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General Pharmacological Study of CJ-11828, an Amlodipine adipate

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Abstract – This study was undertaken to evaluate the general pharmacological properties of CJ-11828, an amlodipine adipate, in experimental animals and *in vitro* system. CJ-11828 had no effects on general behavior, motor coordination, writhing syndromes, pentetrazol-induced chemoshock and electric shock in mice at dose levels of 3, 10, and 30 mg/kg, po. But there were decrease of body temperature, prolongation of sleeping time, and inhibition of intestinal activity in mice treated with CJ-11828 at doses of 10 and 30 mg/kg, po. CJ-11828 decreased the blood pressure in conscious dog at the dose level of 2 mg/kg, po, but it was expected as a result of pharmacological activity of CJ-11828. Any effect on respiratory system was not observed in conscious rat at doses of 3, 10, and 30 mg/kg, po. The slight decrease in spontaneous motor activity was observed in mice treated with CJ-11828 at high dose, 30 mg/kg. *In vitro* experiments, CJ-11828 had no effect on agonists-induced contraction of isolated guinea pig ileum at 0.1, 1, and 10 μM. Based on these results, it was concluded that CJ-11828 had no pharmacological effect in these studies even up to the 36-fold anticipated clinical dose, 3 mg/kg.

Keywords □ CJ-11828, Amlodipine adipate, Anti-hypertension agent, Calcium channel blocker, General pharmacology

INTRODUCTION

Amlodipine (2-(2-aminoethoxy) methyl)-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine), a potent calcium antagonist, is a long-acting first-line drug for the treatment of hypertension. CJ-11828 is an amlodipine adipate developed by CJ Corp. as a generic salt form of amlodipine besylate (Norvasc®). Recently, it was shown that CJ-11828 has an equivalent antihypertensive effect to that of amlodipine besylate in hypertensive rat models, such as spontaneously hypertensive rats (SHR) and renal hypertensive rats (RHR) (Byung Ho Lee *et al,* 2004) and the bioequivalence in rats and Beagle dogs pharmacokinetic studies with amlodipine besylate (not published). Meanwhile, the adipic acid is a safe material used as a food additive and metabolized by β-oxidation in the body and recorded in several pharmacopoeia.

Also, CJ-11828 has a number of advantages compared with amlodipine besylate. For exemple, CJ-11828 has a better water solubility than amlodipine besylate or amlodipine free base (MCDaid & Deasy, 1996).

In the present study, the general pharmacological properties of CJ-11828 were investigated on central nervous system, autonomic nervous system, digestive system and cardiovascular and respiratory system at the dose levels of 36-360 times of anticipate clinical dose in accordance with the "General Pharmacological Testing Standards for Pharmaceuticals" KFDA (Korea Food and Drug Administration) notice 1998-62 and "S7A" ICH guideline.

MATERIALS AND METHODS

Test Substances

CJ-11828 (Lot No. A120001, purity 100.9%) manufactured by the CJ Corp. was suspended in 0.5% Tween 80 for mouse and rat and inserted in gelatin capsule (Size 12, Torpac Inc.) for dog and dissolved in Kreb's modified solution for isolated guinea pig ileum test. The vehicle used in the preparation of each test material was used as a negative control material.

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Dose Selection

For the animal studies, the doses of 0.1, 0.5, 2, 10, and 30 mg/kg, which are 1.2, 6, 24, 36, 120, and 360 times of anticipated human dose (5 mg/70 kg/men), respectively, were selected. The concentrations of 0.1, 1 and 10 uM, which are 26.6, 266 and 2660 times of the IC_{50} value (3.76 nM in Ca^{2+} induced contraction of rat aorta) were applied for the *In vitro* guinea pig ileum study.

