Diuretic Effects of KW-3902, a Novel Adenosine A_1-Receptor Antagonist, in Various Models of Acute Renal Failure in Rats

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ABSTRACT—Using various models of acute renal failure (ARF) in rats, the diuretic effects of 8-(noradamantan-3-yl)-1,3-dipropylxanthine (KW-3902), a novel adenosine A_1-receptor antagonist (0.01 and 0.1 mg/kg, p.o.), were determined and compared with those of furosemide (30 mg/kg, p.o.) and trichlormethiazide (TCM; 1 mg/kg, p.o.). In cisplatin-induced ARF rats, KW-3902 and TCM, but not furosemide, increased Na excretion. KW-3902 did not affect creatinine clearance (C_{CRE}), while TCM decreased C_{CRE}. In gentamicin-induced ARF rats, KW-3902 increased urine volume (UV) and Na excretion. In glycerol-induced oliguric ARF rats, KW-3902, but not furosemide or TCM, increased UV, Na and K excretion and tended to improve the depressed C_{CRE}, suggesting that the improvement of renal hemodynamics might also contribute to the diuretic effect of KW-3902. In glycerol-induced polyuric ARF rats, only KW-3902 significantly increased UV and Na excretion. These results demonstrate that KW-3902 induces natriuretic effects in various models of ARF and that the effect of KW-3902 is more prominent than those of furosemide and TCM. The present results suggest that endogenous adenosine may be involved in various forms of ARF via adenosine A_1-receptors.

Keywords: KW-3902, Adenosine A_1-receptor antagonist, Diuretic effect, Acute renal failure

Diuretics are clinically prescribed for the treatment of edema associated with congestive heart failure, hepatic cirrhosis and various renal diseases. However, when diuretics are used for the patients with renal diseases, especially for those with acute or chronic renal failures, their efficacy cannot sufficiently be achieved in many cases, because the renal tubule, or the site of action of diuretics, is damaged in such patients (1). Acute renal failures (ARF) are classified into two types: the oliguric one that shows oliguria, and the non-oliguric one that maintains a urinary volume of more than 500 ml/day but exhibits a rise in serum creatinine (S-CRE). Patients with oliguric renal failures usually are treated with diuretics, such as loop diuretics or mannitol, for accelerating urination, since thiazides, aldosterone antagonists and carbonic anhydrase inhibitors are scarcely effective in such patients in general (2). Some investigators have suggested that therapy with furosemide in large doses may significantly improve the clinical course of acute renal failure (3, 4), although such therapy sometimes causes side effects, such as loss of hearing.

KW-3902 (8-(noradamantan-3-yl)-1,3-dipropylxanthine) is a newly synthesized and selective adenosine A_1-receptor antagonist, which is the most potent one reported to date (5). In the receptor-binding study, the dissociation constant values of KW-3902 for adenosine A_1-receptor and A_2-receptor are 1.3 nM and 380 nM, respectively (5, 6). In anesthetized rats, KW-3902 antagonizes the 5'-*N*-ethycarboxamidoadenosine (NECA)-induced bradycardic response mediated via adenosine A_1-receptors, with little influence on the NECA-induced hypotensive response mediated via adenosine A_2-receptors (7). In saline-loaded normal rats, blockade of adenosine A_1-receptors with KW-3902 induces significant increases of urine volume and sodium excretion with little change of potassium excretion (7, 8). From the results of a Li clearance study and the stop-flow method, KW-3902 is assumed to act mainly on the proximal tubule, resulting in diuresis and natriuresis (8). Additionally, we previously reported that KW-3902 possesses renal protective effects against glycerol- or cisplatin-induced ARF (7, 9). Thus, the diuretic and renal protective effects of KW-3902 have been ascribed to the blockade of adenosine A_1-receptors.

In the present study, to examine the effects of diuretics

on the established ARF, the diuretic effects of KW-3902 were determined and compared with those of furosemide and trichlormethiazide (TCM) in rats with ARF induced by cisplatin, gentamicin or glycerol.

