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Na^+, K^+, and BP homeostasis in man during furosemide: Effects of prazosin and captopril

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Na^+, K^+, and BP homeostasis in man during furosemide: Effects of prazosin and captopril. Furosemide increases sodium (Na^+) and potassium (K^+) excretion but if dietary salt is provided, a compensatory reduction in Na^+ and K^+ excretion follows which restores neutral balances within 18 to 24 hours. This compensation is not interrupted by blockade of the renin–angiotensin–aldosterone system (RAA) alone with captopril. Since plasma norepinephrine concentration increases after furosemide and $alpha_1$ adrenoreceptors can mediate enhanced Na^+ reabsorption, we administered prazosin (2 mg 6 hr^{-1}) to six normal volunteers consuming a daily intake of 270 mmol of Na^+ and 75 mmol of K^+, and added captopril (25 mg 6 hr^{-1}) for an additional day to block the RAA system concurrently. Furosemide (40 mg day^{-1}) was given for the last four days. Prazosin given alone before the diuretic reduced ($P < 0.05$) BP and plasma angiotensin II (AII) concentration and increased body weight and heart rate. However, when given with furosemide, neither prazosin nor prazosin with captopril modified the short–term natriuretic or kaliuretic responses to furosemide, or the ensuing compensatory reductions in Na^+ and K^+ excretion. Accordingly, cumulative balances for Na^+ and K^+ remained neutral over four days of diuretic administration. Neither drug altered the renal responsiveness to the diuretic which was assessed from the relationship between renal Na^+ and K^+ excretion and diuretic elimination. Although the BP was maintained when furosemide was given alone, when given with prazosin and captopril, the mean BP fell by 13 ± 5 mm Hg ($P < 0.05$). In conclusion, in normal human subjects consuming a liberal salt intake, neither the $alpha_1$ adrenoreceptor nor the RAA systems are required for maintenance of Na^+ and K^+ balances during administration of furosemide.

In previous studies, we found that even a large loss of fluid, sodium (Na^+) and potassium (K^+) induced by furosemide does not ensure weight loss, negative salt balance, K^+ depletion, or a fall in blood pressure (BP) in normal human subjects [1–3]. This was explained by a precise renal compensation which resulted in reduced excretion of fluid Na^+ and K^+ in the post-diuretic period. The plasma concentrations of angiotensin II (AII), aldosterone and norepinephrine increased consistently after furosemide. However, when captopril was used to block activation of the renin–angiotensin–aldosterone (RAA) system, the pattern of fluid and electrolyte losses with furosemide were not modified; a precise restoration of balance occurred after the acute losses just as in the compensation phase following administration of furosemide alone [2]. Since the sympathetic nervous system (SNS) may be critical for Na^+ and BP homeostasis during Na^+ and fluid depletion in man [4, 5], and since recent studies in animals have shown that enhanced Na^+ reabsorption during renal SNS activation is mediated by $alpha_1$ adrenoreceptors [6–10], we have studied the importance of these receptors in mediating Na^+, K^+ and BP homeostasis during administration of furosemide. We administered prazosin to block $alpha_1$ adrenoreceptors and captopril to inhibit generation of AII during furosemide administration to normal human subjects.

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Methods

Six normal volunteers (five male and one female) aged 23 to 37 years participated after giving informed consent for a study approved by the Human Subjects Investigation Committee of the Brigham and Women's Hospital. The results were compared to those obtained in a previous study (protocol 1) of six normal subjects, matched for age and sex, who were treated identically but received no prazosin or captopril [1]. An additional control group of four subjects received prazosin and captopril but no diuretic; balance data are available on three of these and BP data on four. Before starting the protocols, the subjects were weighed and their BP and heart rate (HR) measured while lying and after two minutes of standing. Mean BP (MBP) was calculated as the sum of the diastolic BP and one–third the pulse pressure. Thereafter, the subjects received a closely regulated diet of three meals per day taken at 6 to 8 a.m., 12 to 1 p.m., and 6 to 8 p.m. This diet provided 20 mmol day^{-1} of Na^+ and 75 mmol day^{-1} of K^+, and was supplemented with five tablets of 1 g NaCl taken with each meal; the total daily Na^+ intake was 270 mmol. As in previous studies, fluids were not restricted and the subjects continued their usual daily activities, except that undue exercise and smoking were prohibited. None of the subjects was taking any drugs.

