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An orally active adenosine A_1 receptor antagonist, FK838, increases renal excretion and maintains glomerular filtration rate in furosemide-resistant rats

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1 Loop and thiazide diuretics are common therapeutic agents for the treatment of sodium retention and oedema. However, resistance to diuretics and decreases in renal function can develop during diuretic therapy. Adenosine causes renal vasoconstriction, sodium reabsorption, and participates in the tubuloglomerular feedback mechanism for the regulation of glomerular filtration rate.

2 We tested the hypothesis that the selective adenosine A_1 receptor antagonist FK838 is orally active and causes diuresis and natriuresis, but maintains glomerular filtration rate in normal rats or in rats with furosemide resistance.

3 In normal male Sprague – Dawley rats, FK838 dose-dependently increased urine flow and sodium and chloride excretion while sparing potassium. In combination with furosemide, FK838 enhanced the diuretic and natriuretic actions of furosemide to the same extent as hydrochlorothiazide and did not increase the potassium loss in normal rats. In furosemide-resistant rats, FK838 increased urine flow and electrolyte excretion to a greater extent than hydrochlorothiazide. In addition, hydrochlorothiazide significantly decreased glomerular filtration rate, whereas FK838 maintained glomerular filtration rate in furosemide-resistant rats.

4 This study shows that the adenosine A_1 receptor antagonist FK838 is orally active and causes potent diuresis and natriuresis and maintains glomerular filtration rate in normal or furosemide-resistant rats. Adenosine A_1 receptor antagonists may be novel therapeutics for the treatment of oedema in normal or otherwise diuretic-resistant patients.
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Abbreviations: CPX, 8-cyclopentyl-1, 3-dipropylxanthine; CVT-124, 1,3-dipropyl-8-[2-(5, 6-epoxynorbornyl)] xanthine; DPCPX, 1,3-dipropyl-8-cyclopentylxanthine; FK838, 6-oxo-3-(2-phenylpyrazole(1,5-a)pyridin-3-yl)-(6 H)-pyridazinebutyric acid; FURO, furosemide; HCTZ, hydrochlorothiazide

Introduction

Sodium retention and oedema are common sequelae of patients with chronic renal failure, severe congestive heart failure, and decompensated cirrhosis (Schrier, 1988; Gottlieb, 2001). Diuretics such as furosemide (FURO) and hydrochlorothiazide (HCTZ) are frequently used in increasing doses or in combination for the treatment of fluid retention in these patients. However, the effectiveness of these diuretics can be limited due to the development of resistance (Wilcox, 2002). In addition, FURO can reduce glomerular filtration rate in patients with already compromised renal function (Gottlieb *et al*., 2002; Wilcox, 2002). Therefore, effective inhibition of sodium reabsorption without reducing renal function is therapeutically desirable in conditions such as chronic renal failure, congestive heart failure, and cirrhosis.

Adenosine is a nucleoside with both tubular and vascular actions in the kidney. Through activation of A_1 receptors, adenosine causes vasoconstriction of renal afferent arterioles (Munger & Jackson, 1994), sodium reabsorption in the proximal tubule (Knight *et al*., 1993), and participates in tubuloglomerular feedback (Schnermann *et al*., 1990). Inhibition of sodium reabsorption in the proximal tubule would be beneficial in diseases with volume retention such as chronic renal failure, severe congestive heart failure, and decompensated cirrhosis. However, the resulting increase in delivery of sodium and chloride to the macula densa in the thick ascending limb activates tubuloglomerular feedback, which causes a decrease in glomerular filtration rate. Induction of diuresis and natriuresis without causing the compensatory decrease in renal function would be beneficial in otherwise diuretic-resistant patients with volume overload. Blockade of adenosine A_1 receptors may provide such novel therapy.

