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General Pharmacology of IY-80843, a new H_2-Receptor Antagonist: Effects on the Central Nervous and Cardiovascular Systems

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IY-80843, N-[2-(2-Methoxyphenyl)ethyl]-N'-[4-(Imidazole-4-yl) phenyl] formamidine, is a new potent H_2-receptor antagonist. The potential secondary pharmacologic effects of this agent, on the central nervous and cardiovascular systems were studied. IY-80843 caused ptosis, suppression of locomotion, hypothermia, prolongation of sleeping time and hypotensive effects in mice, rats and dogs. These results suggest that IY-80843 affects the function of the central nervous and cardiovascular systems in a dose-dependent manner.

Key words: IY-80843, H_2-antagonist, Pharmacology, Central nervous system, Cardiovascular system

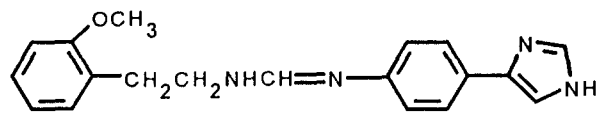
INTRODUCTION

Compounds such as Cimetidine, Ranitidine, Famotidine are the most widely used H_2-blockers for the treatment of peptic ulcer. It is reported that their clinical efficacy is associated with the reduced level of gastric acid secretion (Sabbatini *et al.*, 1990, Chiverton *et al.*, 1988, Ireland *et al.*, 1984, Susumu *et al.*, 1984, Susumu *et al.*, 1981) resulting from a specific interaction with histamine receptors located on parietal cells (Domschke *et al.*, 1980). Recently, IY-80843 (N-[2-(2-Methoxyphenyl)-ethyl]-N'-[4-(Imidazole-4-yl)phenyl] formamidine) has been developed by Il-Yang pharmaceutical company as a novel H_2-receptor antagonist of the imidazolylphenyl-formamidine type.

Results from *in vivo* and *in vitro* studies have shown that the compound is a potent competitive H_2-receptor antagonist, comparable to mifentidine, from which it is derived (Kim *et al.*, 1991).

The purpose of the present study was to examine the pharmacologic properties of high dosage of IY-80843 in an attempt to gain some insight into the potential side effects on the central nervous and cardiovascular systems resulting from the secondary pharmacologic activity of high doses of the agent. The doses utilized in the present study were selected such that they give full description of the potential pharmacologic activity of test compound, the chemical structure of which is shown below.

IY-80843



N-[2-(2-Methoxyphenyl)ethyl]-N'-[4-(Imidazole -4-yl)phenyl] formamidine

MATERIALS AND METHODS

Animals

The experiments were performed on male and female ICR mice (20-25 g), Sprague-Dawley rats (120-150 g), spontaneously hypertensive rats (SHRs, male, 12-14 week old, SPB>180 mmHg) and male mongrel dogs (14-16 kg).

The animals were provided from the Department of Experimental Animals, KRICT and kept in a storage room under the conditions of constant temperature (20.7± 0.6℃), relative humidity (55.6± 4.1%) and illumination (9 h-light, 15 h-dark cycle), until the day of experiment (at least one week). All animals were fed standard animal chow daily and had access to drinking water ad libitum. Animals were divided into groups at random and fasted overnight prior to testing.

Chemicals

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IY-80843, a colorless crystalline powder, was chemically synthesized and provided by Il-Yang pharmaceutial company. Diazepam was a gift from Shionogie, Japan. Hexobarbital sodium was commercially purchased from Bayer A.G.

IY-80843 was suspended in the aqueous solution of CMC (0.5%) for cental nervous system (CNS) studies and in propylene glycol for cardiovascular (CV) studies. Diazepam was suspended in aqueous solution of tween 80 (1%) and hexobarbital sodium was dissolved in distilled water.

Acute toxicity

IY-80843 in different dose levels was given once as an oral suspension to rat and mice, each group consisting of 5 males and 5 females. The animals were closely observed for general symptoms and death daily for two weeks, recording body weights on day 0, 1, 3, 7, and 14 following drug administration. For the calculation of LD_{50} values, probit analysis was used.

Effect on general behavior

Groups of 4 male and 4 female mice were used after 20 h fasting. According to the modified method of Irwin (1964), the behavior of the animals was observed at 0.5, 1, 2, 3, 5 and 24 h after oral administration of IY-80843.

Effect on spontaneous motility

Ten groups of 4 female mice were used for single dose experiments with IY-80843 (30-300 mg/kg, p.o.). Mice were placed in a plastic cage (26×25×40 cm) and the locomotor activity was measured using a motility meter (Rhema 2100) at 5 min interval for 15 min from 10 to 420 min after administration of test drugs.

