Effects of Repeated Administration of KW-3902, a Novel Adenosine A₁-Receptor Antagonist, on Its Pharmacological Actions

Hideaki Kusaka and Akira Karasawa

Department of Pharmacology, Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411, Japan

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ABSTRACT—Effects of repeated administration of KW-3902, a novel adenosine A₁-receptor antagonist, on its pharmacological actions were studied with regards to: 1) in vivo adenosine A₁-antagonism, 2) diuretic effects and 3) renal protective effects against glycerol-induced acute renal failure (ARF). After repeated oral administration of KW-3902 (0.1 mg/kg/day) for 24 days, neither enhancement of the sensitivity to 5'-N-ethylcarboxamidoadenosine (NECA) nor reduction of the inhibitory effect of KW-3902 on the NECA-induced bradycardic response were observed. After repeated oral administration of KW-3902 (0.01 and 0.1 mg/kg/day) for 20 days, the diuretic effects of KW-3902 did not change. Renal protective effects against glycerol-induced ARF were not reduced by repeated oral administration of KW-3902 (0.01 and 0.1 mg/kg/day) for 23 days. These results suggest that repeated oral administration of KW-3902 has no effect on its pharmacological actions. Additionally, changes in serum parameters, which occurred after repeated administration of furosemide or trichlormethiazide, were minimal after repeated oral administration of KW-3902 (0.001–1 mg/kg/day) for 27 days. From these results, KW-3902 proved to be a diuretic which has renal protective effects with less side effects.

Keywords: KW-3902, Adenosine A₁-receptor antagonist, Diuretic effect, Renal protective effect, Tolerance

KW-3902 (8-(noradamantan-3-yl)-1,3-dipropylxanthine) is a selective and the most potent adenosine A₁-receptor antagonist reported to date (1). KW-3902 induces significant increases of urine volume and sodium excretion with little change of potassium excretion in saline-loaded rats (2, 3). Our previous studies have demonstrated that KW-3902 increases lithium clearance and does not affect the distal dip of the stop-flow pattern following its diuretic effects (3). These results suggest that KW-3902 produces diuretic effects by inhibiting the reabsorption of water and sodium mainly at the proximal nephron segments. Thus, KW-3902 is a new type diuretic in comparison with furosemide, a loop diuretic, and trichlormethiazide (TCM), a early distal tubular diuretic. Additionally, KW-3902 possesses renal protective effects against glycerol-induced acute renal failure (ARF) (2, 4). Therefore, it is assumed that the diuretic and renal protective effects against glycerol-induced ARF of KW-3902 are due to the blockade of adenosine A₁-receptors (5, 6).

Long-term treatment of animals or tissues with hormone-like or autacoid-like substances sometimes causes the decline of their specific effects or the down-regulation of their receptors as the compensatory action (7). Such a decline of effects or down-regulation has also been demonstrated in the case of the long-term administration of an adenosine A₁-agonist. For example, in fat cells treated with an adenosine A₁-agonist, the decrease of adenosine A₁-receptors (down-regulation) (8), increase of cyclic AMP contents stimulated by catecholamine, and enhancement of lipolysis were observed (9, 10). In the heart, chronic treatment with phenylisopropyladenosine (R-PIA) causes the down-regulation of adenosine A₁-receptors and reduces the negative inotropic response caused by adenosine (11). On the other hand, the receptor up-regulation or the enhancement of sensitivity to the agonist can be caused by the long-term administration of an adenosine antagonist. In fact, in the brain of rats repeatedly treated with theophylline, an adenosine antagonist, the receptor-binding of cyclohexyladenosine (CHA), an adenosine A₁-agonist, is increased (12). In the myocardial cells of guinea pigs repeatedly treated with theophylline, the up-regulation of A₁-receptors is caused and the sensitivity to adenosine or the adenosine A₁-agonist is enhanced (13).
In the present study, we determined if the in vivo adenosine antagonism, diuretic effects and renal protective effects against glycerol-induced ARF of KW-3902 were changed after repeated oral administration of KW-3902. Furthermore, we determined whether rebound phenomena (e.g., antidiuretic condition, aggravation of glycerol-induced ARF and enhancement of sensitivity to 5'-N-ethylcarboxamidoadenosine (NECA)) were observed when KW-3902 was withdrawn after repeated oral administration. In addition, the effects of repeated administration of KW-3902 on serum parameters were studied in comparison with those of furosemide and TCM.