FK838 is a competitive, selective adenosine A_1 receptor antagonist (Maemoto *et al*., 1997; Ito *et al*., 1999). Using radioligand-binding assays, FK838 is 181-fold more potent for A_1 than A_{2A} receptors, as determined in rat striatal membranes (Maemoto *et al*., 1997). In anaesthetized dogs, FK838 inhibits the decrease in renal blood flow induced by adenosine, but does not inhibit the adenosine-induced increase in coronary blood flow (Kusunoki *et al*., 1994). This study indicates that FK838 is functionally more selective for adenosine A_1 than A_2

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receptors *in vivo*. In an isolated, perfused renal afferent arteriole with macula densa attached preparation, FK838 blocked the tubuloglomerular feedback response to increased sodium chloride delivery to the distal tubule (Ren *et al*., 2002). These results suggest that FK838 may block the compensatory decrease in glomerular filtration rate during natriuresis. In the present study, we tested the hypothesis that blockade of adenosine A_1 receptors with FK838 causes diuresis and natriuresis and enhances the effect of FURO under normal conditions. We also tested the hypothesis that oral administration of FK838 increases water and electrolyte excretion without altering glomerular filtration rate in otherwise diuretic-resistant rats. In all studies, we compared the renal response to FK838 with FURO and HCTZ.

Methods

Animals

Procedures were approved by the Institutional Animal Care and Use Committee of GlaxoSmithKline Pharmaceuticals and were in accordance with NIH Guidelines for the care and use of animals.

Male Sprague – Dawley rats (250–400 g) were obtained from Charles River Labs (Rayleigh, NC, U.S.A.). They were housed in a light-controlled room with a 12 h light/dark cycle and were allowed *ad libitum* access to food and water. Rats in Groups 1 and 2 were maintained on standard rodent diet (5001, Purina Mills). To study the response during furosemide resistance, rats in Group 3 were maintained on low-salt diet (5700-B, Purina Mills) as previously established (Kahn *et al*., 1983). All studies were conducted using metabolism cages for the accurate, timed collection of urine. Blood was collected from the tail vein as needed.

Experimental protocols

Group 1: Dose–response to oral diuretic agents in normal rats The purpose of this series was to determine the renal excretory response to oral administration of FK838 (0.03, 0.1, 0.3, 1, 3, 10, 30, 100 mg kg^{-1}, gavage) in normal rats ($n=12$ each dose). These responses were compared to the renal excretory responses in rats gavaged with either vehicle (0.5% methyl cellulose, $n=26$), FURO (1, 3, 10, 30, 100 mg kg^{-1}, $n=12$ each dose), or HCTZ (0.03, 0.3, 3, 30, 100 mg kg^{-1}, $n=12$ each dose). The protocol for the acute evaluation of oral diuretic agents in normal rats has been previously published (Rao & Fonteles, 1991; Humphrey, 1995). Briefly, all rats were housed in metabolic cages (two rats/cage) for at least 2 days prior to study for acclimitization. Rats were fasted overnight and deprived of water for 90 min before and during the study. At the beginning of the experiment, all rats were gavaged with 25 ml kg^{-1} 0.9% NaCl containing vehicle or a dose of FURO, HCTZ, or FK838 to ensure that fluid and electrolyte homeostasis were maintained throughout the study. Urine was collected for 4 h and electrolyte concentrations were measured.

Group 2: Combined oral administration of diuretic agents in normal rats Since increasing the dose of a diuretic also increases the likelihood of toxicity, it is common clinical practice to use diuretics in combination when a single diuretic is not effective. Therefore, the purpose of this series was to compare the renal excretory response of FURO + FK838 or FURO + HCTZ to FURO alone. The doses used in this series were equivalent to the ED_{50} of the diuretic responses to FURO (20 mg kg^{-1}), HCTZ (2 mg kg^{-1}), and FK838 (1 mg kg^{-1}), which were determined from studies in Group 1. All rats were housed in metabolic cages (two rats/cage) for at least 2 days prior to study. Rats were fasted overnight and deprived of water for 90 min before and during the study. At the beginning of the study, rats ($n=12$ each group) were gavaged with 25 ml kg^{-1} 0.9% NaCl containing vehicle, FURO, HCTZ, FK838, FURO + FK838, or FURO + HCTZ. Urine was collected for 4 h and electrolyte concentrations were measured.