MATERIALS AND METHODS

Animals

Male Wistar rats, weighing 170–300 g (Japan Shizuoka Laboratory Animal Center, Inc., Hamamatsu), were used in the present study. All animals received humane care in compliance with the "Guiding Principles for the Care and Use of Laboratory Animals" formulated by the Japanese Pharmacological Society and the protocol was approved by the Bioethical Committee of Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd. The animals were kept at 22℃ with a 12-hr light-dark cycle. They had free access to tap water and commercial chow.

Drugs used

KW-3902 (8-(noradamantan-3-yl)-1,3-dipropylxanthine) and furosemide were synthesized in our laboratories. TCM and gentamicin sulfate were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Cisplatin (Randa®) was purchased from Nihon Kayaku Co., Ltd. (Tokyo). All other chemicals and solvents were used in their analytically pure form. For oral administration, KW-3902 (0.01 and 0.1 mg/kg), furosemide (30 mg/kg) and TCM (1 mg/kg) were suspended in saline containing 0.05% Tween 80.

Diuretic effects in normal rats

Diuretic effects of drugs in normal rats were determined with a slight modification of the previous method (10). In brief, rats were fasted for 18 hr, and the drug suspension or the vehicle was orally administered to the rat at a volume of 25 ml/kg. After the administration, the rats were housed individually in metabolic cages without food and water. Urine was collected for 4 hr, and its volume was measured. The concentrations of sodium and potassium in the urine were measured by a flame photometer (775-A; Hitachi Ltd., Tokyo), and the urinary excretions of sodium and potassium were calculated.

Induction of ARF

Cisplatin-induced ARF: Cisplatin-induced ARF was produced according to the previous method (11). Cisplatin at 4 mg/kg was intravenously injected to rats through the tail vein. Ninety-six hours after the cisplatin injection, the rats, which had been fasted for 18 hr, were used for the experiment.

Gentamicin-induced ARF: The gentamicin-induced ARF was produced by the previously described method (12). Gentamicin sulfate was injected subcutaneously to rats at 200 mg/kg/day for 5 days. On the 9th day from the beginning of the administration, the rats, which had been fasted for 18 hr, were used for the experiment.

Glycerol-induced ARF (oliguric model): Glycerol-induced ARF was produced by the previously described method (13–15). To rats kept away from water overnight, 50% (v/v) glycerol was subcutaneously injected at 8 ml/kg under ether anesthesia. Ninety minutes after glycerol injection, 10 ml/kg of water was given orally, and the experiment was started 3 hr later.

Glycerol-induced ARF (polyuric model): The rats were injected with glycerol as described above. For 6 hr after the glycerol administration, the rats had free access to tap water and commercial chow. Twenty four hours later, the rats, which had been fasted for 18 hr, were used for the experiment.

Diuretic effects in rats with ARF

Before the evaluation of the diuretic effect in each ARF rat, a blood sample was collected from the tail vein, and S-CRE was measured with an autoanalyzer (AU510; Olympus, Tokyo). From the obtained value of S-CRE, an index of renal failure, the rats were divided into 5 groups, and the diuretic effects of the test compound were determined in the same way as described for the normal rats. After obtaining urine, the blood was collected from the abdominal descending aorta under ether anesthesia, and the serum was separated. S-CRE, serum urea nitrogen (S-UN) and urinary creatinine (U-CRE) were measured with the autoanalyzer. As an index of glomerular filtration rate (GFR), creatinine clearance (C_{CRE}), was calculated by the following standard formula:

$$C_{CRE}\ (\mathrm{l/kg/4\ hr}) = \frac{\text{U-CRE (mg/dl)} \times \text{Urinary volume (ml/kg/4 hr)}}{\text{S-CRE (mg/dl)} \times 1000}$$

Preparation and staining of renal tissue slices

The left kidney in the control group of each ARF model was excised for histopathological examination. The excised kidney was fixed in 10%-formalin-buffered solution (pH 7.25), embedded in paraffin routinely and sliced about 3 μm in thickness by a microtome. After they were stained with hematoxylin/eosin, the slices were observed under an optical microscope (FX-A model; Nikon, Tokyo).

Statistic analyses

All the results are given as means±S.E. To define statistically significant differences among the groups, the data were subjected to Student's t, the Aspin-Welch test, or analysis of variance (ANOVA) followed by the Dunnett or Steel test. A P value of less than 0.05 was consi-

dered to be statistically significant.

