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Acute Effects of Acetylsalicylic Acid in Patients with Chronic Renal Insufficiency

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Summary. The effect of acetylsalicylic acid (ASA) in patients with renal insufficiency has been examined. In one investigation (A), in patients with a mean GFR of 23.0 ml/min the acute effects of ASA 750 mg i.v. 'vsine-ASA 7.5 ml) and 0.9% NaCl 7.5 ml on renal ater and solute output and on the clearance of inulin, creatinine and PAH were compared. In another (B) the effects of simultaneous administration of ASA 750 mg or 0.9% NaCl 7.5 ml i.v. with an infusion of furosemide 250 mg were investigated in six patients (mean GFR 12.9 ml/min) in a cross-over study. In study A there was a significant fall in urinary sodium excretion within the first 15 min after ASA administration, with a maximal decrease to 21% of the control period. Urine flow fell to 35%, osmolal clearance to 41%, inulin clearance to 54% and PAH clearance to 66%, whilst tubular reabsorption of sodium increased. The effect of ASA lasted for 2–6 h. The mean salicylic acid concentration during the first two hours after ASA administration was 60.0 µg/ml, and the mean protein bound salicylic acid (SA) was 70.4%. There was no effect of placebo (0.9% NaCl 7.5 ml) on renal function. Pretreatment with ASA 750 mg i.v. attenuated the diuretic effect of furosemide 250 mg, d reduced creatinine clearance significantly within υ–2 h after drug administration.

Key words: Acetylsalicylic acid, chronic renal insufficiency, renal plasma flow, furosemide, glomerular filtration rate, sodium excretion.

A previous study of normal subjects showed that peroral treatment with acetylsalicylic acid (ASA) 70 mg per kg body weight for 24 h significantly reduced urinary sodium excretion (Berg, 1977). The effect was most pronounced during day time and on days with low sodium balance. Creatinine clearance was unchanged, nor did ASA interfere with the plasma renin activity. There was no observable interaction of ASA with the effect of furosemide (40 mg) on sodium excretion or creatinine clearance.

Robert and coworkers (1973) reported a 30% decrease in the renal clearances of inulin and para-aminohippuric acid (PAH) after infusion of ASA 30 mg/kg in patients with normal renal function, and in one study a 10% reduction in GFR was found after a single oral dose of 20 mg/kg ASA in normal subjects (Beeley and Kendall, 1971); the mean serum salicylic acid (SA) concentration in these experiments was 100–120 µg/ml, as compared to the 150 µg/ml in our study (Berg, 1977).

Previous reports on dogs have clearly shown that another inhibitor of prostaglandin synthesis, indomethacin (Vane et al., 1971), inhibits the increase in renal blood flow which follows treatment with furosemide (Williamson et al., 1975). Indomethacin has also been shown to reduce renal plasma flow and GFR in patients with renal failure, but not in normal subjects (Donker et al., 1975). Until now, the effects of ASA on renal haemodynamics and urinary water and solute output in patients with renal failure have not been reported.

The purpose of the present study was to investigate the effects of ASA on renal function in patients with stable chronic renal insufficiency, and to compare the effects of high doses of furosemide in patients pretreated either with ASA or placebo.

Methods

Three groups of patients, each of 6 subjects, with stable, non-oedematous renal failure, were allocated to two separate studies-A and B (Table 1). In *Study A*

Table 1. Details of the patients. In study A the effects of ASA and placebo (0.9% NaCl 7.5 ml) on renal function were examined, and in study B the interaction of ASA or placebo with the renal effect of furosemide

Study A						Study B		
Age Years		S_{Cr} mg/100 ml		GFR ml/min		Age Years	S_{Cr} mg/100 ml	GRF ml/min
ASA	Placebo	ASA	Placebo	ASA	Placebo			
61	70	9.4	9.5	7.6	4.2	52	6.2	12.3
52	28	3.1	7.0	28.7	12.5	73	3.4	21.0
37	28	2.2	2.6	20.3	22.7	74	6.6	11.2
66	76	9.6	8.2	6.5	10.2	67	9.6	3.2
54	58	2.2	4.1	21.1	25.8	82	2.8	23.0
53	52	1.6	1.6	55.5	60.8	79	9.2	6.9
53.8[a]	52.0	4.7	5.5	23.3	22.7	71.2	6.3	12.9
4.0[b]	8.3	3.8	3.2	7.3	20.3	4.4	1.1	3.2