Animals

SPF (specific pathogen free) male and female ICR mice (Orient, Korea), SPF male Sprague-Dawley rats (Orient, Korea), SPF Hartley guinea-pig (Charles River Lab, Canada), and Beagle dog (Covance, USA) were used after one or four weeks of acclimating period. Animals were housed in a controlled environment (temperature: 23 ± 3°C, humidity: 55 ± 15%, light-darkness cycle of 12 hours) and provided diet and water *ad libitum*. All animal studies were conducted in facilities approved by the AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care) with approval of IACUC (The Institutional Animal Care and Use Committee) in KIT.

Effects on the Central Nervous System

Effects on General Behavior

Four male and female mice of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. The general behaviors (catalepsy, traction, pinna reflex, righting reflex, exophthalmos, piloerection, salivation, lacrimation, diarrea, skin coloration, tremor, convulsion, abdominal tone, tail elevation, eyelid, locomotion, and respiration rate) and death were observed at pre, 1, 2, 4, 8, and 24 h after administration of CJ-11828 by the Irwin multi-dimensional observation method (Irwin, 1968).

Effect on Spontaneous Locomotor Activity

Eight male mice of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. Each mouse was placed in an activity cage and the spontaneous locomotor activity was recorded for 5 min by using cage rack photobeam activity system (PAS, USA) at pre, 0.5, 1, 4, 6, 8, and 24 h after administration of CJ-11828.

Effect on Motor Coordination (Rota-rod Test)

Eight male mice of each group were administered with CJ-11828 at doses of 0, 3, 10, and 30 mg/kg orally. The number of mice fallen from the rota-rod within 60 sec was counted at pre, 1, 2, 4, 6, 8, and 24 h after administration of CJ-11828 (Dunham *et al*, 1957).

Effect on Body Temperature

Eight male mice of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. At pre, 1, 2, 4, 6, 8, and 24 h after dosing, the rectal temperature of each mouse was measured by using an electrothermometer (MGA-III, Japan).

Effect on Hexobarbital-Induced Sleeping Time

Eight male mice of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. At 5 h following CJ-11828 administration, each mouse was injected intraperitoneally with hexobarbital-Na (70 mg/kg, Bayer, Germany). The onset time and duration of sleeping were measured by loss and reappearance of righting reflex as an index of sleeping.

Effect on Acetic Acid-Induced Writhing Syndrome

Eight male mice of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. At 5 h following CJ-11828 administration, each mouse was injected intraperitoneally with 1% acetic acid (10 mg/kg kg, Dong-yang Chemical, Korea). At 10 min after injection of acetic acid, the number of writhing syndrome was counted for 10 min (Koster *et al*, 1959).

Effect on Pentetrazol (PTZ)-Induced Convulsion

Eight male mice of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. At 5 h following CJ-11828 administration, each mouse was injected intraperitoneally with PTZ (100 mg/kg, sigma, USA) and the incidence of convulsion and mortality were measured (Swinyard, *et al*, 1952).

Effect on Electric Shock-Induced Convulsion

Eight male mice of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. At 5 h following CJ-11828 administration, each mouse was subjected to electic shock (10 mA, 0.3 sec, HSE, Germany) and the incidence of convulsion and mortality were counted (Woodbury *et al*, 1952).

Effects on Cardiovascular and Respiratory Systems

Effects on the Blood Pressure and Heart Rate in Conscious Dogs

Four male Beagle dogs were anesthetized with the mixture

of anesthetics (Atropine (0.05 mg/kg)+ Rumpun (3.49 mg/kg)+ Ketamine (12.5 mg/kg)). A sensor for HR (heart rate), a catheter for BP (blood pressure), and electrodes of ECG (electrocardiogram) of telemetry system were implanted in left side, left femoral artery and chest, respectively by surgical procedures (Alycia A., *et al.*, 19958; Mark I., *et al.*, 1994; Alycia A., *et al.*, 1996). After recovery period for 1 day, CJ-11828 at dose levels of 0, 0.1, 0.5, and 2 mg/kg were administered orally with an interval of 3 day and the blood pressure, heart rate, and ECG parameters (QT-interval, RR-interval, QRS interval, QTcB) were measured by using a telemetry system for 10 min (at pre, 1, 4, 6, 12, 24 and 48 h after dosing).