MATERIALS AND METHODS

Experimental animals
Male Wistar rats weighing 180–250 g (Japan Shizuoka Laboratory Animal Center, Inc., Hamamatsu) were used in the present studies. The animals were kept at 22°C under a 12-hr light-dark cycle. They had free access to tap water and commercial chow.

Materials
KW-3902 (1), furosemide and TCM were synthesized in our laboratories. NECA was purchased from Research Biochemicals, Inc. (Natick, MA, USA). All other chemicals and solvents were used in their analytical pure form.

In vivo adenosine A₁-antagonism
Effects of repeated oral administration of KW-3902 on the NECA-induced bradycardic response were examined according to the previous method (14). Rats were divided into 2 groups (8 rats in each group), i.e., the group of repeated oral administration of vehicle and the group of repeated oral administration of KW-3902 (0.1 mg/kg/day). KW-3902 was suspended in 0.3% sodium carboxymethylcellulose containing 0.25% Tween 80 (vehicle 1). Vehicle 1 or KW-3902 suspension was orally administered at a volume of 5 ml/kg once a day for 24 days. After a 1-day withdrawal of the administration, the rats in each group were further divided into 2 groups, i.e., control group, KW-3902 (0.01 mg/kg) and KW-3902 (0.1 mg/kg) groups (6 rats in each group, 9 groups in total). Diuretic effects of KW-3902 were examined according to the previously described method (15). In brief, rats were fasted for 18 hr and treated with KW-3902 suspension or vehicle 2 at a volume of 25 ml/kg. KW-3902 was suspended in saline containing 0.05% Tween 80 (vehicle 2). After the administration, the rats were individually placed in metabolic cages without food or water. Urine was collected for 4 hr and its volume was measured. The sodium concentration was measured by flame photometry (775-A; Hitachi, Ltd., Tokyo), and sodium excretion was calculated.

Renal protective effects against glycerol-induced ARF
Rats were divided into 3 groups (12 rats in each group), i.e., the group of repeated oral administration of vehicle 1 and the two groups of repeated oral administration of KW-3902 (0.01 and 0.1 mg/kg/day). KW-3902 was suspended in vehicle 1. Vehicle 1 or KW-3902 suspension was orally administered to rats at a volume of 5 ml/kg once a day for 24 days. After a 1-day withdrawal of the administration, the rats in each group were further divided into 2 groups, i.e., control group and KW-3902 (0.1 mg/kg) group (4 rats in each group, 4 groups in total). Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and the trachea was intubated. The left carotid artery and right femoral vein were cannulated for blood pressure measurement and NECA administration, respectively. After a 15-min stabilization period, NECA dissolved in saline was cumulatively administered into the femoral venous cannula (0.1–1000 μg/kg). Heart rate was triggered from the blood pressure pulse wave and measured by a cardiotachometer (RT-5; Nihon Kohden, Tokyo). Vehicle 1 or KW-3902 suspended in vehicle 1 was orally administered to rats at a volume of 5 ml/kg at 1 hr before the administration of NECA. Relative values are shown with the heart rates before NECA administration regarded as 100%.

Diuretic effects
Rats were divided into 3 groups (18 rats in each group), i.e., the group of repeated oral administration of vehicle and the two groups of repeated oral administration of KW-3902 (0.01 and 0.1 mg/kg/day). KW-3902 was suspended in vehicle 1. Vehicle 1 or KW-3902 suspension was orally administered to rats at a volume of 5 ml/kg once a day for 20 days. After a 2-day withdrawal of the administration, the rats in each group were further divided into 3 groups, i.e., control group, KW-3902 (0.01 mg/kg) and KW-3902 (0.1 mg/kg) groups (6 rats in each group, 9 groups in total). Diuretic effects of KW-3902 were examined as 100%.