Induction of hexobarbital-induced sleeping time

Groups of 4 female mice were used for single dose experiments with IY-80843. Hexobarital sodium (70 mg/kg) was intraperitoneally injected 30 min after oral administration of test drug. The duration of a loss of the righting reflex was measured as an indication of the sleeping time.

Effect on motor function (rota-rod test)

Groups of 8 female mice were used for single dose experiments with IY-80843 (30-300 mg/kg, p.o.). The animals which sustained on the rotarod (10 rpm/min) for more than 3 min were preselected and randomly distributed to 4 groups. According to the method of Dunham and Miya (1957), the animals of each group were placed on the rotarod at 30, 60, 120, 180, 240 and 300 min after oral administration of the drugs. The numbers of mice falling within 1 min from a rotating rod (10 rpm/min) were counted.

Effects on blood pressure and heart rate in conscious SHRs

Systolic blood pressure (SBP) and heart rate (HR) were measured from male SHRs by the tail cuff method using a TSE multichannel 8006 blood pressure monitor. Rats were prewarmed in a warming box at 36± 0.2℃ for about 15 min and gently placed in a restraining cage. SBP and HR were measured prior to and then 0.5, 1, 2, 4, and 6 h following oral administration of drug. An average of three consecutive measurements was taken from each rat.

Hemodynamic studies in anesthetized dogs

Male mongrel dogs were anesthetized with sodium pentobarbital (35 mg/kg, i.v.) and prepared for hemodynamic parameters as follows. After tracheal intubation, dogs were ventilated artificially with room air using a Bird 8 respirator. About 1 ml of blood was withdrawn from the catheter inserted in the brachial artery at regular time intervals for blood gas analysis using a blood gas analyzer (280 blood gas system, Ciba-Corning), and the amount of oxygen in room air was readjusted to keep blood gas pressures within normal ranges. Anesthetized dog was heparinized (250 IU/kg, i.v.) before commencing instrumentation. Anesthesia levels were maintained throughout the experiment with a continuous i.v. infusion of sodium pentobarbital (3.5 mg/kg/h) via a catheter fixed in the left cephalic vein. Systemic arterial blood pressure was measured with a Statham P23XL pressure transducer connected to a cannula inserted in the right femoral artery. The left ventricular pressure (LVP) was continuously monitored via a millar micro-tip catheter, which was advanced through the left carotid artery into the left ventricle and an indirect measure of myocardial contractility (± 6 dp/dt_{max}) was obtained from the first differential of the left ventricular pressure pulse. Heart rate (HR) was derived electronically from the left ventricular pressure using a Gould 2000 Biotachometer. To monitor pulmonary artery pressure, the thermal dilution catheter was inserted in jugular vein and positioned at the point of pulmonary artery wedge with the help of X-ray and then the pressure catheter was connected to a Statham P23XL pressure transducer. Compounds were dissolved in propylene glycol and administered intraduodenally (i.d.) via a tube inserted into the caudal part of the pylorus. All the parameters were recorded continuously on a Gould 2000 physiograph. Data are expressed as mean percentage changes from predrug values ± SEM.

Statistics

Data were expressed as mean ± SEM or number of animals showing positive sign. The difference between groups was evaluated by Student t test and Kruskal Wallis-test as appropriate, with $P<0.05$ being considered statestically significant.

RESULTS

Acute toxicity

As shown in Table I, the estimated oral LD_{50} values of IY-80843 were 2200-3375 mg/kg for male and female mice, and 1281 and 996 mg/kg for male and female rats, respectively. There were no significant differences in LD_{50} values between male and female of both species.

In rats and mice of either sex, IY-80843 produced the symptoms such as decreased locomotor activity, ptosis and hypothermia. Death occurred within 48 h in mice and 96 h in rats after the oral administration. In survivors, the symptoms dissappered from 1 to 8 hours after the administration. Body weight changes were not noted after the administration of the drug

Table I. LD_{50} values of IY-80843

Species	Sex	Route	LD_{50} (mg/kg)
Mouse	Male	p.o.	2200~3375
	Female	p.o.	2200~3375
Rat	Male	p.o.	1281
	Female	p.o.	996

Table II. Body weights of IY-80843 in male and female mice after oral administration