Effect on Respiratory System in Conscious Rats

Eight male rats of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. At pre, 0.5, 1, 2, 4, 6, and 24 h following CJ-11828 administration, the minute volume, tidal volume, and respiratory rate in each rat were measured for 10 min by using plethysmometer (BUXCO, USA).

Effect on Isolated Organ

Effect on Isolated Ileum of Guinea Pig

A segment of ileum approximately 2.0–2.5 cm long was removed from male Hartley guinea pig and mounted vertically in organ bath (Letica 13206, Spain) containing Krebs modified solution (pH 7.4, 32°C, 95% O_2 and 5% CO_2) and were equilibrated for about 1 h. To evaluate the effects of test article on direct or agonist (acetylcholine, histamine, or $BaCl_2$) -induced contractile, the segments were exposed to CJ-11828 at concentrations of 10^{-7}, 10^{-6}, and 10^{-5} M for 5 min, and then acetylcholine (5×10^{-7} M), histamine (2×10^{-6} M), or $BaCl_2$ (2×10^{-3} M) was added into the organ bath. The contraction value of the segments was expressed as the relative percentage to the maximum contraction (100%) induced by KCl (Sigma, USA 30 nM).

Effect on Gastrointestinal Mobility (Charcoal meal propulsion Test)

Eight male mice of each group were administered with CJ-11828 at dose levels of 0, 3, 10, and 30 mg/kg orally. At 5 hr following CJ-11828 administration, each mouse was administered with 5% charcoal meal (10 ml/kg, Sigma, USA) suspended in 10% arabic gum solution. At the 30 min following the administration of charcoal, all mice were sacrificed and the distance of charcoal meal had traveled from the pyloric sphincter towards the cecum was measured and the intestinal motility was expressed as a percentage of the total length of the gut.

Statistics

All results were expressed as mean ± SD or number of occurrences/total number of cases and the homogeneity of mean value was examined using in Battlett test. If there is homogeneity in the test, the significance between the vehicle and test groups was examined using Dunnett's t-test. If there is no homogeneity in Battlett test, executed Kruska-Wallis's H test for significance between the vehicle and test groups. The result of Kruska-Wallis's H test is $p<0.05$, execute Dunnett's t-test. Differences at $p<0.05$ were considered to be statistically significant. It was performed using the GraphPad InStat® program (GraphPadsoftware Inc., USA).

RESULTS

Effects on Central Nervous System

Effects on General Behavior

There were no changes in general behavior in mice administered with CJ-11828 at dose levels of 3, 10, and 30 mg/kg orally.

Effect on Spontaneous Locomotor Activity

Oral administration of CJ-11828 at dose levels of 3 and 10 mg/kg caused no significant change in spontaneous motor activity when compared to vehicle-treated mice. At the dose level of 30 mg/kg, a decrease of spontaneous motor activity was observed at 1 and 8 hr after dosing, but recovered at 24 h (Table I).

Table I. Effects of CJ-11828 on spontaneous locomotor activity in mice

Treatment	Dose (mg/kg)	Counts/5min						
		pre	1 h	2 h	4 h	6 h	8 h	24 h
Control	0	73.9±35.9	79.6±33.2	46.6±22.9	55.3±25.5	32.6±24.9	69.5±25.6	57.3±25.6
CJ-11828	3	72.1±39.8	82.8±39.1	24.6±21.1	29.6±41.4	32.3±29.4	60.0±50.6	73.4±23.0
	10	94.1±47.5	58.4±35.7	63.6±35.0	59.3±29.1	53.5±35.7	61.1±43.1	73.0±39.6
	30	105.1±30.7	28.6±22.6*	29.3±29.3	19.7±9.6	13.4±12.4	13.9±13.5*	72.9±32.3

Each value represents the mean ± S.D., n=8.