RESULTS

Diuretic effects in normal rats

Table 1 shows the diuretic effects of the three test compounds in normal rats. Urinary volume was significantly increased with KW-3902 (0.01, 0.1 mg/kg, p.o.), furosemide (30 mg/kg, p.o.) and TCM (1 mg/kg, p.o.), as compared with that in the control group. Excretion of sodium increased significantly in all the drug-treated groups. Furosemide and TCM, but not KW-3902, significantly increased potassium excretion.

Rats with cisplatin-induced ARF

Intravenous injection of cisplatin at 4 mg/kg significantly increased S-CRE and S-UN and nearly halved C_{CRE}. Treatment with cisplatin had no influence on the urinary volume but decreased potassium excretion. The histopathological examination revealed damages at the renal cortico-medullary junction following the administration of cisplatin in rats. The cortico-medullary junction includes the straight portion of the proximal tubule, Henle's loop, the straight portion of the distal tubule, and the collecting duct. Focal necrosis and degeneration of tubular epithelium were observed mainly at the proximal tubule (Fig. 1).

Table 2 shows the effects of the test compounds in rats with cisplatin-induced ARF. TCM significantly increased urinary volume. KW-3902 and TCM significantly increased sodium excretion; however, potassium excretion was significantly increased only with TCM. The Na/K ratio was significantly elevated following the injection of cisplatin, and this was further elevated by the administration of KW-3902 at 0.01 mg/kg. All three compounds scarcely influenced S-CRE and S-UN. C_{CRE} scarcely changed in the KW-3902 group, tended to fall in the furosemide group and significantly fell in the TCM group, as compared with the control group.

Rats with gentamicin-induced ARF

Subcutaneous consecutive administration of gentamicin (200 mg/kg/day) for 5 days significantly increased S-CRE and S-UN and reduced C_{CRE} to about 1/5. Gentamicin increased urinary volume but decreased sodium excretion. In the histological examination, epithelial necrosis and degeneration were observed at the proximal tubule and at a part of the distal tubule, respectively (Fig. 1). Significant necrosis or degeneration was not observed at the glomerular area.

Table 1. Effects of KW-3902, furosemide and trichlormethiazide (TCM) in normal rats

Drugs	Dose (mg/kg, p.o.)	n	Urinary volume (ml/kg/4 hr)	Na excretion (mEq/kg/4 hr)	K excretion (mEq/kg/4 hr)	Urine Na/K ratio
Control		7	15.9±2.2	2.23±0.23	1.05±0.12	2.16±0.09
KW-3902	0.01	7	29.3±0.9**	4.23±0.10**	1.26±0.09	3.46±0.25**
	0.1	7	30.1±1.0***	4.24±0.12**	1.22±0.07	3.53±0.18**
Control		7	10.9±1.0	1.82±0.20	0.77±0.05	2.35±0.15
Furosemide	30	7	43.9±2.1**	6.31±0.23**	1.62±0.09**	3.94±0.17**
TCM	1	6	24.7±0.9**	4.01±0.01**	1.35±0.10**	3.04±0.20*

Each value is the mean±S.E. *,**: Significantly different from the control at $P<0.05$ and 0.01, respectively.

Table 2. Effects of KW-3902, furosemide and trichlormethiazide (TCM) in rats with cisplatin-induced acute renal failure

Drugs	Dose (mg/kg, p.o.)	n	S-CRE (mg/dl)	S-UN (mg/dl)	C_{CRE} (l/kg/4 hr)	Urinary volume (ml/kg/4 hr)	Na excretion (mEq/kg/4 hr)	K excretion (mEq/kg/4 hr)	Urine Na/K ratio
Normal		5	0.43±0.01**	13.2±0.5**	1.10±0.07**	20.5±2.2	28.5±0.19	2.23±0.17**	1.28±0.05**
Control		8	1.22±0.13	41.7±5.5	0.47±0.04	20.8±1.5	3.20±0.12	0.72±0.02	4.50±0.27
KW-3902	0.01	8	1.21±0.06	36.9±2.8	0.48±0.02	24.7±1.4	4.14±0.23*	0.75±0.03	5.56±0.29*
	0.1	8	1.27±0.14	40.5±5.1	0.46±0.02	25.2±1.5	4.05±0.01**	0.78±0.06	5.41±0.36
Furosemide	30	8	1.24±0.11	39.1±3.7	0.38±0.03	21.1±1.8	3.11±0.26	0.75±0.05	4.15±0.21
TCM	1	8	1.51±0.08	46.7±3.8	0.33±0.03*	28.5±1.7*	4.50±0.26**	0.88±0.06*	5.20±0.30

Each value is the mean±S.E. C_{CRE}=renal clearance of creatinine. *,**: Significantly different from the control at $P<0.05$ and 0.01, respectively.