Group 3: Oral diuretic agents in furosemide-resistant rats The purpose of this series was to determine the renal excretory and glomerular filtration rate responses to FK838 compared to HCTZ in an animal model of diuretic resistance. As previously described (Kahn *et al*., 1983), 4 days of FURO treatment (10 mg kg^{-1} day^{-1}, i.p.) in rats causes significant diuresis and natriuresis on the first day of treatment, but renal excretion returns to basal levels by the third day. As renal excretion is similar to baseline after 3 and 4 days of repeated FURO, the renal resistance to FURO is clearly present at this time. Therefore, we used this animal model of furosemide resistance to evaluate the renal response to FK838 or HCTZ. Rats were divided into three groups ($n=6$ in each group): FURO + vehicle, FURO + HCTZ, or FURO + FK838. Rats were housed in metabolic cages (one rat/cage) for at least 4 days prior to study for acclimitization. During the following 4-day control period, all rats were daily administered vehicle (1.0 ml, 0.9% saline, i.p.) and 24-h urine was collected. On the fourth day, glomerular filtration rate was determined. After control, FURO (10 mg kg^{-1} day^{-1}, i.p.) was administered to all rats for 4 days. On the fourth day of FURO administration, rats were also gavaged with either vehicle, FK838 (30 mg kg^{-1}), or HCTZ (30 mg kg^{-1}). Daily, 24-h urine was collected during FURO administration and glomerular filtration rate was determined on the fourth day.

Data analysis

Urinary and plasma concentrations of electrolytes and creatinine were measured by an Olympus AU640 Clinical Analyzer. Glomerular filtration rate was determined from the 24-h renal clearance of creatinine. Clearance and excretion rates were calculated using standard formulas.

Data are reported as mean ± s.e.m. One-way analysis of variance (ANOVA) followed by Newman – Keuls multiple comparison test were used to evaluate the excretion responses between treatments in Groups 1 and 2. Overall significance of results in Group 3 was determined using two-way ANOVA with repeated measures. To evaluate the differences between treatments in the same period, one-way ANOVA followed by Newman – Keuls test were used. $P<0.05$ was considered to be statistically significant.

Drugs

FK838 provided by Fujisawa Pharmaceutical Co., Ltd was used. FK838, HCTZ, and FURO (Sigma-Aldrich Co., U.S.A.) were dissolved in 0.5% w w^{-1} methyl cellulose vehicle for oral

administration. FURO was dissolved in 0.9% saline vehicle for intraperitoneal injection.

Results

Group 1 Dose–response to oral diuretic agents in normal rats

The renal excretory responses to vehicle, FK838, FURO, or HCTZ are summarized in Table 1. FK838, HCTZ, and FURO dose-dependently increased urine flow, sodium excretion, and chloride excretion in normal rats. FK838 ($\geqslant 0.3\,mg\,kg^{-1}$) significantly increased urine flow by 46–116%, HCTZ ($\geqslant 3\,mg\,kg^{-1}$) significantly increased urine flow by 63–100%, and FURO ($\geqslant 10\,mg\,kg^{-1}$) significantly increased urine flow by 78–249%. A significant diuresis occurred at lower doses of compound in rats treated with FK838 ($ED_{50} = 1\,mg\,kg^{-1}$) than with HCTZ ($ED_{50} = 2\,mg\,kg^{-1}$) or FURO ($ED_{50} = 20\,mg\,kg^{-1}$); however, FURO had a larger maximal effect than FK838 or HCTZ. Sodium excretion was significantly increased by 78–157% in rats treated with FK838 ($\geqslant 3\,mg\,kg^{-1}$) and by 90–136% in rats treated with HCTZ ($\geqslant 3\,mg\,kg^{-1}$) with no change in rats treated with FURO ($3\,mg\,kg^{-1}$). Higher doses of FURO ($\geqslant 30\,mg\,kg^{-1}$) significantly increased sodium excretion by 190–269%. Chloride excretion was significantly increased by 73–107% in rats treated with HCTZ ($\geqslant 3\,mg\,kg^{-1}$), but remained at vehicle levels in rats treated with FURO ($3\,mg\,kg^{-1}$) or FK838 ($3\,mg\,kg^{-1}$). FURO ($\geqslant 10\,mg\,kg^{-1}$) or FK838 ($\geqslant 10\,mg\,kg^{-1}$) significantly increased chloride excretion by at least 71% and 56%, respectively. FURO ($\geqslant 30\,mg\,kg^{-1}$) caused significantly greater renal excretion of sodium and chloride than FK838 or HCTZ at equivalent doses. There were no significant changes in potassium excretion in rats treated with FK838 or HCTZ. However, FURO ($30\,mg\,kg^{-1}$) significantly increased potassium excretion by 135% compared to vehicle. In the FURO-treated groups, only half of the rats responded with kaliuresis at each dose, which contributed to the variability and lack of significant difference at lower doses of FURO.