After baseline blood samples were drawn, prazosin was administered every six hours throughout the study, starting at

Table 1. Effects of prazosin administered alone

	Before	Change during prazosin
MBP *mm Hg* lying	96.7 ± 3.3	−3.3 ± 1.5
standing	99.4 ± 3.4	−6.9 ± 1.8[a]
HR *min*$^{-1}$ lying	68.3 ± 2.8	+7.7 ± 2.7[a]
standing	77.5 ± 4.5	+12.2 ± 4.2[a]
Wt *kg*	72.9 ± 4.8	+1.0 ± 0.38[a]
PRA *ng ml*$^{-1}$ *hr*$^{-1}$	1.3 ± 0.5	+0.4 ± 0.8
Plasma AII *pg ml*$^{-1}$	39.0 ± 3.7	−10.8 ± 2.1[b]
Plasma aldosterone *ng dl*$^{-1}$	22.4 ± 3.0	−9.1 ± 4.8
Plasma norepinephrine *pg ml*$^{-1}$	153.6 ± 40.9	+85.6 ± 36.5
Plasma epinephrine *pg ml*$^{-1}$	49.0 ± 6.4	−11.6 ± 10.6

Mean (±SEM) values in six subjects before drug administration and changes recorded after five days of prazosin administration. These measurements were made before furosemide was administered.
[a] $P < 0.05$
[b] $P < 0.01$

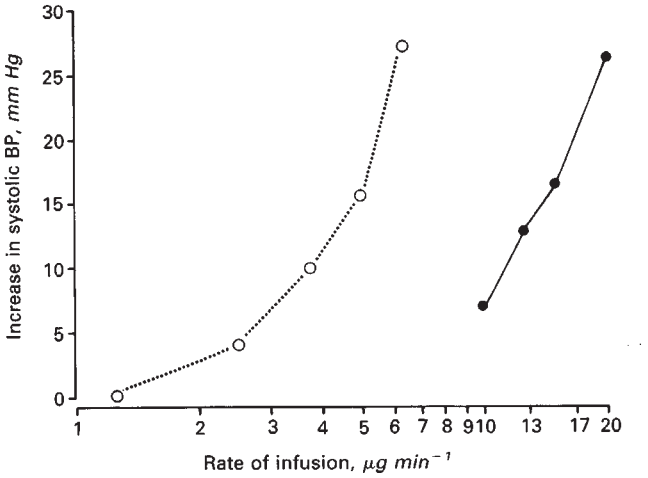

Fig. 1. *Individual values for one subject receiving the regulated diet for five days without (open circles) or with (closed circles) prazosin.* Values shown are for increases in systolic BP recorded five minutes after starting an intravenous infusion of norepinephrine at the rates shown (log scale).

midnight on the first day. For the first day, the dose was 1 mg six hours^{-1}; thereafter the dose was increased to 2 mg six hours^{-1}.

After three days of equilibration to prazosin and the regulated diet, all urine was collected in consecutive six hours samples for the subsequent six days; each sample was analyzed for volume, Na^+, K^+ and creatinine. Data from the first two of these days (control days) were used to determine the basal patterns of $U_{Na}V$, U_KV, and creatinine clearance (C_{Cr}). During the subsequent four days (days six through nine), the subjects received 40 mg of furosemide intravenously as a bolus injection at 8 a.m. on days six, eight, and nine; it was given orally on day seven as in previous protocols [1–3]. Captopril (25 mg six hours^{-1}) was given on day nine; the first dose was taken one hour before the diuretic was administered since we had found that this blocked the furosemide–induced rise in AII [2]. Before furosemide was given on days six, eight, and nine, an intravenous cannula was inserted and, after 30 minutes of quiet sitting, a blood sample was withdrawn; a second blood sample was obtained five hours after furosemide was given. On these same days, urine was collected each 30 minutes for five hours after furosemide to measure Na^+, K^+ and furosemide concentrations.

Urine and plasma concentrations of Na^+, K^+, chloride (Cl^-), bicarbonate (HCO_3^-), albumin (Alb), creatinine, plasma renin activity (PRA), AII and aldosterone were measured as described previously [1–3]. Plasma epinephrine and norepinephrine concentrations were measured by a radioenzymatic method [2] and furosemide was measured using a high–performance liquid chromatography technique with a fluorometric detection system [1].