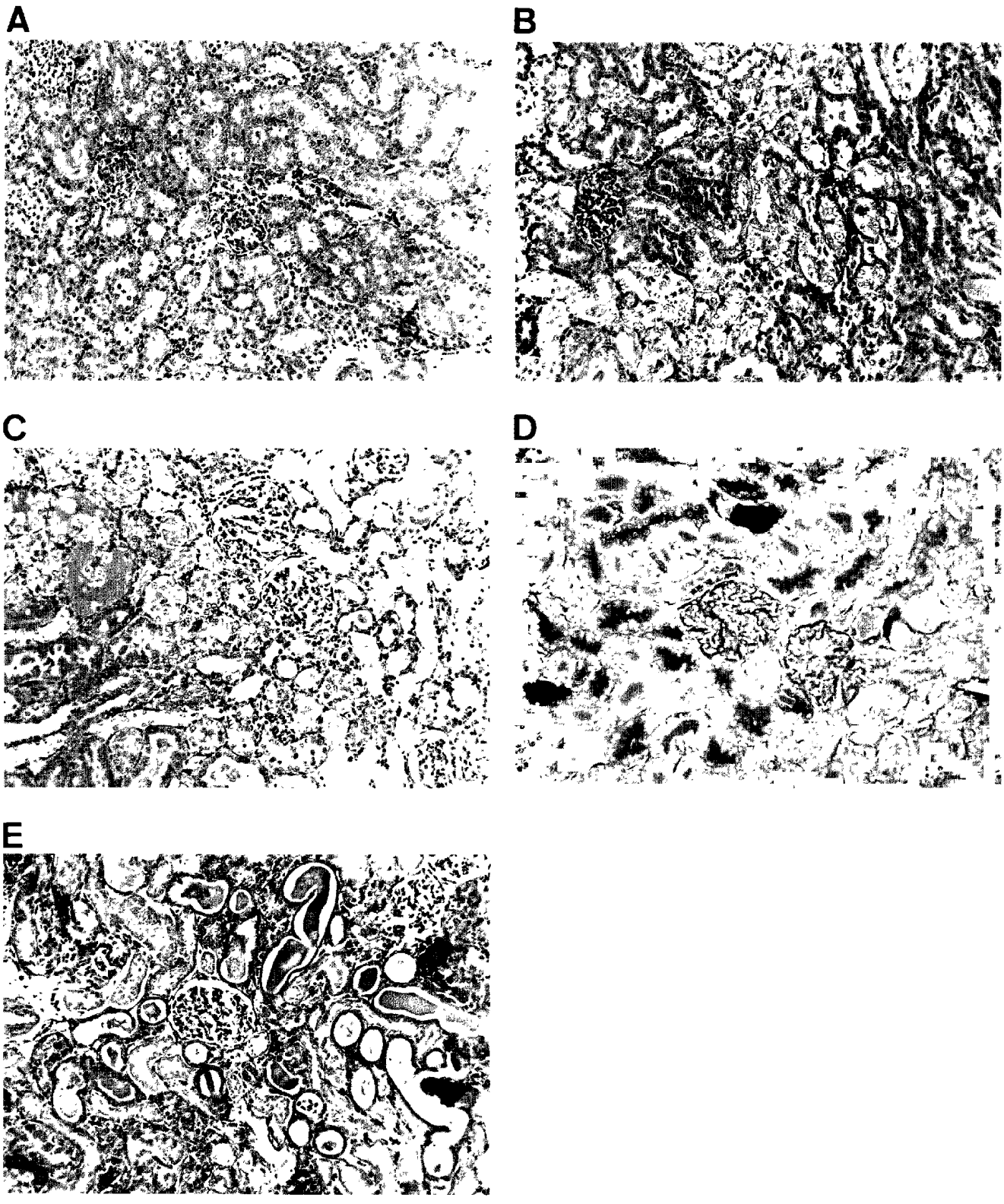

Fig. 1. Light microphotographs of the kidney from normal (A), cisplatin-induced acute renal failure (ARF) (B), gentamicin-induced ARF (C), glycerol-induced oliguric ARF (D) and glycerol-induced polyuric ARF (E) rats. Scale bar = 100 μm.