Effect on Motor Coordination (Rota-rod Test)

Oral administration of CJ-11828 at dose levels of 3, 10, and 30 mg/kg showed no observable changes in motor coordination (Table II).

Effects on Body Temperature

No significant changes in body temperature were observed in mice at the dose level of 3 mg/kg. But there were significant decrease in body temperature at 6 h ($p<0.05$) or 6 and 8 h ($p<0.01$) after administration of CJ-11828 at dose levels of 10 and 30 mg/kg in mice (Table III).

Effect on Hexobarbital-Induced Sleeping Time

There was no significant difference in mice treated with CJ-11828 at the dose level of 3 mg/kg, when compared with control. But, at dose levels of 10 and 30 mg/kg sleeping time was significantly prolonged ($p<0.05$, $p<0.01$, respectively) (Table IV).

Effect on Acetic Acid-Induced Writhing Syndrome

Oral administration of CJ-11828 at dose levels of 3, 10, and 30 mg/kg did not cause any significant alteration of acetic acid-induced writhing in mice (Table V).

Effect on Pentetrazol (PTZ)-Induced Convulsion

A single oral administration of CJ-11828 at dose levels of 3, 10, and 30 mg/kg produced no proconvulsant or anticonvulsant activities in mice (Table VI).

Table IV. Effects of CJ-11828 on hexobarbital-induced sleeping time in mice

Treatment	Dose(mg/kg)	Sleeping time (min)	Control ratio(%)
Control	0	41.8 ± 8.0	100.0
CJ-11828	3	46.0 ± 6.0	110.2
	10	52.1 ± 4.1*	124.9
	30	71.6 ± 7.7**	171.6

*; $p<0.05$ compare with control group, **; $p<0.01$ compare with control group.
Each value represents the mean±S.D., n=8.

Table V. Effects of CJ-11828 on acetic acid-induced writhing syndrome in mice

Treatment	Dose(mg/kg)	No. of writhings
Control	0	21.3 ± 6.6
CJ-11828	3	19.8 ± 9.4
	10	20.1 ± 8.0
	30	18.0 ± 7.1

Each value represents the mean ± S.D., n=8.

Table VI. Effects of CJ-11828 on pentetrazol -induced convulsion in mice

Treatment	Dose (mg/kg)	No. of convulsion	No. of death
Control	0	8/8[a)]	7/8
CJ-11828	3	8/8	6/8
	10	8/8	4/8
	30	8/8	3/8

[a)]is the number of positive/tested, n=8.

Table II. Effects of CJ-11828 on motor coordination (rota-rod test) in mice

Treatment	Dose (mg/kg)	No. of fallen mice within 60 sec						
		pre	1 h	2 h	4 h	6 h	8 h	24 h
Control	0	0	0	0	0	0	0	0
CJ-11828	3	0	0	0	0	0	0	0
	10	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0

n=8.

Table III. Effects of CJ-11828 on body temperature in mice

Treatment	Dose (mg/kg)	Rectal temperature(°C)						
		pre	1 h	2 h	4 h	6 h	8 h	24 h
Control	0	37.7 ± 0.53	37.6 ± 0.57	37.7 ± 0.54	37.3 ± 0.45	37.6 ± 0.36	37.8 ± 0.37	37.8 ± 0.32
CJ-11828	3	37.9 ± 0.31	38.0 ± 0.38	37.7 ± 0.41	37.4 ± 0.31	37.6 ± 0.62	37.8 ± 0.37	37.6 ± 0.58
	10	38.0 ± 0.59	37.8 ± 0.32	37.2 ± 0.28	37.4 ± 0.62	37.0 ± 0.39*	37.3 ± 0.51	37.7 ± 0.63
	30	37.6 ± 0.41	37.8 ± 0.34	37.2 ± 0.41	36.7 ± 0.53	36.0 ± 0.35**	36.1 ± 0.49**	37.7 ± 0.40

*; $p<0.05$ compared with control group, **; $p<0.01$ compared with control group.
Each value represents the mean±S.D., n=8.