Effects of repeated oral administration of KW-3902 on serum parameters were studied in comparison with those of furosemide and TCM.
Effects on serum parameters

Rats were divided into 5 groups (8 rats in each group): control group and four KW-3902 (0.001, 0.01, 0.1 and 1 mg/kg/day) groups. KW-3902 was suspended in vehicle 1. Vehicle 1 or KW-3902 suspension was orally administered to rats at a volume of 5 ml/kg once a day for 27 days. One hour after the last administration, blood was collected from the abdominal aorta under ether anesthesia, and serum was obtained by centrifugation (3000 rpm, 10 min, 4°C). Serum GPT (S-GPT), GOT (S-GOT), triglyceride (S-TG), total cholesterol (S-TC), S-CRE, S-UN, uric acid (S-UA) and glucose (S-GLU) were measured with the autoanalyzer, while the serum concentrations of sodium (S-Na) and potassium (S-K) were measured by flame photometry.

In a separate series of experiments, furosemide (1, 10 and 100 mg/kg/day) or TCM (0.1, 1 and 10 mg/kg/day) was orally administered to rats once a day for 27 days, and similar examinations were performed. The doses of furosemide and TCM were determined in a preliminary experiment examining the diuretic effect of each drug. TCM at single doses of 0.1, 1 and 10 mg/kg (p.o.) produced increases in urine volume and sodium excretion to a similar extent to KW-3902 (0.01 and 0.1 mg/kg, p.o.). Furosemide at a single dose of 100 mg/kg (p.o.) produced marked increases in urine volume and sodium excretion in comparison with KW-3902 (0.01 and 0.1 mg/kg, p.o.). However, the diuretic effects of furosemide at single doses of 1 and 10 mg/kg (p.o.) were less prominent than those of KW-3902 (0.01 and 0.1 mg/kg, p.o.).

Statistical analyses

Data are presented as means±S.E. Statistical significance was estimated by Student’s t-test or analysis of variance (ANOVA) followed by Dunnett’s test. A P value of less than 0.05 was considered statistically significant.

RESULTS

In vivo adenosine antagonism

Effects of KW-3902 on the NECA-induced bradycardic response after repeated oral administration of vehicle 1 or KW-3902 (0.1 mg/kg/day) are shown in Fig. 1. Basal heart rates before NECA administration were not different among the 4 groups (in animals subjected to repeated oral administration of vehicle: 363±33 beats/min in the control group and 413±46 beats/min in the group given KW-3902 (0.1 mg/kg, p.o.); in animals subjected to repeated oral administration of KW-3902 (0.1 mg/kg/day): 436±28 beats/min in the control group and 422±31 beats/min in the group given KW-3902 (0.1 mg/kg, p.o.)). KW-3902 significantly and similarly inhibited the NECA-induced bradycardic response both in
the group of repeated oral administration of vehicle 1 and in the group of repeated oral administration of KW-3902 (0.1 mg/kg/day). Moreover, no significant difference was found in the bradycardic response between the respective control groups.

**Diuretic effects**

Diuretic effects of KW-3902 after repeated oral administration of vehicle 1 or KW-3902 (0.01 or 0.1 mg/kg/day) are shown in Fig. 2. KW-3902 at doses of 0.01 and 0.1 mg/kg caused significant increases of urine volume and sodium excretion compared with those in each control group. The potency of the diuretic effects of KW-3902 was similar among the groups of repeated oral administration of vehicle 1 and KW-3902 (0.01 or 0.1 mg/kg/day). No significant difference was found in urine volume and sodium excretion among the respective control groups.