Within–subject comparisons were made by using a paired *t*-test and between–group comparisons with an unpaired *t*-test. Results were judged to be statistically significant at $2P \leq 0.05$. Mean values ± SEM are presented.

Results

As shown in Table 1, there were three prominent effects of five days of prazosin administration before any furosemide was given: a decrease in the MPB while standing of 7%, accompanied by an increase in HR of 16% and an increase in body weight (body wt) of 1 kg. Plasma AII concentration decreased but there were no significant changes in PRA or the plasma concentrations of aldosterone, norepinephrine or epinephrine.

One additional normal subject received the regulated diet for five days on two separate occasions; during the second, prazosin (1 mg six hours^{-1} for 24 hours, then 2 mg six hours^{-1} for four days) was administered. At 10 a.m. on day five on each occasion, this subject received a graded intravenous infusion of norepinephrine while he was recumbent. Norepinephrine was infused via a Harvard motor–driven syringe at incremental doses for five minute periods, with 10 minutes between infusions. The log dose–response relationships for changes in systolic blood pressure are shown in Figure 1. It is apparent that the dose of norepinephrine required to raise the systolic BP by 20 mm Hg was increased during prazosin administration by about threefold.

During the control days (four and five) before furosemide was administered, daily rates of excretion of Na^+ and K^+ were 241 ± 28 mol and 77 ± 11 mmol, respectively. These were not significantly different from the levels of intake, implying that daily Na^+ and K^+ balances were neutral at the time that furosemide was administered. On days six, eight, and nine of intravenous furosemide administration, the excretion of Na^+ and K^+ increased to maximal values within the first 30 minutes, and levels greater than baseline persisted for two to four hours. This short–term increase in Na^+ and K^+ excretion was not significantly different between days six, eight, or nine and did not differ from that found previously [1, 3]. There followed a compensatory reduction in $U_{Na}V$ and U_KV below levels of intake; the magnitude of this compensation was not different on days six, eight, and nine nor did it differ from that recorded when furosemide was given alone [1, 3].

The pattern of renal Na^+ excretion, in mmol six hours^{-1}, is shown in Figure 2. Panel A depicts for comparison the pattern shown previously when furosemide was given alone [1]. It is apparent that Na^+ balance was neutral before furosemide on both protocols although Na^+ excretion tended to be lower ($P = 0.05$) in the period 12 midnight to 6 a.m. when prazosin was

administered (Fig. 2B). The diuretic induced a sharp increase in $U_{Na}V$ on each day resulting in negative Na^+ balance as indicated by the solid shading. During the following 18 hour (the compensation period) $U_{Na}V$ fell below the levels of intake, resulting in positive Na^+ balance, as indicated by the diagonal shading. During administration of prazosin (panel B), each dose of diuretic produced the same pattern of Na^+ loss, followed by a quantitative reduction in Na^+ excretion in the compensation period whether the diuretic was given during administration of prazosin alone, or during prazosin with captopril. Accordingly, Na^+ balance was restored precisely within 24 hour of receiving furosemide on each day regardless of whether prazosin ± captopril was administered. Indeed, there was a tendency toward positive cumulative Na^+ balance by the final day (+96 ± 43 mmol), although this was not statistically significant. With the rather small number of subjects studied, there is the possibility of a beta–type error [11]. Therefore, we studied the cumulative Na^+ balance of three normal subjects who received the same regulated diet with prazosin and later captopril but without any furosemide. There was the same positive trend in Na^+ balance (+118 ± 49 mmol). The cumulative Na^+ balance of the subjects who received three days of furosemide alone was +48 ± 35 mmol. In no protocol was the cumulative Na^+ balance significantly different from zero on any day.