[a] = mean value [b] = SEM S_{Cr} = serum creatinine GFR = C_{IN} (see Methods)

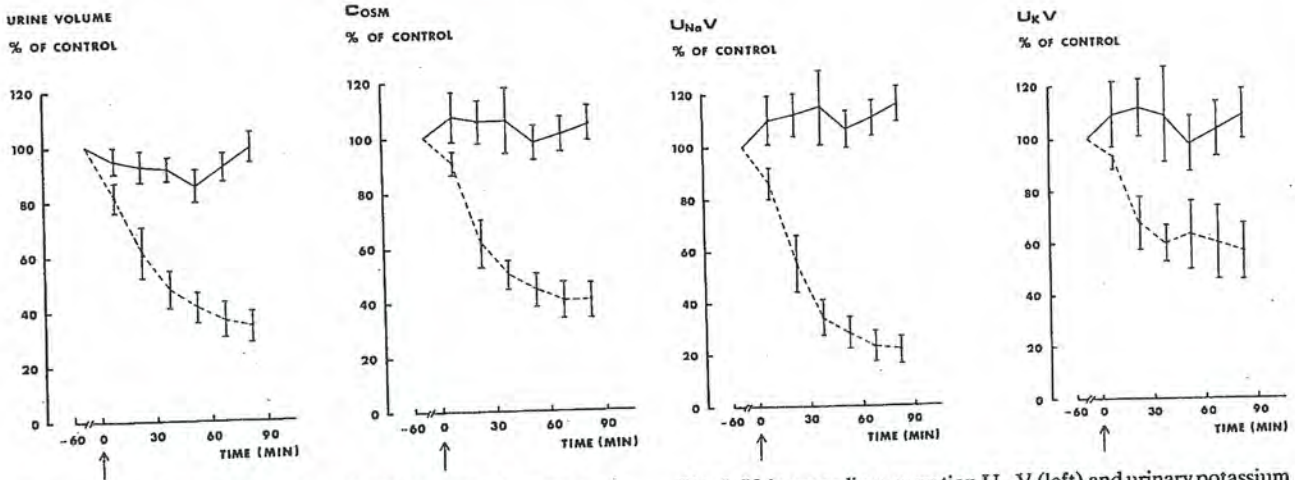

Fig. 1. Urine volume (left) and C_{osm} (right) expressed as percentage of the respective control group in subjects treated with ASA ●---● (n = 6) or placebo ●—● (n = 6) at zero time (arrow). Mean ± SEM. Experimental conditions and urine sampling periods are described in Methods

Fig. 2. Urinary sodium excretion $U_{Na}V$ (left) and urinary potassium excretion U_KV (right) expressed as percentage of controls in ASA-treated ●---● (n = 6) and placebo-treated ●—● (n = 6) subjects; cf. legend to Fig. 1

the effects of ASA and placebo on renal function were examined. In *Study B* the consequences of simultaneous administration of ASA or placebo and furosemide were investigated in a cross over design. In both studies all diuretic treatment was withdrawn at least 3 days before the experiments started. Analgesic or anti-inflammatory agents with possible actions on urinary electrolyte excretion were not administered on experimental days, but other drugs were continued. The patients received a 100 m mol sodium diet and approximately 2000 ml fluid daily. Potassium supplements were not given.

Study A

Twelve patients (mean GFR 23.0 ml/min) were randomized into two groups; six patients (mean age 52.0 years) in a placebo group, and 6 (mean age 53.8 years) were treated with ASA (Table 1). The patients were in stable fluid and electrolyte balance and had no signs of liver impairment or cardiac decompensation.

The patients already had bladder catheters in place for other medical reasons. When urine flow was stable (approximately 2 ml/min), a priming dose of inulin 2.5 g (Inulin Laevosan AG, Linz, Austria) and PAH 1.0 g (Sodium para-aminohippurate®, Merck, Sharp & Dohme, USA) was given, and continuous intravenous doses were adjusted to give a plasma inulin concentration of 15–25 mg/100 ml and a PAH concentration of 2–4 mg/100 ml. The inulin/PAH infusion was given in 0.9% NaCl, at a constant rate of 3 ml/min, using an infusion pump (Infusomat, B. Braun, Melsungen, Germany). After infusion for half an hour urine sampling was started in periods of 15 min. The control period (C) was the mean of 8 clearance periods (–2–0 h).