**Renal protective effects against glycerol-induced ARF**

Renal protective effects of KW-3902 against glycerol-induced ARF after repeated oral administration of vehicle 1 or KW-3902 (0.01 and 0.1 mg/kg/day) are shown in Fig. 3. KW-3902 significantly inhibited the increases of S-CRE and S-UN induced by glycerol injection in both repeated oral administration groups of vehicle 1 and KW-3902 (0.01 and 0.1 mg/kg/day). No significant difference was found in S-CRE and S-UN among the respective control groups.

**Effects on serum parameters**

Serum parameters after repeated oral administration of KW-3902 (0.001–1 mg/kg/day) for 27 days are shown in Table 1. With the exception of S-TC, KW-3902 did not affect any other serum parameter (S-GPT, S-GOT, S-TG, S-CRE, S-UN, S-GLU, S-Na and S-K) at any dose. S-TC increased slightly but significantly in the rats treated with KW-3902 at doses of 0.01 and 1 mg/kg/day.

Table 2 shows the serum parameters after repeated oral administration of furosemide (1, 10 and 100 mg/kg/day) or TCM (0.1, 1 and 10 mg/kg/day) for 27 days. Furosemide induced significant increases of S-GPT and S-GOT, parameters of hepatic function; S-UN, a parameter of renal function; and S-TG. TCM also in-

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**Table 1. Effects of repeated oral administration of KW-3902 on serum parameters**

|                | S-GPT (IU/L) | S-GOT (IU/L) | S-TG (mg/dl) | S-TC (mg/dl) | S-CRE (mg/dl) | S-UN (mg/dl) | S-GLU (mg/dl) | S-Na (mg/dl) | S-K (mg/dl) |
|----------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|-------------|
| Control        | 42.6 ± 3.3   | 80.4 ± 5.6   | 198.4 ± 15.0 | 66.5 ± 1.5   | 0.48 ± 0.01  | 17.5 ± 0.5   | 185.2 ± 5.9  | 142 ± 0.7    | 5.2 ± 0.2    |
| KW-3902 0.001 mg/kg/day (p.o.) | 41.2 ± 2.5    | 78.0 ± 2.5   | 193.9 ± 10.7 | 73.5 ± 2.5   | 0.48 ± 0.02  | 17.6 ± 0.4   | 193.8 ± 13.3 | 142 ± 0.3    | 4.9 ± 0.2    |
| KW-3902 0.01 mg/kg/day (p.o.)   | 42.7 ± 1.5    | 80.7 ± 4.1   | 195.8 ± 22.5 | 74.3 ± 1.6   | 0.05 ± 0.01  | 17.2 ± 0.4   | 190.1 ± 6.7  | 142 ± 0.4    | 4.9 ± 0.1    |
| KW-3902 0.1 mg/kg/day (p.o.)    | 37.6 ± 2.5    | 75.9 ± 2.0   | 191.6 ± 19.5 | 70.3 ± 1.6   | 0.48 ± 0.02  | 16.4 ± 0.1   | 174.1 ± 6.2  | 143 ± 0.5    | 5.1 ± 0.2    |
| KW-3902 1 mg/kg/day (p.o.)      | 41.3 ± 1.8    | 78.9 ± 2.7   | 216.7 ± 3.8  | 76.7 ± 3.8   | 0.49 ± 0.02  | 17.8 ± 0.6   | 203.6 ± 13.6 | 142 ± 0.5    | 5.1 ± 0.2    |

The presented values are means ± S.E. of 8 animals. *P < 0.05, when compared with the control value (Dunnett's test).
duced significant increases of S-GOT, S-UN and S-TG. Both furosemide and TCM elicited decreases of S-Na and S-K at all the examined doses.

DISCUSSION

Some receptor antagonists induce and others do not induce tolerance after repeated administration of a receptor antagonist (12, 13, 16). The present study was conducted to determine if chronic treatment with KW-3902, an adenosine A₁-receptor antagonist, induces tolerance in rats.