Renal K^+ excretion increased sharply in the six hours after furosemide; the increase was not significantly different during administration of furosemide alone (+27 ± 2 mmol), when furosemide was given with prazosin (+30 ± 3 mmol), or with prazosin plus captopril (+28 ± 1 mmol). As on previous studies, within two to four hours of furosemide, U_KV was reduced below levels of intake resulting in a compensatory period in which K^+ balance was positive [2]; this compensatory response was unaltered by prazosin ± captopril. The cumulative daily K^+ balance, assessed from the difference between K^+ intake and excretion, averaged +14 ± 22 mmoles. The cumulative K^+ balance for the three subjects who had received the regulated diet with prazosin and later captopril but no furosemide was +52 ± 30 mmoles; for those who received three days of furosemide alone it was −9 ± 14 mmoles. In no protocol was the cumulative K^+ balance significantly different from zero on any day.

To study possible mechanisms for the compensatory response, creatinine clearance and changes in hormones were measured. Creatinine clearance was measured each six hours from days three to eight, except during the six hours after the diuretic was administered when sharp changes in urine flow rate precluded calculating accurate clearance results. The mean C_{Cr} in the control days was 120 ± 6 ml min^{-1} 1.73 m^{-2}. There were no significant differences from control values in any six hour period during the four days of furosemide administration (average value: 129 ± 7 ml min^{-1} 1.73 m^{-2}) nor from the values recorded previously when furosemide was given alone [1].

Before starting the protocol, the mean BP of the four subjects who received the regulated diet with prazosin and later captopril, but without furosemide, was 99.1 ± 4.6 mm Hg. By 8 a.m. on day five, it had fallen by 10.1 ± 2.4 mm Hg to 89.1 ± 6.3 mm Hg. Over the subsequent five hours, it tended to increase slightly (+2.9 ± 0.8 mm Hg). By 8 a.m. on the final day, the mean BP was 83.3 ± 8.4 mm Hg. Over the subsequent five hours, the mean BP did not change significantly (+2.5 ± 1.9 mm Hg). As shown in Table 2, the average MBP measured before furosemide was similar during protocols 1 and 2. During administration of prazosin, furosemide did not reduce MBP. In contrast, when prazosin was combined with captopril, the MBP fell with furosemide in each subject. The mean fall of 12.5 ± 4.9 mm Hg was different from the rise of 2.5 ± 1.9 mm Hg ($P < 0.05$) observed over the five hour period in the three control subjects who received prazosin and captopril but no furosemide.

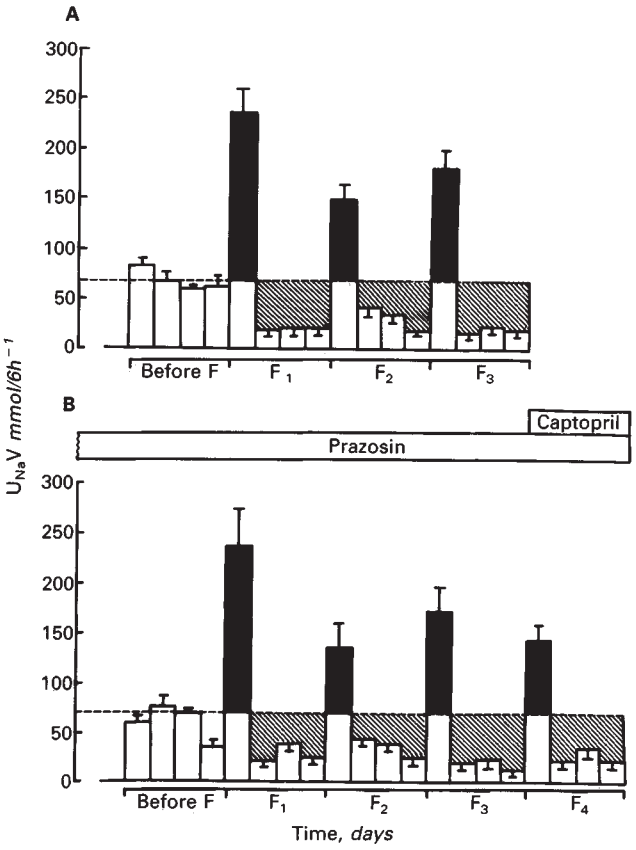

Fig. 2. *Mean (± SEM) values for renal Na^+ excretion in succeeding six hourly periods of the day, commencing at 6:00 a.m.* Before F represents the average of two control days before furosemide was administered. F1 to F4 represent the days of furosemide administration. **A.** Results with no additional drugs; **B.** Results during prazosin administration with captopril added for the last 24 hours. The horizontal broken line indicates the level of Na^+ intake. Solid shading shows periods of negative Na^+ balance and diagonal shading periods of positive Na^+ balance.