Effect on Maximal Electric Shock (MES)-Induced Convulsion

No alterations in the maximal electric shock induced convulsion were observed in mice treated with CJ-11828 at the dose level of 3, 10, and 30 mg/kg (Table VII).

Table VII. Effects of CJ-11828 on electroshock-induced convulsion in mice

Treatment	Dose (mg/kg)	No. of convulsion	No. of death
Control	0	8/8[a)]	8/8
CJ-11828	3	8/8	6/8
	10	8/8	8/8
	30	8/8	6/8

[a)]is the number of positive/tested, n=8.

Effects on Cardiovascular and Respiratory Systems

Effects on the Blood Pressure and Heart Rate in Conscious Dogs

Oral administrations of CJ-11828 at dose levels of 0.1 and 0.5 mg/kg showed no significant differences in blood pressure (Table VIII), heart rate (Table IX), and ECG (Table X) when compared with control. But there was decrease in blood pressure at 4 ($p<0.05$) and 6 hr ($p<0.05$) after administration of high, 2 mg/kg.

Effect on Respiratory System in Rats

No significant changes in tidal volume, respiratory rate, and minute volume were observed in rats administered CJ-11828 at dose levels of 3, 10, and 30 mg/kg (Table XI).

Effect on Isolated Organ

Table VIII. Effects of CJ-11828 on blood pressure in conscious beagle dogs

Systolic pressure (mmHg)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	0.1	0.5	2.0
pre	129.07 ± 22.283	112.83 ± 16.739	115.25 ± 23.112	114.15 ± 21.065
1 h	123.87 ± 10.596	112.83 ± 21.080	107.40 ± 27.975	97.87 ± 12.045
4 h	118.81 ± 15.220	109.08 ± 14.912	102.76 ± 28.011	80.98 ± 18.778*
6 h	121.18 ± 19.537	100.54 ± 15.829	100.49 ± 25.155	82.46 ± 13.656*
12 h	111.60 ± 19.450	97.26 ± 7.418	97.33 ± 18.405	84.42 ± 19.335
24 h	119.79 ± 16.179	100.35 ± 24.608	98.85 ± 29.588	94.26 ± 21.444
48 h	111.28 ± 23.266	103.41 ± 22.155	108.80 ± 24.929	108.12 ± 21.919
Diastolic pressure (mmHg)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	0.1	0.5	2.0
pre	89.28 ± 16.268	76.51 ± 8.443	79.06 ± 16.933	75.85 ± 16.159
1 h	83.35 ± 12.234	75.60 ± 15.306	72.66 ± 14.170	64.39 ± 7.173
4 h	81.17 ± 12.584	76.47 ± 8.504	66.28 ± 17.767	52.19 ± 14.754*
6 h	81.75 ± 12.252	68.89 ± 13.054	67.59 ± 12.690	55.73 ± 7.849*
12 h	76.91 ± 19.029	62.99 ± 7.152	65.72 ± 17.178	55.65 ± 16.965
24 h	81.11 ± 9.912	66.13 ± 15.137	63.96 ± 20.686	64.13 ± 17.436
48 h	74.83 ± 15.804	68.54 ± 12.995	73.00 ± 18.502	72.33 ± 17.265
Mean blood pressure (mmHg)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	0.1	0.5	2.0
pre	102.41 ± 14.662	90.05 ± 10.601	91.09 ± 17.971	88.47 ± 15.230
1 h	98.98 ± 9.775	89.59 ± 16.304	83.12 ± 20.243	75.22 ± 10.082
4 h	94.33 ± 12.274	83.10 ± 6.250	79.03 ± 20.600	63.83 ± 18.783*
6 h	96.14 ± 12.924	76.69 ± 9.883	77.96 ± 19.240	64.82 ± 11.486*
12 h	96.08 ± 18.170	75.65 ± 5.838	75.77 ± 15.274	67.36 ± 16.937
24 h	95.41 ± 10.894	78.66 ± 18.145	77.03 ± 23.821	73.17 ± 18.455
48 h	88.35 ± 17.111	80.30 ± 16.186	85.06 ± 19.286	84.27 ± 17.231