At zero time (0) 750 mg acetylsalicylic acid (ASA) (7.5 ml of 90% lysine-ASA, 10% glycine; Bay g 4600, Bayer AG, Leverkusen, Germany) was administered intravenously to one group of 6 patients (ASA group), and 0.9% NaCl 7.5 ml to the other (placebo group). The injections of ASA or placebo were followed by 6–8 clearance periods (0–2 h = period I) before the inulin/PAH infusion was ended. Venous blood samples were collected every 15 min at the midpoint of the clearance period for determination of SA, and inulin and PAH concentration in serum. Urine samples were then collected through the indwelling catheter from 2 to 6 h (period II), 6–10 h (period III) and 10–22 h (period IV) after the administration of ASA or placebo, for estimation of urine flow, creatinine and electrolyte excretion.

Study B

Six patients (mean age 71.2 years, mean GFR 12.9 ml/min) took part in this study (Table 1). Four of the patients were catheterized and in the other 2 patients urine was sampled by spontaneous voiding. All 6 patients (A–F) received furosemide 250 mg (Lasix®, Hoechst AG, Frankfurt, Germany) as an infusion over 60 min from 8 a.m. to 9 a.m. At 8 a.m. on the first and third treatment day three of the patients (A, B, C) were given ASA 750 mg i.v. and three (D, E, F) 0.9% NaCl 7.5 ml i.v. (placebo). On the following day the treatment schedules were reversed, so that each patient received ASA or saline on alternate days.

Urine samples were collected from 8 a.m. to 10 a.m. (0–2 h), 10 a.m. to 12 noon (2–4 h), 12 noon to 4 p.m. (4–8 h) and 4 p.m. to 8 a.m. the next morning (8–24 h).

In both sets of experiments the following parameters were measured in urine: volume, creatinine, osmolality, sodium and potassium content; and in serum creatinine and osmolality.

Analytical Methods

The methods used for determination of sodium, potassium, creatinine, osmolality and total and free salicylic acid are described elsewhere (Berg, 1977). Inulin in serum and urine was measured by the method of Schreiner (1950), and PAH according to Smith et al., (1945). All urine and blood samples were analysed in duplicate.

Urine flow (U_v) was expressed in ml/min, urinary sodium and potassium excretion ($U_{Na}V$, U_KV) as μmol/min and total SA in μg/ml. Protein-bound SA = Total SA − Ultrafiltrable SA.

Osmolal clearance (C_{osm}) and free water clearance (C_{H_2O}) were calculated using conventional formulae. Clearances of inulin (C_{IN}), creatinine (C_{Cr}) and PAH (C_{PAH}) were expressed in ml/min/1.73 m^2. C_{IN} = glomerular filtration rate (GFR), C_{PAH} = effective renal plasma flow (ERPF), filtration fraction (FF) = C_{IN}/C_{PAH}.

Per cent filtered sodium excreted (E_{Na}%)

$$= \frac{U_{Na}\,V \times 100}{S_{Na} \times f \times GFR}$$

where f = Gibbs-Donnan factor (0.95).

The mean and standard error of the mean (SEM) were calculated and statistical comparisons carried out according to Wilcoxon's method for paired differences.

In Study A the results were expressed as percentages of the control periods for the ASA and placebo-treated patients, respectively. In Study B, concurrent administration of furosemide + ASA was compared with furosemide + placebo, the patients serving as their own controls.

Results

Study A: Comparison of ASA and Saline (Placebo)

The acute effects of intravenous administration of ASA 750 mg and NaCl 0.9 per cent (placebo) on urinary water and electrolyte excretion are shown in Figures 1 and 2. After administration of ASA there was a significant ($p < 0.05$) decrease in urine flow, osmolal clearance and sodium and potassium excretion. The effect on sodium excretion was significant within the first 15 min clearance period after ASA administration, and on the other parameters within 30 min. Ninety minutes after drug administration, urinary sodium output had decreased to 21 ± 5.6% of the control excretion. As potassium excretion only fell to 57% of the control value, the urinary Na/K ratio decreased. Urine flow fell to 35% and osmolal clearance to 41% of the controls.

The acute effects of ASA and saline on inulin and PAH clearance are shown in Figure 3. C_{IN} decreased to 54 ± 7.8% and C_{PAH} to 66 ± 5.3% in the ASA-treated subjects as compared to the controls. The acute changes in GFR and ERPF were found in all patients and were significant from the second clearance period, 15–30 min after drug administration.