The NECA-induced bradycardic response is mediated via adenosine A₁-receptor stimulation (2, 4, 6, 17). No significant difference was found in the bradycardic response between the respective control groups (i.e., vehicle repeated administration and KW-3902 repeated administration). If adenosine A₁-receptor up-regulation had occurred after repeated administration of KW-3902, the NECA-induced bradycardic response in the control group after repeated administration of KW-3902 should have been more prominent than that in the control group after repeated administration of vehicle 1. In other words, the NECA-dose-bradycardia curve in the control group after repeated administration of KW-3902 should have been shifted to the left when compared with that in the control group after repeated administration of vehicle 1. However, such a phenomenon was not observed in the present study (Fig. 1).

It is known that adenosine A₁-receptor activation in the rat kidney causes the constriction of afferent arterioles and mesangial cells (18, 19), which would reduce the glomerular filtration rate (GFR) and could be antidiuretic. On the other hand, our recent study demonstrated that KW-3902 inhibits the antidiuretic effects of an adenosine A₁-agonist by accelerating reabsorption of water and sodium at tubular sites (20). Thus, the diuretic effects of KW-3902 may result from inhibition of the antidiuretic action of endogenous adenosine. In the present study, the diuretic effects of KW-3902 were not dose-dependent. The reason why the diuretic effects of KW-3902 are not dose-dependent seems to be due to the fact that 0.01 mg/kg (p.o.) of KW-3902 was enough to antagonize endogenous adenosine in the kidney. If adenosine A₁-receptor up-regulation or enhancement of the sensitivity to adenosine A₁-agonists had been caused by repeated administration of KW-3902, the rats after repeated administration of KW-3902 should have exhibited the antidiuretic condition after the drug withdrawal. In other words, urine volume, sodium excretion in the control group after repeated administration of KW-3902 should have been lower than those in the control after repeated administration of vehicle 1. However, such results were not obtained in the present study (Fig. 2).

It is known that adenosine A₁-receptor activation plays an important role in the pathogenesis of glycerol-induced ARF (2, 4, 6). It has been postulated that adenosine has a deleterious effect by increasing afferent arteriolar resistance, probably via an action at adenosine A₁-receptors (21, 22). In fact, we have observed that concentration of adenosine in plasma increases after the administration of glycerol (unpublished observation). Thus, it seems that KW-3902 exerted renal protective effects by inhibiting the decrease in renal plasma flow caused by adenosine A₁-receptor activation. Similarly to the in vivo adenosine A₁-antagonism and diuretic effects, if adenosine A₁-receptor up-regulation had been caused by repeated administration of KW-3902, aggravation of glycerol-induced ARF