Administration of furosemide with prazosin alone or with prazosin plus captopril raised the heart rate (Table 2). Furosemide increased the PRA in each protocol, and this led to a consistent increase in plasma AII concentrations after furosemide when given alone or with prazosin. However, captopril prevented the rise in AII despite a major increase in PRA. The change in plasma aldosterone concentrations were more variable. Aldosterone increased when furosemide was given alone, but when the diuretic was given with the blockers no significant changes were detected. The plasma norepinephrine concentration increased when furosemide was given alone or with prazosin; norepinephrine remained high when furosemide was

Table 2. Mean blood pressure, heart rate and hormone concentrations before, and changes produced five hours after furosemide

	MBP *mm Hg*	HR *min^{-1}*	PRA *ng ml^{-1} hr^{-1}*	AII *pg ml^{-1}*	Aldosterone *ng dl^{-1}*	Norepinephrine *pg ml^{-1}*	Epinephrine *pg ml^{-1}*
Protocol 1. Furosemide alone							
Before F	92.8 ± 2.5	79.1 ± 3.0	2.2 ± 0.3	23.6 ± 1.7	8.0 ± 1.4	328.4 ± 41.7	72.2 ± 10.8
Change with F	+0.4 ± 2.1	+3.9 ± 4.1	+3.8 ± 0.5[g]	+34.9 ± 8.8[f]	+5.6 ± 1.8[f]	+132.0 ± 47.3[e]	+5.9 ± 14.6
Protocol 2. Furosemide with prazosin							
Before F	93.5 ± 2.8	91.6 ± 3.6[a]	2.2 ± 0.3	28.0 ± 1.6	14.1 ± 2.5	247.2 ± 24.3	37.6 ± 3.8[a]
Change with F	−0.4 ± 3.7	+6.6 ± 2.8	+2.3 ± 0.3[g]	+6.0 ± 1.4[f]	+3.4 ± 3.4	+155.0 ± 34.5[f]	+7.6 ± 3.5
Protocol 2. Furosemide with prazosin and captopril							
Before F	92.3 ± 3.8	98.2 ± 4.9[b]	12.3 ± 4.0[a,c]	20.8 ± 2.0[d]	10.4 ± 2.8	446.0 ± 120.3	46.7 ± 7.4
Change with F	−12.5 ± 4.9[e]	+13.0 ± 5.6	+15.3 ± 6.3[e]	+3.2 ± 2.4	+7.4 ± 6.1	+84.0 ± 90.0	+25.7 ± 0.7[c]

Mean (±SEM) values from protocols 1 and 2 recorded while subjects were seated for 30 minutes. Before furosemide (F) refers to the mean values recorded immediately before intravenous furosemide and change with F to the mean change recorded five hours later.
Significance of differences of values measured before F with P ± C compared to before F alone: [a] $P < 0.05$; [b] $P < 0.01$.
Significance of differences of values measured before F with P and C compared to before F with P: [c] $P < 0.05$; [d] $P < 0.01$.
Significance of changes produced by furosemide: [e] $P < 0.05$; [f] $P < 0.01$; [g] $P < 0.001$

Table 3. Plasma electrolytes and albumin concentrations

	Day 6		Day 8		Day 9	
	Before F	After F	Before F	After F	Before F	After F
P_{Na} *mmol liter^{-1}*	143.0 ±1.1	141.0 ±0.4	145.2 ±0.5	142.7 ±0.5	144.7 ±0.7	141.0 ±0.6
P value	<0.02		<0.02		<0.005	
P_K *mmol liter^{-1}*	4.23 ±0.13	3.85 ±0.05	4.00 ±0.13	3.58 ±0.10	4.05[b] ±0.13	3.60 ±0.09
P value	<0.02		<0.005		<0.001	
P_{Cl} *mmol liter^{-1}*	109.3 ±1.2	103.5 ±1.3	108.8 ±2.4	102.2 ±0.5	109.2 ±1.1	105.4 ±0.8
P value	<0.005		<0.01		<0.01	
P_{HCO_3} *mmol liter^{-1}*	25.0 ±0.7	26.3 ±0.9	25.8 ±0.8	26.8 ±1.4	26.6[a] ±0.7	27.4 ±1.1
P value	NS		NS		NS	
P_{Alb} *g dl^{-1}*	4.20 ±0.11	4.62 ±0.13	4.23 ±0.11	4.58 ±0.12	4.28 ±0.16	4.40 ±0.14
P value	<0.005		<0.005		<0.05	