The mean values of the various parameters investigated 2 h before and 2 h after treatment are shown in Table 2. Urinary Na/K ratio fell from 2.42 to 1.13 and the percentage of filtered sodium excreted (E_{Na}%) from 3.4 to 1.6 in the ASA group. Filtration fraction decreased from 23.8 to 18.9 (n.s.). Free water clearance (C_{H_2O}) was unchanged. There was no effect on renal function after treatment with 7.5 ml normal saline (placebo) in this acute clearance study.

Urine volume and creatinine, sodium and potas-

Table 2. Effect of acetylsalicylic acid (ASA) and placebo on renal function. Mean values and SEM

Parameter	2 hours before (C)		2 hours after (I)	
	ASA	Placebo	ASA	Placebo
U_V ml/min	2.19± 0.33	2.35± 0.66	0.81± 0.18	2.20± 0.62
C_{osm} ml/min	1.79± 0.27	1.67± 0.28	0.75± 0.16	1.72± 0.32
C_{H_2O} ml/min	0.30± 0.26	0.68± 0.48	0.06± 0.14	0.47± 0.58
C_{IN} ml/min	23.3 ± 7.4	22.7 ± 9.3	13.9 ± 5.7	20.7 ± 8.2
C_{PAH} ml/min	97.9 ±34.3	123.8 ±53.4	73.7 ±30.1	134.6 ±55.6
FF %	23.8 ± 7.4	18.3 ± 3.6	18.9 ± 6.4	15.4 ± 4.3
$U_{Na}V$ µmol/min	102.2 ±16.5	76.5 ±16.8	27.9 ±13.4	86.6 ±15.7
U_KV µmol/min	42.3 ± 4.5	47.1 ±11.2	24.7 ± 5.5	48.7 ±12.2
E_{Na} %	3.4 ± 1.1	2.6 ± 1.4	1.6 ± 0.8	3.3 ± 1.5
U_{Na}/U_K	2.42± 0.52	1.62± 0.42	1.13± 0.32	1.81± 0.44

For abbreviations, see Methods. C = 2 h period before administration of ASA or placebo; I = 2 h period after treatment

Table 3. Acute effect of furosemide 250 mg on renal function in patients pretreated with acetylsalicylic acid (ASA) or placebo. Mean values and SEM

Period	0–2 h		2–4 h	
Parameter	ASA	Placebo	ASA	Placebo
U_V ml/min	1.36± 0.18[b]	2.61± 0.71	1.86± 0.32[a]	2.55± 0.68
C_{Cr} ml/min	14.7 ± 2.4[b]	20.9 ± 3.4	22.5 ± 5.7	21.4 ± 5.3
$U_{Na}V$ µmol/min	90.5 ±21.9[c]	239.3 ±79.9	215.7 ±44.9	305.7 ±92.0
U_KV µmol/min	40.3 ± 6.6[b]	66.5 ±10.6	60.7 ± 6.2	65.1 ± 8.3
E_{NA} %	4.5 ± 0.7[c]	8.9 ± 1.9	7.6 ± 1.1[b]	11.2 ± 3.6
Na/K ratio	2.25± 0.48[b]	3.60± 0.71	3.55± 0.53[a]	4.70± 1.11

[a] = $p < 0.05$ [b] = $p < 0.01$ [c] = $p < 0.001$
For abbreviations, see Methods. ASA or placebo was administered at zero time (0), and furosemide from 0–1 h. For urine sampling, see Methods

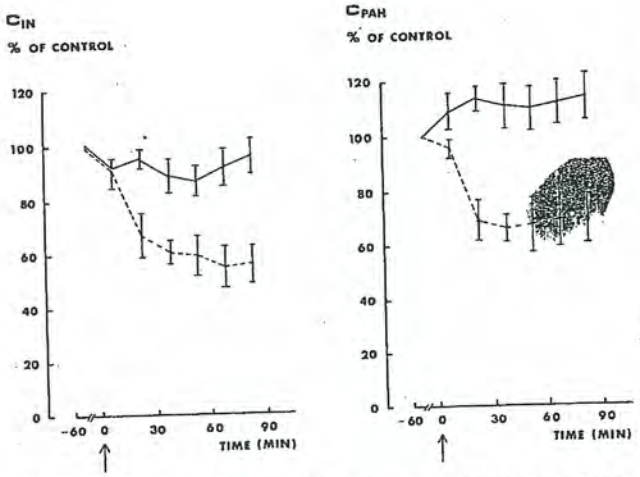

Fig. 3. C_{IN} (left) and C_{PAH} (right) expressed as percentage of controls for ASA-treated ●----● (n = 6) and placebo-treated ●——● (n = 6) subjects; cf. legend to Fig. 1