|                      | S-GPT (IU/L) | S-GOT (IU/L) | S-TG (mg/dl) | S-TC (mg/dl) | S-CRE (mg/dl) | S-UN (mg/dl) | S-GLU (mg/dl) | S-Na (mg/dl) | S-K (mg/dl) |
|----------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|-------------|
| Control              | 61.0         | 91.2         | 98.6         | 77.0         | 0.35         | 19.7         | 108.2        | 154          | 6.1         |
|                      | ± 9.4        | ± 9.2        | ± 4.1        | ± 2.4        | ± 0.02       | ± 0.5        | ± 2.5        | ± 0.5        | ± 0.1       |
| Furosemide 1 mg/kg/day (p.o.) | 86.9         | 139.5*       | 130.0        | 70.6         | 0.43         | 22.5*        | 115.8        | 143**        | 5.1*        |
|                      | ± 18.8       | ± 15.7       | ± 13.4       | ± 2.4        | ± 0.03       | ± 0.8        | ± 7.3        | ± 1.1        | ± 0.1       |
| Furosemide 10 mg/kg/day (p.o.) | 85.8         | 141.0**      | 130.5        | 77.7         | 0.43         | 24.5**       | 111.1        | 144*         | 5.4**       |
|                      | ± 8.5        | ± 10.0       | ± 15.6       | ± 2.2        | ± 0.02       | ± 0.7        | ± 7.4        | ± 0.9        | ± 0.1       |
| Furosemide 100 mg/kg/day (p.o.) | 108.2*       | 158.2**      | 132.3**      | 82.9         | 0.45         | 36.7**       | 96.9         | 144**        | 4.8**       |
|                      | ± 17.4       | ± 13.7       | ± 5.2        | ± 5.5        | ± 0.03       | ± 1.0        | ± 5.1        | ± 0.6        | ± 0.1       |
| TCM 0.1 mg/kg/day (p.o.) | 91.3         | 128.6*       | 142.7**      | 74.3         | 0.40         | 23.7**       | 108.7        | 147*         | 4.9**       |
|                      | ± 8.3        | ± 5.9        | ± 13.2       | ± 0.9        | ± 0.01       | ± 0.8        | ± 6.0        | ± 4.0        | ± 0.1       |
| TCM 1 mg/kg/day (p.o.) | 79.4         | 128.0*       | 122.3        | 71.5         | 0.44         | 25.1**       | 102.1        | 144*         | 4.7**       |
|                      | ± 7.5        | ± 4.1        | ± 6.9        | ± 2.9        | ± 0.02       | ± 0.8        | ± 6.4        | ± 1.2        | ± 0.1       |
| TCM 10 mg/kg/day (p.o.) | 92.3         | 146.7**      | 112.9        | 75.3         | 0.39         | 25.7**       | 103.2        | 145*         | 4.6**       |
|                      | ± 7.5        | ± 10.2       | ± 2.5        | ± 2.3        | ± 0.04       | ± 0.7        | ± 4.6        | ± 0.7        | ± 0.1       |

The presented values are means ± S.E. of 8 animals. *P < 0.05, **P < 0.01, when compared with the control value (Dunn's test).
should have been observed in rats of the control group after repeated administration of KW-3902. Namely, S-CRE and S-UN in the control group after repeated oral administration of KW-3902 should have been higher than those in the control group after vehicle 1. However, such results were not obtained in the present study (Fig. 3).

The results in the present study demonstrated that the diuretic effect, the renal protective effects against glycerol-induced ARF and the in vivo adenosine A₁ antagonism of KW-3902 do not disappear or decline, even after KW-3902 is repeatedly administered once a day at doses that cause these effects by single administration. These results suggest that neither adenosine A₁-receptor up-regulation nor enhancement of sensitivity to the adenosine agonist are caused by repeated administration of KW-3902. It has been suggested that G₁₂-type G proteins or some other pertussis toxin substrates are involved in the development of enhanced sensitivity to stimulatory hormones in a variety of cells when they are treated with the hormones coupling adenylate cyclase (7). The lack of tolerance after repeated administration of KW-3902 may be due to the fact that the diuretic and renal protective effects of KW-3902 are not mediated via a pertussis toxin sensitive mechanism (2).

Additionally, KW-3902 caused minimal abnormalities in serum parameters, even when KW-3902 was repeatedly administered. In contrast, furosemide and TCM caused several abnormalities in serum parameters, particularly the decrease of S-K and the increases of S-GOT and S-UN, when they were repeatedly administered. These results suggest that the side effects of KW-3902 are less common than those of furosemide and TCM in terms of serological abnormalities. Furthermore, KW-3902 exhibits diuretic effects in various rat models of ARF, and this drug had no influence or rather improving effects on damaged renal functions, in contrast to the effects of furosemide and TCM (H. Kusaka et al., unpublished observations). Thus, KW-3902 may have some advantages over furosemide and thiazides, since electrolyte abnormalities are common side effects of the conventional diuretics (23). In the present study, KW-3902 did not show the decrease of S-Na following its chronic treatment, although KW-3902 caused natriuretic effects. Further studies are necessary to determine the mechanism involved for this observation.

In summary, the present results demonstrated that KW-3902 does not elicit tolerance nor induce prominent serological abnormalities by its repeated oral administration once a day. The results also suggest that KW-3902 could become a diuretic with renal protective effects and less side effects.

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