Table 3 shows the effects of the test compounds. Only KW-3902 significantly increased urinary volume and sodium excretion. The Na/K ratio, which had been significantly reduced following the injection of gentamicin, was significantly increased by the administration of KW-3902. None of the compounds had any significant influence on S-CRE, S-UN or C_{CRE}.

Rats with glycerol-induced ARF (oliguric model)

In 3 of 7 rats of the control group, no urine was excreted during the experiment, indicating that the oliguric condition was induced. Thus, C_{CRE} apparently became nearly zero. In the histological examination, eosinophilic materials formed casts in the tubular lumen. At the tubular epithelium, the increase of hyalin droplets was observed, and degeneration and necrosis were observed focally. At the glomerular area, congestion of the capillary was observed (Fig. 1).

Table 4 shows the effects of the test compounds in rats with glycerol-induced oliguric ARF. Urinary volume in the rat treated with KW-3902 was significantly increased, almost to that in normal rats. KW-3902 significantly increased sodium excretion and, at the same time, it also increased potassium excretion. In the rats treated with KW-3902 at 0.1 mg/kg, the increase of S-CRE and S-UN was significantly attenuated. C_{CRE} was significantly increased in the rats treated with KW-3902 at 0.01 mg/kg. On the other hand, the diuretic effects of furosemide and TCM were slight, although in the rats treated with furosemide, the increase of S-CRE was significantly attenuated.

Rats with glycerol-induced ARF (polyuric model)

At 24 hr after subcutaneous injection of glycerol, S-CRE and S-UN significantly increased, and C_{CRE} fell to about 1/10. Urinary volume and sodium excretion were increased by the glycerol administration. In the histological examination, no significant change was observed at the glomerular area; however, degeneration was widely scattered at the renal tubule (Fig. 1). Especially, epithelial necrosis and protein casts were observed at the proximal tubule in the whole cortical area.

Table 5 shows the effects of the test compounds in rats with glycerol-induced ARF. KW-3902 significantly increased urinary volume, whereas furosemide and TCM did not alter urinary volume. KW-3902 significantly increased sodium excretion; and the Na/K ratio, which had significantly been increased following the glycerol injection, was further increased by the KW-3902 administration. None of the compounds had any significant influence on S-CRE, S-UN or C_{CRE}.

Table 3. Effects of KW-3902, furosemide and trichlormethiazide (TCM) in rats with gentamicin-induced acute renal failure

Drugs	Dose (mg/kg, p.o.)	n	S-CRE (mg/dl)	S-UN (mg/dl)	C_{CRE} (l/kg/4 hr)	Urinary volume (ml/kg/4 hr)	Na excretion (mEq/kg/4 hr)	K excretion (mEq/kg/4 hr)	Urine Na/K ratio
Normal		5	0.51±0.01**	14.6±0.45**	0.98±0.08**	11.6±0.8*	2.03±0.11*	0.90±0.14	2.41±0.19*
Control		8	3.89±0.70	110.3±18.3	0.21±0.06	18.3±2.0	1.29±0.22	0.74±0.07	1.66±0.17
KW-3902	0.01	8	3.85±0.60	108.0±15.7	0.20±0.04	26.8±1.5**	2.53±0.34*	0.91±0.05	2.76±0.32*
	0.1	8	3.85±0.54	111.3±14.2	0.22±0.04	28.9±1.9**	2.73±0.28**	0.96±0.08	2.94±0.34**
Furosemide	30	8	3.88±0.52	108.8±13.5	0.18±0.03	25.6±2.8	1.93±0.36	0.90±0.09	2.03±0.27
TCM	1	8	4.50±0.59	124.0±13.7	0.14±0.03	22.3±2.7	2.07±0.43	0.87±0.16	2.29±0.20*

Each value is the mean±S.E. C_{CRE}=renal clearance of creatinine. *,**: Significantly different from the control at $P<0.05$ and 0.01, respectively.