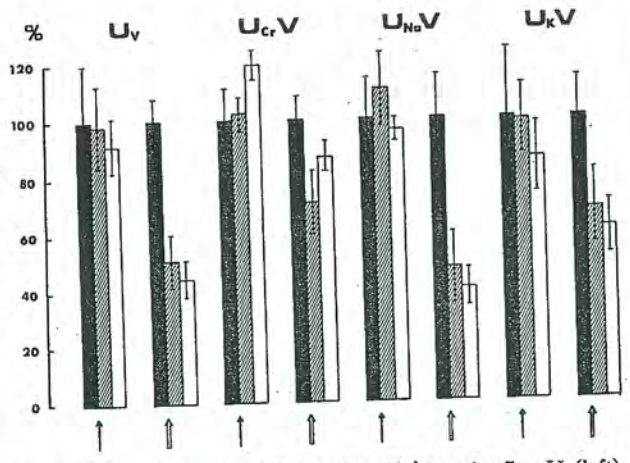

Fig. 4. Effect of ASA ⇑ or placebo (NaCl) ↑ on urine flow U_v (left), urinary creatinine U_{Cr} V, sodium U_{Na} V and potassium excretion U_K V, expressed as percentage of controls (C = 100%). Experimental conditions and urine sampling periods are as described in Methods. Height of column = mean value, vertical lines at the top of each column represent SEM for control (C) period (dark), period I (hatched) and period II (light)

sium excretion 0–2 h (period I) and 2–6 h (period II) after drug administration, expressed as percentage of the control values (− 2–0 h), are shown in Figure 4. At time zero either ASA or saline was given intravenously. As can be seen, the effects of ASA on urine flow and sodium and potassium excretion, which were pronounced during the first two hours after drug administration (period I, hatched columns) was of the same magnitude 2–6 h after ASA (period II, white columns). Mean urine flow was 43%, sodium excretion 40% and potassium excretion 61% of the control group ($p < 0.05$). Urinary creatinine excretion was still significantly lower, although the effect was less marked than in period I. No detectable effect on the parameters investigated was found 6–10 h after ASA administration. The 24 h urine volume was 1.93 ± 0.21 l in the ASA group and 2.68 ± 0.60 l in the placebo group, sodium excretion being 102.2 ± 18.7 and 116.1 ± 23.3 m mol, respectively.

Total serum salicylic acid (SA) concentration was 60.0 ± 4.0 µg/ml (mean of 12 patients ± SEM) and mean percentage of SA protein bound was 70.4 ± 3.3. The SA concentration was stable during the first two hours after ASA administration when the SA measurements were performed.

Study B: Effects of ASA on the Diuretic Action of Furosemide

The results of rapid simultaneous injection of ASA 750 mg or 0.9% NaCl 7.5 ml (placebo) with infusion of furosemide 250 mg are shown in Table 3. The diuretic effects of furosemide measured during two urine sampling periods after administration of the diuretic have been expressed as the mean ± SEM for "ASA days" and "placebo days".

During the first period, 0–2 h after commencement of the furosemide infusion, urine flow was 1.36 ± 0.18 ml in the ASA group and 2.61 ± 0.71 ml in the placebo group ($p < 0.01$). Sodium excretion in these groups was 90.5 ± 21.9 and 239.3 ± 79.9 µmol/min ($p < 0.001$), potassium excretion 40.3 ± 6.6 and 66.5 ± 10.6 µmol/min ($p < 0.01$) and creatinine clearance 14.7 ± 2.4 and 20.9 ± 3,4 ml/min ($p < 0.01$), respectively. The percentage of filtered sodium not excreted (E_{Na}%) was 4.5 ± 0.7 in the ASA group, 8.9 ± 1.9 in placebo-treated subjects ($p < 0.001$), and the Na/K ratios were 2.25 ± 0.48 and 3.60 ± 0.71, respectively ($p < 0.01$).

During the second clearance period, 2–4 h after the administration of ASA, creatinine clearance did not differ from the control period. The effect of concurrently administered ASA on the renal action of furosemide gradually subsided after 2–4 h, but there was still a 37% difference in urine volume ($p < 0.05$) and a 42% difference in sodium excretion (n.s.), whilst the percentage of filtered sodium not excreted was 7.6 in the ASA group and 11.2 in the placebo treated subjects ($p < 0.01$). During the clearance periods 4–8 h and 8–24 h after the onset of the furosemide infusion, results in the ASA group did not differ from the placebo group.

