs *(NAP + PIR)*			
	E_{Na} (%)		E_{Urate} (%)		E_{Na} (%)		E_{Urate} (%)	
0–4 h	2.34 ± 0.26	*vs* 1.87 ± 0.12	7.55 ± 0.29	*vs* 6.02* ± 0.45	4.32 ± 0.37	*vs* 4.21 ± 0.10	5.44 ± 0.82	*vs* 4.51 ± 0.58
4–8 h	2.09 ± 0.20	*vs* 1.83 ± 0.28	6.89 ± 0.67	*vs* 6.57 ± 0.79	0.44 ± 0.06	*vs* 0.81 ± 0.21	5.59 ± 0.70	*vs* 6.15 ± 0.78
8–24 h	1.17 ± 0.07	*vs* 1.36 ± 0.15	4.84 ± 0.51	*vs* 5.92 ± 0.34	0.44 ± 0.04	*vs* 0.69* ± 0.08	6.28 ± 0.70	*vs* 7.55 ± 0.56

E_{Na} = fractional clearance of sodium (%), E_{Urate} = fractional clearance of urate (%). * = $P < 0.05$.

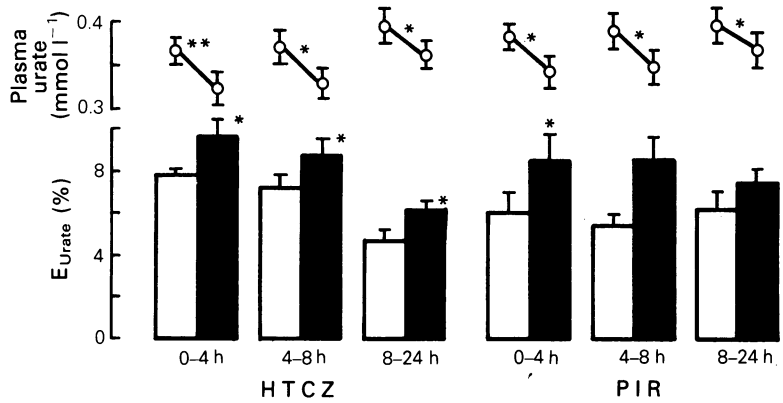

Figure 4 Effect of superimposition of hydrochlorothiazide (HCTZ) and piretanide (PIR) on top of chronic sulindac therapy (■) on plasma urate (mmol l^{-1}) and E_{Urate} compared to when the diuretics were given alone (□). (E_{Urate} = fractional clearance of urate (%). * = $P < 0.05$, ** = $P < 0.01$).

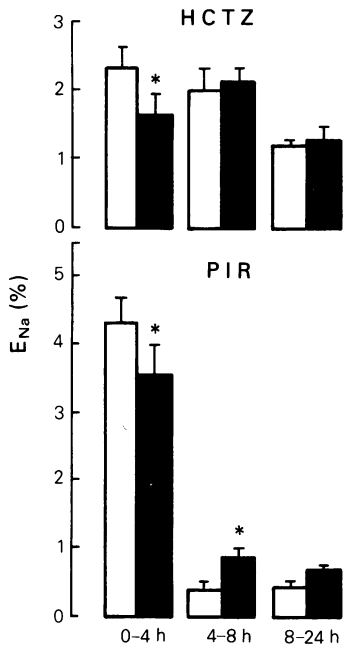

Figure 5 Effect of superimposition of hydrochlorothiazide (HCTZ) and piretanide (PIR) on top of chronic sulindac therapy (■) on E_{Na} compared to when the diuretics were given alone (□). (E_{Na} = fractional clearance of sodium (%) * = $P < 0.05$).

$P < 0.05$) (Figure 4): the rise in E_{Urate} persisted over 0–8 and 0–24 h, and was accompanied by significant falls in plasma urate (Figure 4).

(c) PIR challenge with NAP pretreatment (Table 3) The only renal responses to PIR that were significantly influenced by NAP were: E_K (0–4 h), which was reduced from 29.77 ± 1.06 to 25.57 ± 1.61 ($P < 0.05$); E_{Na} (8–24 h) which was increased from 0.44 ± 0.04 to 0.69 ± 0.08 ($P < 0.05$; Table 3); E_{Cl} (8–24 h) which was increased from 0.37 ± 0.05 to 0.68 ± 0.10 ($P < 0.05$). No other changes were observed in the remaining urinary or plasma parameters measured.

(d) PIR challenge with SUL pretreatment (Figures 4 and 5) The PIR-induced rise in E_V was reduced significantly by SUL (from 4.82 ± 0.35 (mean ± s.e. mean) to 4.10 ± 0.38: $P < 0.05$, $n = 5$). Similarly, SUL attenuated the natriuretic response to PIR at 0–4 h (4.32 ± 0.37 *vs* 3.60 ± 0.45, $P < 0.05$) and caused an increased natriuresis between 4–8 h (0.44 ± 0.06 *vs* 0.85 ± 0.15, $P < 0.05$) (Figure 5). The PIR-induced rise in E_{Cl} was also reduced by SUL over 0–4 h (7.15 ± 0.61 *vs* 6.09 ± 1.03, $P < 0.05$). Combined treatment of PIR and SUL resulted in increased urate clearance throughout the 24 h period with the rise in E_{Urate} reaching significance at 0–4 h and 0–8 h and over 0–24 h (6.02 ± 0.67 *vs* 8.02 ± 0.59, $P < 0.05$) (Figure 4). Likewise, the increased urinary urate loss was accompanied by significant falls in plasma urate (Figure 4).