Table 4. Effects of KW-3902, furosemide and trichlormethiazide (TCM) in rats with glycerol-induced acute renal failure (oliguric model)

Drugs	Dose (mg/kg, p.o.)	n	S-CRE (mg/dl)	S-UN (mg/dl)	C_{CRE} (l/kg/4 hr)	Urinary volume (ml/kg/4 hr)	Na excretion (mEq/kg/4 hr)	K excretion (mEq/kg/4 hr)	Urine Na/K ratio
Normal		7	0.51±0.01**	16.3±0.6**	0.75±0.06**	10.0±1.4**	1.43±0.15**	0.74±0.04**	1.92±0.13
Control		7	2.12±0.09	84.9±2.0	0.01±0.01	2.2±1.1	0.16±0.10	0.06±0.03	2.43±0.92
KW-3902	0.01	7	1.55±0.28	71.7±7.1	0.18±0.07*	10.5±3.4	1.02±0.35*	0.41±0.13*	3.31±1.11
	0.1	7	1.50±0.17*	69.2±3.7*	0.15±0.04**	14.8±2.2**	1.27±0.23**	0.44±0.07*	3.05±0.58
Furosemide	30	7	1.87±0.05*	85.7±3.1	0.01±0.00	2.7±1.1	0.53±0.21	0.05±0.02	5.52±1.67
TCM	1	7	1.94±0.15	82.5±3.2	0.03±0.02	5.0±1.9	0.32±0.13	0.15±0.01	4.43±1.43

Each value is the mean±S.E. C_{CRE}=renal clearance of creatinine. *,**: Significantly different from the control at $P<0.05$ and 0.01, respectively.

Table 5. Effects of KW-3902, furosemide and trichlormethiazide (TCM) in rats with glycerol-induced acute renal failure (polyuric model)

Drugs	Dose (mg/kg, p.o.)	n	S-CRE (mg/dl)	S-UN (mg/dl)	C_{CRE} (l/kg/4 hr)	Urinary volume (ml/kg/4 hr)	Na excretion (mEq/kg/4 hr)	K excretion (mEq/kg/4 hr)	Urine Na/K ratio
Normal		5	0.50±0.02**	13.4±0.4**	0.87±0.17**	6.9±1.2**	1.04±0.01*	0.88±0.09*	1.20±0.05**
Control		7	4.47±0.24	145.2±5.9	0.07±0.01	22.0±2.3	1.94±0.33	0.57±0.08	3.42±0.27
KW-3902	0.01	7	4.60±0.25	146.5±9.8	0.10±0.02	32.2±2.9*	3.38±0.41*	0.72±0.06	4.65±0.36**
	0.1	7	4.88±0.31	159.4±10.0	0.09±0.02	31.8±3.5	3.28±0.54	0.61±0.12	5.59±0.24**
Furosemide	30	7	5.40±0.28	163.1±8.4	0.05±0.02	15.8±3.9	1.26±0.36	0.40±0.12	3.42±0.26
TCM	1	7	4.86±0.23	156.2±6.9	0.08±0.01	24.0±3.2	2.50±0.36	0.71±0.11	3.69±0.26

Each value is the mean±S.E. C_{CRE} = renal clearance of creatinine. *,**: Significantly different from the control at $P < 0.05$ and 0.01, respectively.

DISCUSSION

Large doses of furosemide are used to produce diuresis in patients with ARF associated with advanced renal dysfunction, whereas Epstein et al. (16) reported that furosemide did not improve renal function and renal hemodynamics. On the other hand, Greven and Klein (17) reported that the glycerol-induced renal failure in rats was rather aggravated with furosemide. The present study demonstrated that in various models of ARF, KW-3902 induces the natriuretic effect, which is more prominent than those of furosemide and TCM.

Cisplatin is commonly used as an anticancer agent for the treatment of solid tumors (18). It is known that the high dose of cisplatin frequently causes ARF as its side effect (19). In the present study, only TCM was found to have a significant diuretic effect in the rats with cisplatin-induced ARF, though this drug significantly decreased C_{CRE}. The present observation is in accordance with the previous report that hydrochlothiazide decreased renal blood flow in ischemic ARF (20).