Pooled 24 h sodium excretion was 158.7 ± 34.0 mmol in the ASA group as compared to 201.9 ± 56.6 mmol (placebo) ($p < 0.05$), and urine flow 2.81 ± 0.31 and 3.10 ± 0.61 l, respectively (n.s.).

The effect of simultaneous administration of ASA and furosemide was not influenced by the treatment schedule. There was no significant differences in the mean effects of ASA on days 1 and 3 as compared to days 2 and 4.

Discussion

Patients with severe impairment of renal function eliminate small doses of salicylates at an almost normal rate (Lowenthal et al., 1974; Daneels et al., 1975). However, the protein binding of SA is reduced in uraemia (Andreasen, 1973; Lowenthal et al., 1974; Sjøholm et al., 1976), and this was confirmed in the present study. The free SA concentration was still low in this study at "analgesic" dose levels.

Intravenous injection of ASA 750 mg caused a decrease in renal sodium excretion within 15 min, which persisted for 2–6 h. Glomerular filtration rate decreased to 54% and renal plasma flow to 66% of the control period. The haemodynamic effects were significant 15–30 min after ASA administration.

Vane (1971) has shown that ASA, like indomethacin, inhibits the synthesis of PGE_2 and $PGF_{2\alpha}$ from arachidonic acid in homogenates derived from guinea pig lungs. Inhibition of PG synthesis in dogs by indomethacin 2–3 mg/kg is known to reduce RBF by from 15 (Aiken and Vane, 1973) to 45% (Longiro et al., 1973), and to redistribute renal blood flow from the inner to the outer cortex (Kirchenbaum et al., 1974). A 10–20% reduction in RBF was found after i.v. administration of "therapeutic" doses of ASA to anaesthetized dogs (Berg and Bergan, 1976).

Oral treatment with indomethacin 150 mg per day decreased GFR by 35% and RPF by 23% in nephrotic patients with impaired renal function (Arisz et al., 1976). Changes in GFR and renal plasma flow did not occur in normal subjects (Donker et al., 1975).

In the present study, urinary sodium excretion fell in parallel with C_{IN} and C_{PAH} and it seems reasonable to conclude that the effect of ASA on sodium excretion is secondary to reduced GFR and renal plasma flow, probably due to renal cortical vasoconstriction.

If ASA reduces renal plasma flow and urinary sodium excretion by inhibition of PG-synthesis, it is still necessary to explain why the drug exerts more pronounced effects on these parameters in patients with renal failure than in normal subjects.

Prostaglandin inhibitors can augment the vasoconstrictor action of angiotensin (Aiken and Vane, 1973). The angiotensin I generation rate unrelated to endogeneous renin activity has been found to be significantly greater in uraemic patients than in normals (Kotchen et al., 1972). It seems reasonable to assume that potentiation of the renin-angiotensin effects by ASA is more pronounced in patients with renal failure than in normal subjects. Potentiation of this system could also account for the more pronounced effect of indomethacin on GFR and RPF in patients on a low sodium diet who have high plasma renin activity (Arisz et al., 1976). Plasma renin activity was not investigated in the present study.

Pretreatment with ASA 750 mg attenuated the natriuretic effect and reduced creatinine clearance 0–2 h after treatment with furosemide 250 mg. As furosemide and ethacrynic acid have been found to inhibit human placental 15-OH prostaglandin dehydrogenase, a prostaglandin-like mechanism of these drugs has been postulated (Paulsrud and Miller, 1974). An increase in urinary PGE excretion (Olsen and Rønne, 1976) and increased renal venous PGE concentration (Williamson et al., 1975b) have been found at the time of vasodilatation following loop diuretics. Pretreatment with indomethacin diminishes the increase in plasma renin activity and blocks the increase in RBF found after administration of loop diuretics in dogs (Williamson et al., 1975a; Olsen and Rønne, 1976).

The action of loop diuretics seems, therefore, to depend upon a balance between the vasodilator effect of local hormones in the kidney and the vasoconstrictor action of the renin-angiotensin system. ASA probably potentiates the vasoconstrictor effects of the latter system and, in consequence, inhibits the increase in renal blood flow and natriuresis that should follow administration of furosemide.

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