Group 2: Combined oral administration of diuretic agents in normal rats

The renal excretory responses to combined oral administration of diuretic agents in normal rats are summarized in Table 2. FK838, FURO + FK838, and FURO + HCTZ significantly increased urine flow, sodium excretion, and chloride excretion compared to rats treated with FURO alone. FK838, FURO + FK838, and FURO + HCTZ significantly increased urine flow by 21, 47, and 44%, respectively. HCTZ significantly increased sodium (39%) and chloride (18%) excretions with no major effect on urine flow compared to FURO alone. FK838, HCTZ, FURO + FK838, and FURO + HCTZ significantly increased sodium excretion by 46, 39, 62, and 63%, respectively, and chloride excretion by 15, 18, 42, and 51%, respectively, compared to FURO alone. Addition of FK838 or HCTZ to FURO did not significantly change potassium excretion compared to FURO treatment alone. The body weight remained unchanged during the study and was higher than rats in Group 1. The difference in age/body weight may have contributed to the lower urine flow response to vehicle and larger electrolyte excretory response to FK838 in Group 2.

Group 3: Oral diuretic agents in furosemide-resistant rats

The renal responses to vehicle, FK838, or HCTZ in furosemide-resistant rats are summarized in Figures 1–3. As shown in these figures, there were no significant differences during control conditions (Control) between groups of rats.

Table 1 Does – response (4-h) to vehicle, FK838, hydrochlorothiazide (HCTZ), or furosemide in normal rats (Group 1)

Treatment	*Dose* ($mg\,kg^{-1}$)	*UF* ($\mu l\,h^{-1}\,100\,g^{-1}$)	*UnaV* ($\mu mol\,h^{-1}\,100\,g^{-1}$)	*UKV* ($\mu mol\,h^{-1}\,100\,g^{-1}$)	*UC1 V* ($\mu mol\,h^{-1}\,100\,g^{-1}$)
Vehicle	—	403±33	42±5	23±4	55±7
FK838	0.03	412±42	26±8	8±1	31±9
	0.1	495±20	31±7	7±1	32±7
	0.3	588±21*	44±11	11±1	50±12
	1	648±17*	47±8	11±1	52±8
	3	749±42*†	75±12*†	14±1	76±11
	10	669±37*	96±5*†	18±2	104±4*
	30	795±56*†	78±8*†	23±2†	86±7*†
	100	870±55*†	108±9*†	26±2	114±4*†
HCTZ	0.03	364±58	42±7	12±2	50±8
	0.3	517±48	34±5	12±1	44±5
	3	657±27*	95±4*†	22±1	114±4*†
	30	806±30*†	80±3*†	20±1†	95±3*†
	100	722±25*†	99±4*†	24±2	113±4*†
Furosemide	1	496±40	41±5	36±12	60±9
	3	516±61	30±8	40±15	48±15
	10	716±45*	58±7	42±11	94±13*
	30	1265±55*	122±9*	54±13*	169±15*
	100	1405±68*	155±7*	44±4	200±8*

The renal excretory response to each dose of treatment was determined in separate groups of rats ($n = 12$ in each dose). Urine flow (UF), sodium excretion (UNaV), potassium excretion (UKV), chloride excretion (UC1 V). *$P < 0.05$ vs vehicle. †$P < 0.05$ vs furosemide at the same dose.

Table 2 Renal excretory response (4-h) to combination treatment in normal rats (Group 2)

Treatment	*Dose* ($mg\,kg^{-1}$)	*UF* ($\mu l\,h^{-1}\,100\,g^{-1}$)	*UNaV* ($\mu mol\,h^{-1}\,100\,g^{-1}$)	*UKV* ($\mu mol\,h^{-1}\,100\,g^{-1}$)	*UC1 V* ($\mu mol\,h^{-1}\,100\,g^{-1}$)
Vehicle	–	280±44*	41±5*	12±3*	52±7*
Furosemide	20	553±17	71±4	20±1	98±3
FK838	1	671±38*	104±6*	15±1	113±6*
HCTZ	2	609±24	99±3*	17±2	116±3*
Furosemide	20				
+FK838	1	813±25*	115±3*	21±1	139±2*
Furosemide	20				
+HCTZ	2	796±29*	116±3*	26±2	148±5*

The renal excretory response to treatment was determined in six separate groups of rats ($n=12$ in each treatment group). Hydrochlorothiazide (HCTZ), urine flow (UF), sodium excretion (UNaV), potassium excretion (UKV), chloride excretion (UC1 V). *$P<0.05$ vs furosemide.