Mean (±SEM) values for plasma sodium, potassium, chloride, bicarbonate and albumin concentrations measured before and five hours after furosemide. The *P* values refer to results of paired *t*-tests comparing before and after furosemide. [a] $P < 0.05$ [b] $P < 0.01$ comparing before furosemide on day 6 with before furosemide on day 9, using paired *t*-tests

given with prazosin plus captopril. The plasma epinephrine concentration tended to be lower during administration of prazosin but increased with furosemide when captopril was added to prazosin. Thus, the diuretic increased the plasma concentrations of either norepinephrine or epinephrine in each protocol.

The mean values for the plasma concentrations of electrolytes and albumin are shown in Table 3. Five hours after furosemide, there were consistent falls in P_{Na}, P_K and P_{Cl}, and increases in P_{Alb}, corresponding to increased rates of fluid and electrolyte excretion. However, when data obtained before furosemide administration on day nine are compared with corresponding values before furosemide on day six, no significant changes in P_{Na}, P_{Cl} or P_{Alb} are apparent. In contrast, there was a small fall in P_K of 0.18 ± 0.04 mmol liter^{-1} accompanied by a rise in P_{HCO_3} of 1.6 ± 0.5 mmol liter^{-1} over these three days of furosemide administration.

As in previous studies [1, 2] the renal excretion of furosemide over six hours following the administration of the diuretic averaged 43 ± 2% of the administered dose. Neither prazosin nor prazosin plus captopril affected renal furosemide excretion on any of the days on which the diuretic was given intravenously (15.7 ± 1.9 mg; 18.1 ± 1.9 mg; 17.5 ± 2.5 mg on study days six, eight, and nine, respectively).

The sigmoidal relationship between the rate of Na^+ excretion and the logarithm of the rate of furosemide excretion has been used to assess renal responsiveness to furosemide [12]. As shown in Figure 3, prazosin did not modify the relationships between Na^+ or K^+ excretion and the log of furosemide excretion.

Discussion

Our previous studies have identified two independent mechanisms which can limit Na^+ and K^+ depletion during diuretic administration [1–3, 13]. The first, diuretic extinction, occurred when furosemide was given while salt intake was restricted; there was a progressive reduction in the diuretic responses to repeated doses of the drug. The second, renal compensation,