It is reported that the methylxanthine aminophylline ameliorated the cisplatin nephrotoxicity when administered to the rat during the maintenance phase of acute tubular necrosis (11). Moreover, KW-3902 exhibited renal protective effects against cisplatin-induced ARF (9). These results suggest that adenosine may be involved in cisplatin-induced nephrotoxicity via adenosine A_1-receptors. In the present study using the rats with established cisplatin induced ARF, KW-3902 produced a significant natriuresis without any effect on C_{CRE}, although the increase in urinary volume was not statistically significant. It is, therefore, assumed that KW-3902 produced a natriuretic effect via the blockade of adenosine A_1-receptors.

Gentamicin is an aminosaccharide antibiotic, which occasionally causes ARF as its side effect (21). In the rats with gentamicin-induced ARF, KW-3902, but not furosemide or TCM significantly increased the urinary volume. Furosemide was reported to enhance gentamicin nephrotoxicity because this drug directly accelerates gentamicin accumulation in renal tissues (22). In contrast, KW-3902 possesses a renal protective effect against gentamicin-induced ARF (K. Yao et al., unpublished data). It is therefore likely that KW-3902 is more useful as a diuretic than furosemide or TCM under the treatment of gentamicin.

The intramuscular or subcutaneous injection of glycerol causes regional myolysis and hemolysis, leading to ARF through the contraction of renal vessels (23). In this model, the damage is severe, and, moreover, degeneration occurs in a wide range of renal tubules. Therefore, the diuretics having the site of action only at the renal tubule may be less effective in inducing diuresis. It was reported that the adenosine antagonist 8-phenyltheophylline induces a marked diuretic effect in the glycerol-induced ARF, whereas hydrochlorothiazide does not cause diuresis (24). The absence of a diuretic effect of thiazide in this type of ARF has been suggested to be due to the fact that the impairment of tubular sodium reabsorption was already present in the ARF. In the present study, KW-3902 had significant diuretic effects in both the oliguric and the polyuric models, whereas furosemide and TCM showed minimal diuretic effects. Moreover, KW-3902, but not furosemide or TCM, significantly increased C_{CRE} in the oliguric model. These results suggest that KW-3902 may possibly have a site of action other than the renal tubule or have another mechanism of action to induce diuresis.

One of the actions of KW-3902 different from those of furosemide and TCM was its influence on C_{CRE}. The administration of furosemide did not affect C_{CRE} in any ARF models of the present study. The administration of TCM reduced C_{CRE} in the cisplatin-induced ARF, while KW-3902 had no influence on C_{CRE}. In the glycerol-induced oliguric ARF, KW-3902 increased C_{CRE}, suggesting an improvement of the renal function. In the glycerol-induced ARF, adenosine is suggested to constrict the afferent arterioles, leading to the depressed C_{CRE}, since the out-

flow of adenosine from the renal vein is increased after the glycerol-injection (25). If so, KW-3902 might have improved the C_{CRE} via the blockade of A_1-adenosine receptors, the stimulation of which is known to constrict the afferent arterioles (26). The present results suggest that the renal hemodynamic effect is at least partly involved in the diuretic action of KW-3902 in the glycerol-induced ARF.

In case of clinical ARF, the characteristics of diuretic use have not yet been established. In the present experiment, cisplatin, gentamicin and glycerol increased S-CRE and S-UN, but any of the diuretic drugs tested had little influence on such increases. However, in the glycerol-induced oliguric ARF, KW-3902 inhibited the elevation of S-CRE and S-UN, and improved C_{CRE}, indicating a protective effect against the aggravation of ARF. This may be due to the fact that the experiment was conducted in the model of ARF in progress. In fact, prophylactic administration of KW-3902 protects against glycerol-induced ARF (7). The protective effect of KW-3902 against the aggravation of ARF has been assumed to be due to the adenosine A_1-receptor blockade. The precise role of adenosine in renal failure or renal dysfunction remains unclear, and further investigations are necessary.

In conclusion, the present study demonstrated that KW-3902 exhibits a natriuretic effect even in various ARF models without deteriorating the renal functions. The present results suggest that endogenous adenosine may be involved in various forms of ARF via adenosine A_1-receptors.

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