During the first 2 days of FURO administration alone (Furo 1, Furo 2), urine flow, sodium excretion, and chloride excretion increased significantly from Control by at least three-fold. Furo 1 and Furo 2 minimally increased potassium excretion similarly in rats allocated to the vehicle (13%) and HCTZ (20%) groups, but significantly increased potassium excretion by 50% in rats allocated to the FK838 group. On the third day of FURO administration alone (Furo 3), urine flow returned to Control, and sodium, chloride and potassium excretions were decreased from Control. On the fourth day of FURO administration when combination treatment (Combo) was evaluated, FK838 significantly increased urine flow and chloride excretions by six-fold, sodium excretion by eight-fold, and potassium excretion by 43% in furosemide-resistant rats. HCTZ significantly increased urine flow, sodium excretion, and chloride excretion by three-fold with no effect on potassium excretion. Vehicle did not increase urine flow or electrolyte excretion in furosemide-resistant rats. FK838 caused significantly greater urine flow and electrolyte excretion than either vehicle or HCTZ in furosemide-resistant rats. The 24-h responses to vehicle, FK838, or HCTZ were similar to the responses after 2 h of dosing (data not shown). In association with these changes in renal excretion, HCTZ significantly decreased glomerular filtration rate by 42%. In contrast, vehicle or FK838 maintained glomerular filtration rate at Control in furosemide-resistant rats. Body weight did not significantly change after Combo treatment (FURO + vehicle: 5±1%, FURO + HCTZ: 14±6%, FURO + FK838: 16±1%).

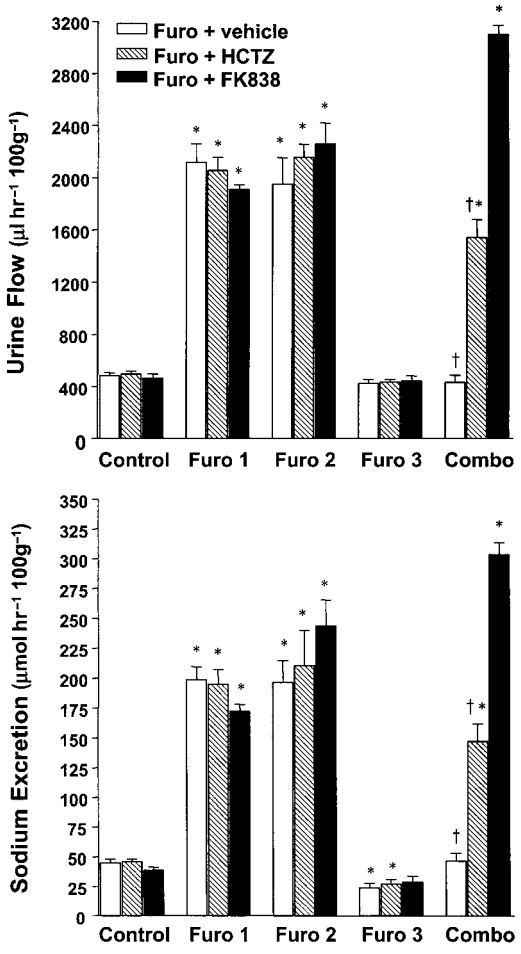

Figure 1 Effect of oral administration of vehicle, HCTZ ($30\,mg\,kg^{-1}$), or FK838 ($30\,mg\,kg^{-1}$) on urine flow and sodium excretion in furosemide-resistant rats (Group 3). Excretions were determined in three separate groups ($n=6$ each) of rats (Furo + vehicle, Furo + HCTZ, Furo + FK838) during control conditions (Control), 3 consecutive days of furosemide administration alone (Furo 1, Furo 2, Furo 3), followed by a fourth day of combination treatment (Combo) with either vehicle (Furo + vehicle), FK838 (Furo + FK838), or hydrochlorothiazide (Furo + HCTZ). *$P<0.05$ compared to Control. †$P<0.05$ compared to FK838 during the same period.