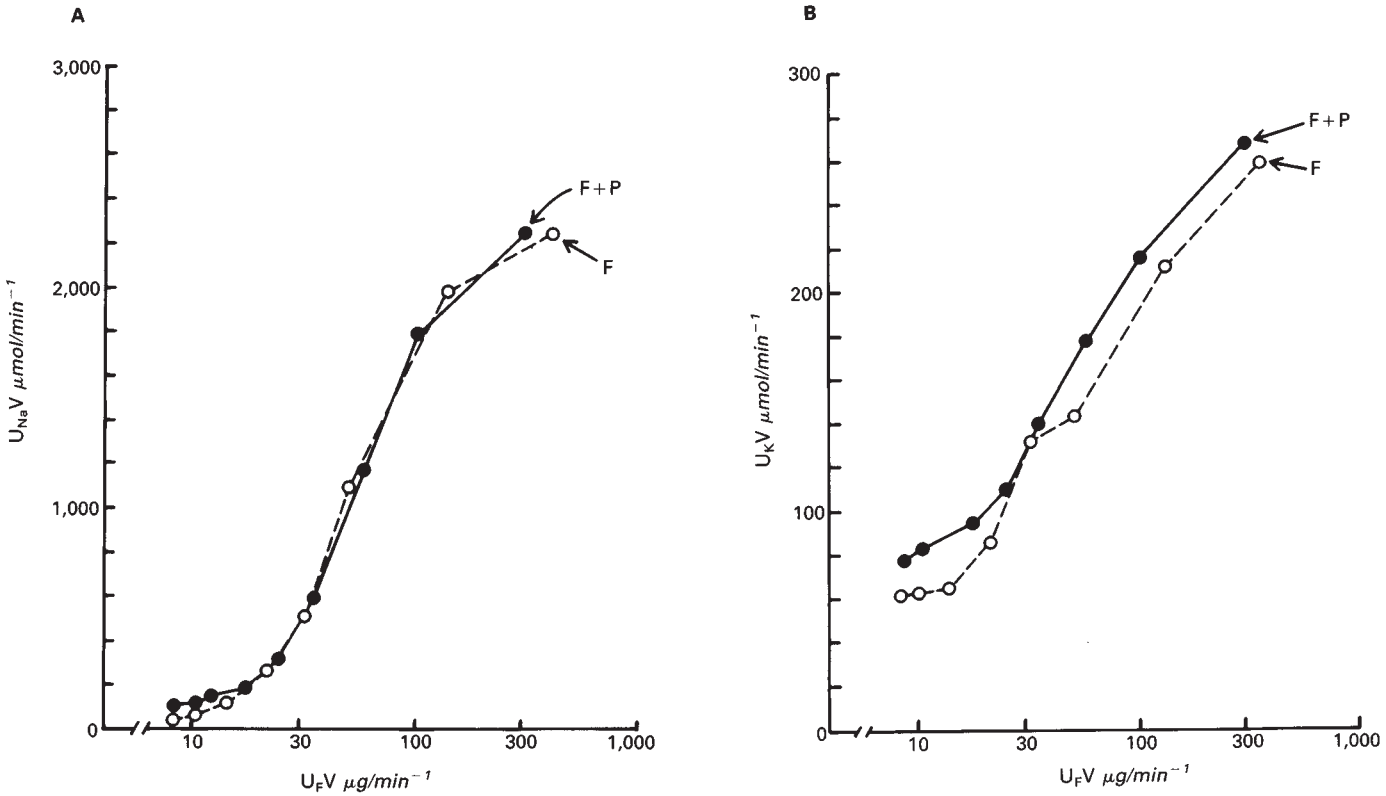

Fig. 3. *Mean values for Na^+ excretion (A) and K^+ excretion (B) as a function of simultaneously-measured rates of furosemide excretion (log scale) after intravenous furosemide alone (F) or intravenous furosemide during administration of prazosin (F+P).*

occurred when the diuretic was given during a more liberal salt intake; there was a decrease in Na^+ and K^+ excretion during the remainder of the day after the short-term response to the diuretic was complete. In a previous study, we administered captopril throughout the period of diuretic administration [2] which abolished the diuretic-induced rises in plasma angiotensin II and aldosterone concentrations. However, neither the acute natriuretic and kaliuretic responses nor the ensuing reductions in Na^+ and K^+ excretion in the compensation period were affected by captopril. There was a small fall in P_K of 0.18 mmol liter^{-1} over three days of furosemide administration with prazosin without a change in the difference between K^+ intake and K^+ excretion. This could represent a redistribution of K^+ into cells since there was an accompanying metabolic alkalosis (P_{HCO_3} rose by 1.6 mmol liter^{-1}). Alternatively, it could represent occult fecal K^+ losses (perhaps augmented by furosemide administration) which were not assessed in these studies.

Furosemide appears to have activated the sympathetic nervous system in these studies since there was a rise in the plasma norepinephrine or epinephrine concentrations in each protocol (Table 2). Direct recordings from renal nerves in conscious rats have shown a 50 to 80% increase after furosemide; this change was augmented by a high salt intake [14]. Activation of the sympathetic nervous system can be important for regulation of Na^+ excretion during hypovolemia. Thus, patients with progressive autonomic failure do not reduce Na^+ excretion even after one week of reduced Na^+ intake, whereas age-matched controls achieve Na^+ balance within four days [4, 5]. This defect in salt conservation was not corrected by mineralcorticosteroids but could relate to renal denervation, since rabbits with bilateral renal nerve section do not conserve Na^+ normally during dietary salt restriction [15]. Results from several studies indicate that enhanced Na^+ reabsorption accompanying low-level renal nerve stimulation or intrarenal norepinephrine infusion is blunted by inhibition of $alpha_1$ adrenoreceptors with prazosin [6–10, 16, 17]. In contrast, inhibition of $alpha_2$ adrenoreceptors with yohimbine, rauwolscine or idozoxan or of $beta_1$ or $beta_2$ adrenoreceptors with propranolol or atenolol either does not change, or even potentiates, the enhanced tubular Na^+ reabsorption in these experiments [6–10, 16, 17].