*; $p<0.05$ compare with control group. Each value represents the mean ± S.D. n=8.

Table IX. Effects of CJ-11828 on heart rate in conscious beagle dogs

Heart rate (BPM)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	0.1	0.5	2.0
pre	94.85 ± 14.864	89.99 ± 13.988	85.69 ± 10.609	77.21 ± 4.679
1 h	97.69 ± 17.190	90.39 ± 13.988	83.2 ± 14.882	95.16 ± 21.972
4 h	84.46 ± 15.816	72.97 ± 13.877	84.66 ± 10.742	105.11 ± 20.059
6 h	88.01 ± 13.795	68.20 ± 10.031	83.71 ± 8.951	107.70 ± 14.565
12 h	100.34 ± 13.978	85.24 ± 1.834	84.43 ± 6.752	119.25 ± 17.332
24 h	84.22 ± 4.388	82.35 ± 5.718	79.59 ± 8.469	88.00 ± 16.484
48 h	84.70 ± 7.266	82.86 ± 6.341	77.156 ± 12.202	72.76 ± 2.457

Each value represents the mean ± S.D., n=4.

Table X. Effects of CJ-11828 on ECG-parameters in conscious beagle dogs

Q-T interval (sec)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	0.1	0.5	2.0
pre	0.197 ± 0.0073	0.205 ± 0.0201	0.202 ± 0.0248	0.216 ± 0.0125
1 h	0.200 ± 0.0051	0.206 ± 0.0233	0.201 ± 0.0218	0.192 ± 0.0430
4 h	0.212 ± 0.0091	0.213 ± 0.0063	0.203 ± 0.0279	0.233 ± 0.0573
6 h	0.202 ± 0.0057	0.217 ± 0.0106	0.202 ± 0.0313	0.201 ± 0.0555
12 h	0.201 ± 0.0130	0.219 ± 0.0343	0.205 ± 0.0314	0.253 ± 0.0458
24 h	0.205 ± 0.0054	0.207 ± 0.0249	0.202 ± 0.0209	0.202 ± 0.0250
48 h	0.214 ± 0.0074	0.208 ± 0.0264	0.210 ± 0.0263	0.220 ± 0.0149
P-R interval (sec)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	0.1	0.5	2.0
pre	0.120 ± 0.0093	0.121 ± 0.0078	0.120 ± 0.0083	0.125 ± 0.0085
1 h	0.117 ± 0.0078	0.118 ± 0.0069	0.117 ± 0.0088	0.114 ± 0.0111
4 h	0.127 ± 0.0068	0.129 ± 0.0098	0.124 ± 0.0132	0.121 ± 0.0260
6 h	0.123 ± 0.0076	0.127 ± 0.0082	0.119 ± 0.0175	0.114 ± 0.0065
12 h	0.123 ± 0.0062	0.119 ± 0.0032	0.125 ± 0.0060	0.115 ± 0.0133
24 h	0.119 ± 0.0074	0.121 ± 0.0105	0.116 ± 0.0167	0.121 ± 0.0123
48 h	0.121 ± 0.0080	0.122 ± 0.0096	0.123 ± 0.0101	0.121 ± 0.0079
QRS duration (sec)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	0.1	0.5	2.0
pre	0.023 ± 0.0024	0.024 ± 0.0028	0.027 ± 0.0013	0.024 ± 0.0025
1 h	0.024 ± 0.0029	0.024 ± 0.0022	0.026 ± 0.0013	0.027 ± 0.0014
4 h	0.024 ± 0.0034	0.025 ± 0.0021	0.025 ± 0.0024	0.024 ± 0.0036
6 h	0.023 ± 0.0025	0.023 ± 0.0026	0.026 ± 0.0025	0.026 ± 0.0051
12 h	0.026 ± 0.0039	0.024 ± 0.0053	0.026 ± 0.0041	0.027 ± 0.0017
24 h	0.025 ± 0.0031	0.026 ± 0.0034	0.025 ± 0.0036	0.025 ± 0.0024
48 h	0.024 ± 0.0029	0.026 ± 0.0027	0.025 ± 0.0024	0.025 ± 0.0021