Discussion

The results from this study show that a selective adenosine A_1 receptor antagonist is orally active and causes significant diuresis and natriuresis under normal conditions and during furosemide resistance. FK838 significantly increased urine flow and sodium and chloride excretion without altering potassium excretion in normal rats. This effect was similar to HCTZ, but markedly improved compared to FURO (20, $30\,mg\,kg^{-1}$), which significantly increased potassium as well as sodium and chloride excretions. When used acutely in combination with FURO, FK838 significantly enhanced the

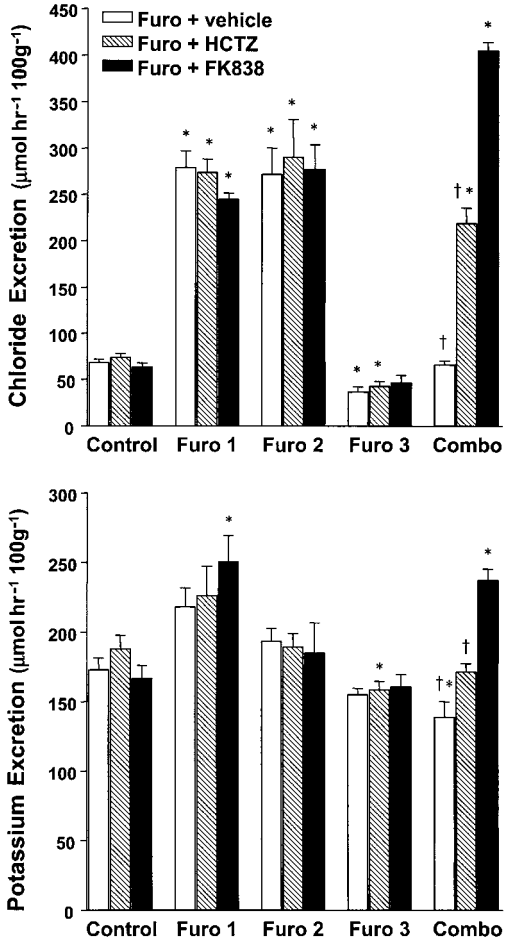

Figure 2 Effect of oral administration of vehicle, HCTZ (30 mg kg^{-1}), or FK838 (30 mg kg^{-1}) on chloride and potassium excretions in furosemide-resistant rats (Group 3). Excretions were determined in three separate groups ($n=6$ each) of rats (Furo + vehicle, Furo + HCTZ, Furo + FK838) during control conditions (Control), three consecutive days of furosemide administration alone (Furo 1, Furo 2, Furo 3), followed by a fourth day of combination treatment (Combo) with either vehicle (Furo + vehicle), FK838 (Furo + FK838), or hydrochlorothiazide (Furo + HCTZ). *$P<0.05$ compared to Control. †$P<0.05$ compared to FK838 during the same period.

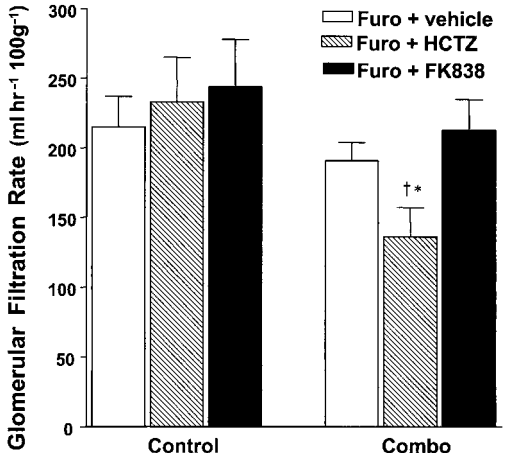

Figure 3 Effect of oral administration of vehicle, HCTZ (30 mg kg^{-1}), or FK838 (30 mg kg^{-1}) on glomerular filtration rate in furosemide-resistant rats (Group 3). Glomerular filtration rate was determined in all rats ($n=6$ in each treatment) during control conditions (Control) and after administration (Combo) of either furosemide + vehicle (Furo + vehicle), Furo + FK838, or Furo + HCTZ. *$P<0.05$ compared to Control. †$P<0.05$ compared to FK838 during the same period.

diuretic and natriuretic activity of FURO and minimally increased potassium excretion by 5%. HCTZ similarly enhanced the diuretic and natriuretic activity of FURO, while modestly increasing potassium excretion by 30%. The ability of FK838 to enhance the diuretic and natriuretic effect of FURO without further increasing potassium loss is an important observation, since several studies show that the combined use of loop and thiazide diuretics can result in hypokalaemia and potentially serious side effects (Knauf & Mutschler, 1995; Dormans & Gerlag, 1996).