Discussion

In our study, both NAP and SUL reduced sodium excretion and urinary flow in volunteers in the first 8 h after administration with no change in CL_{Cr}; with NAP, this reduction in sodium excretion was maintained for the entire 24 h. The sodium retaining ability of NSAIDs has been variously attributed to either a direct action on the renal tubule (Haylor & Lote, 1980; Kaojarern *et al.*, 1983; Mitnick *et al.*, 1980) or secondary

to changes in intrarenal haemodynamics (Kirschenbaum *et al.*, 1974; Lonigro *et al.*, 1973). Our results do not support the claim (Ciabattoni *et al.*, 1980) that SUL is a 'renal sparing' agent, which is based on the observation that SUL does not inhibit intrarenal prostaglandin (PG) production. This characteristic of SUL is not a consistent finding since, in some studies, clear evidence of PG reduction by SUL has been noted both in health (Brater *et al.*, 1985; Roberts *et al.*, 1984; Swainson & Griffiths, 1985) and disease (Berg & Talseth, 1985; Svendsen *et al.*, 1984; Swainson *et al.*, 1986). The relationship between NSAID-induced reduction in salt and water excretion and intrarenal PG inhibition remains unclear. Our findings of a distinct increase in sodium and water reabsorption as well as uricosuria after SUL, indicates a definite renotropic action of the drug. The fact that all clearances were related to simultaneous GFR, as measured by CL_{Cr}, suggests that the observed effects within the kidney relate to actions of SUL at a tubular level. On the other hand, NAP had a more sustained effect on sodium and water reabsorption and, at the same time, reduced urate excretion. It is difficult to relate these contrasting phenomena to what is known about NSAID action and cyclo-oxygenase inhibition. If, as seems likely, we are dealing with a direct drug effect on renal tubular handling of water and selected ions, then the question arises as to which portions of the nephron are being affected. We have shown (Dixey *et al.*, in preparation) that the NSAIDs, indomethacin and piroxicam, are phosphaturic, which implies an effect of the known proximal handling of this ion (Mizgala & Quamme, 1985). Neither SUL nor NAP influenced phosphate excretion, yet each had distinct but opposing effects on the excretion of urate, an ion also known to be transported in the proximal tubule (Weiner, 1979). Our present study thus identifies subtle differences between the renal action of NSAID agents, but does not permit further clarification of how these various tubular responses are realised at a cellular level. The findings imply a heterogeneity of renal response which may have little, if anything, to do with the ability of NSAID agents to block PG production within specific segments of the nephron (Schlondorff & Ardaillou, 1986).

The importance of the interaction between NSAIDs and diuretics arises through the common clinical need to treat iatrogenic salt and water retention generated by the use of NSAIDs. The way in which NSAIDs block diuretic action is not fully understood. One possible mechanism is interference with tubular access of the diuretic to its site of action. Both thiazide and loop diuretics act from within the lumen. The former localises to the cortical diluting site of the early distal tubule, and the latter to the medullary site of the thick ascending limb of the loop of Henle (TAL) (Lant, 1985). Failure to find a clear-cut reduction in the amount of diuretic excreted in the presence of NSAID implies that interference with tubular access does not play a major role in this interaction, a view supported by evidence from other studies (Brater *et al.*, 1985; Chennavasin *et al.*, 1980; Data *et al.*, 1978; Smith *et al.*, 1979). A recent report, however, has shown a decreased renal clearance and increased plasma concentrations of HCTZ in subjects pretreated with SUL, but no alteration in pharmacodynamic response (Koopmans *et al.*, 1985).

A curious paradox emerges when the findings of our NSAID-diuretic combined challenges are analysed. Pretreatment with SUL attenuated the renal responses to both HCTZ and PIR, as might be expected from the effect SUL had on its own in enhancing salt and water reabsorption. However, NAP, on its own, caused an even more pronounced salt and water reabsorption over 24 h yet, when combined with either HCTZ or PIR, no attenuation of the diuretic response was seen. This implies that the tubular events involved in the renal actions of NSAIDs may have distinct features and localisations that, in some instances, overlap with the action of diuretics and, in others, are quite separate. It is also possible that the observed difference in response between NSAIDs and their interaction with diuretics may relate to mass effects that, in turn, depend on drug dosage rather than inherent difference in renal handling between the drugs or their metabolites.

Clearly, the tubular handling of NSAIDs needs to be studied in greater detail, with more emphasis given to the renal response to unchanged drug and metabolites, as well as to dosage. For example, responses within the kidney to a drug such as SUL must take into account the variety of metabolites excreted (Duggan *et al.*, 1977), some of which might not inhibit renal cyclo-oxygenase but could still interact with the tubular epithelium. Once this complicated renal pharmacology has been clarified, perhaps, then, the paradoxical responses seen here will be better understood.

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