Each value represents the mean ± S.D., n=4.

Effects on Isolated Ileum of Guinea Pig

CJ-11668 at concentrations of 10^{-7}, 10^{-6}, and 10^{-5} M had no effect on the spontaneous relaxation or contraction and agonist (acetylcholine, histamine, and $BaCl_2$)-induced contraction of ileum (Table XII).

Effect on Gastrointestinal Mobility

No significant changes in gastrointestinal motility were observed in mice at the dose level of 3 mg/kg. But there was significant inhibition in charcoal meal propulsion of the gut at

Table XI. Effects of CJ-11828 on respiration in rats

Respiration Rate (BPM)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	3	10	30
pre	126.4 ± 10.89	126.1 ± 19.85	122.7 ± 13.42	139.2 ± 24.41
0.5 h	129.7 ± 17.39	149.4 ± 40.34	133.6 ± 20.65	145.3 ± 25.83
1 h	151.3 ± 17.84	135.9 ± 29.98	134.4 ± 20.71	165.9 ± 32.66
2 h	126.7 ± 13.80	112.6 ± 13.26	138.4 ± 14.23	144.1 ± 25.33
4 h	154.9 ± 46.23	124.7 ± 9.61	158.6 ± 45.55	123.9 ± 6.84
6 h	126.7 ± 13.80	112.6 ± 13.26	138.4 ± 14.23	144.1 ± 25.33
24 h	137.7 ± 31.14	151.4 ± 53.82	146.9 ± 48.15	129.4 ± 29.13
Tidal Volume (ml/sec)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	3	10	30
pre	1.2 ± 0.15	1.3 ± 0.19	1.2 ± 0.17	1.2 ± 0.10
0.5 h	1.2 ± 0.18	1.2 ± 0.11	1.2 ± 0.15	1.2 ± 0.15
1 h	1.2 ± 0.17	1.2 ± 0.12	1.2 ± 0.13	1.2 ± 0.11
2 h	1.2 ± 0.19	1.3 ± 0.12	1.3 ± 0.16	1.3 ± 0.19
4 h	1.4 ± 0.17	1.5 ± 0.10	1.4 ± 0.16	1.5 ± 0.08
6 h	2.8 ± 3.92	1.7 ± 0.19	1.5 ± 0.20	1.6 ± 0.09
24 h	1.3 ± 0.23	1.5 ± 0.31	1.4 ± 0.20	1.4 ± 0.39
Minute Volume (ml/sec)				
Treatment	Control	CJ-11828		
Dose (mg/kg)	0	3	10	30
pre	141.6 ± 23.20	159.0 ± 26.78	146.4 ± 27.33	154.6 ± 19.90
0.5 h	148.4 ± 31.06	165.4 ± 46.04	156.4 ± 29.75	168.6 ± 33.46
1 h	164.2 ± 30.37	157.5 ± 38.20	161.7 ± 24.22	194.4 ± 34.73
2 h	141.5 ± 22.58	144.9 ± 18.14	170.4 ± 19.58	183.0 ± 40.11
4 h	198.6 ± 49.56	177.0 ± 17.82	203.4 ± 47.07	178.7 ± 14.81
6 h	143.2 ± 62.15	204.1 ± 41.68	209.1 ± 50.74	193.3 ± 41.68
24 h	172.0 ± 27.99	207.3 ± 43.73	187.2 ± 65.14	170.3 ± 59.93

Each value represents the mean ± S.D., n=4.