The renal excretory response to oral administration of FK838 in the present study is similar to those previously reported for intravenous infusion of an adenosine A_1 receptor antagonist in normal rats (Knight *et al*., 1993; Munger & Jackson, 1994; Gellai *et al*., 1998; Wilcox *et al*., 1999), dogs (Yamagata *et al*., 1994), and man (Gottlieb *et al*., 1999; Gottlieb *et al*., 2002). These studies show that acute intravenous infusion of CVT-124 (Gellai *et al*., 1998; Gottlieb *et al*., 2002), CPX (Knight *et al*., 1993), or DPCPX (Zou *et al*., 1999) significantly increased urine flow and sodium excretion but did not alter potassium excretion. In contrast, intravenous infusion of FURO or HCTZ markedly increased urine flow, sodium excretion, and potassium excretion in normal rats (Gellai *et al*., 1998). In the same study, Gellai *et al*. (1998) also demonstrated that intravenous infusion of CVT-124 in combination with FURO enhanced the diuretic and natriuretic responses but not the kaliuretic response to FURO. However, intravenous infusion of HCTZ + FURO significantly increased urine, sodium, and potassium excretion compared to FURO infusion alone. In the present study, there was a tendency for FURO + HCTZ to increase potassium excretion, but no significant effect was found. The different potassium excretion responses between the present and previous combination studies may be due to the differences in administered dose of FURO + HCTZ or amount of diuresis and natriuresis that occurred.

The results from our studies in normal rats and the unique mechanism of action suggest that adenosine A_1 receptor antagonism may be effective during diuretic resistance. Therefore, we determined the renal excretory and glomerular filtration rate responses to FK838 in furosemide-resistant rats. The results show that FK838 significantly increased urine flow, sodium, chloride, and potassium excretions to a greater extent than HCTZ in furosemide-resistant rats. The enhanced potassium excretion response to FK838 is likely due to the larger distal flow rate, which is a major stimulus for potassium secretion (Good & Wright, 1979). Since adenosine not only stimulates sodium reabsorption in the proximal tubule, but also is a major component in tubuloglomerular feedback, we evaluated whether the compensatory decrease in glomerular filtration rate during marked diuresis and natriuresis would be eliminated during adenosine A_1 receptor blockade. We have demonstrated that addition of the thiazide diuretic significantly decreased glomerular filtration rate, while FK838 maintained normal glomerular filtration rate in furosemide-

resistant rats. This effect is remarkable, considering the stimulus for tubuloglomerular feedback and resulting decrease in glomerular filtration rate was significantly greater in FK838-treated rats (eight-fold increase in sodium excretion, six-fold increase in chloride excretion) than in HCTZ-treated rats (three-fold increase in sodium and chloride excretions). Indeed, previous studies report that intravenous infusion of an adenosine A_1 receptor antagonist has no effect or increases glomerular filtration rate in normal rats (Munger & Jackson, 1994; Gellai *et al*., 1998; Wilcox *et al*., 1999). In humans with congestive heart failure, inhibition of adenosine A_1 receptors has no effect on glomerular filtration rate (Gottlieb *et al*., 1999) and prevents furosemide-induced reductions in glomerular filtration rate (Gottlieb *et al*., 2002).

In summary, FK838 is a potent, orally active adenosine A_1 receptor antagonist with the ability to cause marked diuresis and natriuresis in normal and furosemide-resistant rats. Whereas a thiazide diuretic reduced glomerular filtration rate in association with the diuresis and natriuresis, FK838 maintained glomerular filtration rate in furosemide-resistant rats. The present study suggests that adenosine A_1 receptor antagonists may be novel therapeutic agents for the treatment of patients with sodium retention and oedema. In addition, because of its unique mechanism of action, these therapeutics may be effective without reducing renal function in otherwise diuretic-resistant patients.

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