In the present study, after five days of prazosin administration, the subjects' standing MBP had fallen by 7% and their heart rate had increased by 15%. They were in neutral Na^+ balance before the diuretic was administered (Fig. 1) but at an increased body weight of 1 kg, presumably reflecting a period of fluid retention during the initial days of prazosin administration. A decrease in standing BP, accompanied by little change or a small increase in heart rate and body weight is characteristic of the established phase of prazosin treatment for hypertension [18, 19]. During prazosin, there were no concomitant changes in the plasma norepinephrine and epinephrine concentrations nor the PRA, but AII concentrations decreased by about 25% (Table 1). These results confirm previous studies of long-term treatment with prazosin for hypertension which have revealed little effect on PRA and catecholamine levels [18, 22]. However,

the cause for the fall in plasma AII concentrations without a fall in PRA is unclear.

The combination of lower levels of AII and aldosterone with fluid retention produced by prior prazosin administration might have potentiated the subsequent response to the diuretic. However, diuretic responsiveness, as assessed from the relationship betwen the rates of excretion of Na^+ and K^+ and the log of furosemide excretion [12], was unaltered by prazosin (Fig. 3). Moreover, prazosin did not alter the renal compensation following the short–term diuresis. It seems unlikely that the lack of a response to prazosin was due to inadequate $alpha_1$ adrenoreceptor blockade, since only 0.25 mg of prazosin given intravenously to human subjects leads to an 80% blockade of the pressor response to $alpha_1$ receptor agonists [21] and 13 mg day^{-1} blunts baroreflexes and cold pressor responses of hypertensive patients [22]. Although the half–life of prazosin is only 2.5 to 4 hours the antihypertensive action normally persists for about 10 hours [23, 24]. Thus, the six hour dose interval used in our study should have blocked $alpha_1$ adrenoreceptors throughout the 24 hours of the day. Moreover, the pressor response to infused norepinephrine was clearly attenuated four to six hours after prazosin in the one subject in which it was tested (Fig. 1). Furosemide elimination was unchanged by prazosin, which appears to exclude a major confounding pharmacokinetic interaction. Finally, the lack of an effect of prazosin could not be attributed to concurrent activation of the RAA system because furosemide–induced increases in PRA, AII and aldosterone concentrations were unaltered by prazosin, and concurrent administration of captopril with prazosin did not modify the acute or compensatory responses to furosemide. We, therefore, conclude that $alpha_1$ adrenoreceptors do not modulate the acute response to a loop diuretic in normal subjects receiving a liberal salt intake, nor do they mediate the period of Na^+ and K^+ retention that follows the acute diuresis. Consequently, $alpha_1$ adrenoreceptors are not an essential part of the mechanisms which maintain Na^+ and K^+ balances during diuretic administration in these settings.

In patients with hypertension, prazosin and occasionally captopril may cause fluid retention, perhaps because of a fall in BP [19]. Indeed, weight gain was seen in our normal subjects while they received prazosin (Table 1). However, the response to the subsequent administration of furosemide was not altered by the administration of the two blocking drugs.

Previously, we had found that the BP was maintained over a five hour period of furosemide diuresis, even during administration of captopril [2]. In the present study, the BP fell consistently five hours after furosemide when the diuretic was given with prazosin and captopril. However, the interpretation of this result is not clear because we found previously that captopril alone lowered BP [2], although this effect was not detected in the three normal subjects in this study who were also receiving prazosin.

The mechanisms which subserve reduced Na^+ and K^+ excretion in the post-diuretic phase, independent of $alpha_1$ receptors and the RAA system, have not been disclosed in these studies. Short–term volume depletion can enhance proximal fluid and Na^+ reabsorption [25, 26] and thereby reduce distal fluid delivery, which could limit K^+ secretion [13]. Alternatively, DeWardener [27] has proposed that diuretics evoke a prolonged inhibition of natriuretic hormone(s) which mediate the post-diuretic phase of renal Na^+ retention.

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