Table XII. Effects of CJ-11828 on isolated guinea pig ileum

		Contractile responses (% of relative value to KCl)					
Treatment	Dose (μM)	Alone	ACh.	Alone	His.	Alone	BaCl2
Control	0	0.00 ± 0.00	177.33 ± 124.01	0.00 ± 0.00	337.78 ± 233.10	0.00 ± 0.00	326.19 ± 88.75
CJ-11828	0.1	0.00 ± 0.00	213.61 ± 183.24	0.00 ± 0.00	349.45 ± 235.91	7.54 ± 46.79	277.84 ± 121.84
	1	0.00 ± 0.00	171.95 ± 133.63	0.00 ± 0.00	340.00 ± 202.85	-12.04 ± 27.33	258.53 ± 126.09
	10	0.00 ± 0.00	116.39 ± 79.38	0.00 ± 0.00	264.72 ± 127.86	-1.72 ± 28.51	221.50 ± 105.61

Each value represents the mean ± S.D.(n=4). Ach: Acetylcholine, His: Histamine.

doses of 10 ($p<0.05$) and 30 mg/kg ($p<0.01$) in mice (Fig. 1).

DISCUSSION

In order to assess the safety of CJ-11828, an amlodipine adipate developed by CJ Corp., general pharmacological study was conducted. CJ-11828 was orally administered at dose levels of 0.1, 0.5, 2, 3, 10, and 30 mg/kg, that was 1.2, 6, 24, 36, 120, and 360 times of anticipated dosage for human, in mice, rats, and dogs.

CJ-11828 had no effects on general behavior, motor coordination, writhing syndrome, and chemoshock and electric shock in mice at dose levels of 3, 10, and 30 mg/kg. But decrease in body temperature, prolongation of sleeping time, and inhibition of intestinal activity were observed in mice treated with CJ-11828 at the dose of 10 and 30 mg/kg. The spontaneous loco-

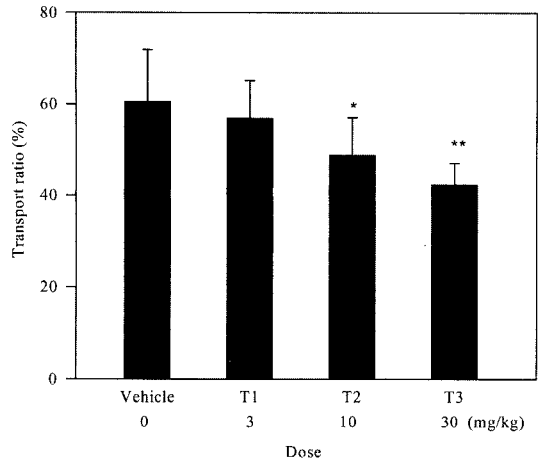

Fig. 1. Effects of CJ-11828 on intestinal transport in mice. Each column indicates the mean and S.D. (n=8). Significant difference from control group (*;$p<0.05$, **; $p<0.01$)

motor activity was decreased in mice at the dose level of 30 mg/kg. Although CJ-11828 showed these effects, as considered hypertension agent had a narrow therapeutic window, the dose induced these effects was 120 and 360 times higher than anticipated clinical dose. It was an expected effect as result of pharmacological activity of Ca^{2+} channel blocker as anti-hypertension agent rather than an adverse effect. Based on these results, it was concluded that CJ-11828 was a relatively safety compound had no pharmacological effect even up to the 36-fold anticipated clinical dose, 3 mg/kg.

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