Sex	DOSE		BODY WT. (G)				
	(mg/kg)		DAY0	DAY1	DAY3	DAY7	DAY14
Male	0	MEAN	26.6	28.2	29.1	31.2	32.9
		SD	0.49	0.65	0.84	0.99	1.75
		N	5	5	5	5	5
	1000	MEAN	27.0	27.9	27.5	30.1	32.5
		SD	1.55	1.61	3.60	2.06	2.21
		N	5	5	5	5	5
	1500	MEAN	26.5	27.0	26.1	29.1	31.1
		SD	1.43	1.56	0.93	0.83	0.86
		N	5	5	5	5	5
	2250	MEAN	26.8	25.9	27.5	29.1	29.9
		SD	2.04	1.88	1.67	2.17	2.46
		N	5	5	5	5	5
	3375	MEAN	26.2	–	–	–	–
		SD	1.49	–	–	–	–
		N	5	–	–	–	–
Female	0	MEAN	21.9	23.8	23.4	23.6	25.4
		SD	0.56	0.36	0.57	0.50	1.60
		N	5	5	5	5	5
	1000	MEAN	21.0	22.0	19.4	23.5	25.3
		SD	1.58	1.29	1.23	1.76	2.02
		N	5	5	5	5	5
	1500	MEAN	20.7	21.1	21.8	22.9	23.5
		SD	0.88	0.57	0.59	0.80	1.09
		N	5	5	5	5	5
	2250	MEAN	21.0	21.1	22.1	23.2	22.5
		SD	0.87	1.43	1.17	0.88	0.43
		N	5	5	5	5	5
	3375	MEAN	20.8	–	–	–	–
		SD	0.68	–	–	–	–
		N	5	–	–	–	–

– DATA UNAVILABLE

Table III. Body weights of IY-80843 in male and female rat after oral administration

Sex	DOSE		BODY WT. (G)				
	(mg/kg)		DAY0	DAY1	DAY3	DAY7	DAY14
Male	0	MEAN	112.2	130.0	152.5	189.9	253.3
		SD	6.87	0.65	0.84	0.99	1.75
		N	5	5	5	5	5
	500	MEAN	129.0	135.0	160.6	184.3	254.2
		SD	5.83	8.02	8.32	7.74	34.03
		N	5	5	5	5	5
	600	MEAN	126.0	138.4	162.2	179.9	252.8
		SD	6.98	12.00	9.64	9.22	14.43
		N	5	5	5	5	5
	720	MEAN	127.8	129.3	155.7	179.9	262.7
		SD	7.50	9.14	8.72	8.44	6.30
		N	5	5	5	5	5
	936	MEAN	123.8	128.3	151.1	174.0	251.0
		SD	6.55	8.50	11.13	10.21	15.23
		N	5	5	5	5	5
	1310	MEAN	128.0	123.6	127.3	183.1	258.7
		SD	10.58	9.71	18.17	9.6	11.81
		N	5	5	5	5	5
	2227	MEAN	128.5	126.2	115.1	–	–
		SD	4.91	5.36	–	–	–
		N	5	5	1	–	–
Female	0	MEAN	101.2	118.2	137.3	157.8	178.9
		SD	5.02	6.45	8.10	11.51	14.86
		N	5	5	5	5	5
	500	MEAN	105.5	111.4	131.4	152.5	180.7
		SD	8.27	13.62	9.93	10.22	14.75
		N	5	5	5	5	5
	600	MEAN	106.4	111.3	130.4	155.0	181.3
		SD	5.98	7.51	8.42	15.16	22.70
		N	5	5	5	5	5
	720	MEAN	105.8	110.3	129.5	147.3	184.2
		SD	6.48	10.21	10.44	12.06	8.92
		N	5	5	5	5	5
	936	MEAN	105.5	106.1	124.4	152.3	179.6
		SD	6.80	8.22	11.08	13.61	17.30
		N	5	5	4	4	4
	1310	SD	8.79	6.49	–	–	–
		N	5	4	–	–	–
	2227	MEAN	102.9	101.3	–	–	–
		SD	6.35	7.06	–	–	–
		N	4	4	–	–	–

– DATA UNAVILABLE

Table IV. Effects of IY-80843 on general behavior in mice

Compounds	Vehicle						IY-80843																	
Dose(mg/kg, p.o)	–						30						100						300					
Time(hr)	0.5	1	2	3	4	8	0.5	1	2	3	4	8	0.5	1	2	3	4	8	0.5	1	2	3	4	8
1. Catalepsy	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
2. Traction	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
3. Tremor	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
4. Convulsion	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
5. Exopthalmos	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
6. Hypothermia	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	4/4	4/4	4/4	4/4	1/4	1/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
7. Piloerection	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
8. Salivation	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
9. Lacrimation	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
10. Dirrhea	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
11. Skin coloration	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
12. Pinna reflex	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
13. Righting reflex	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
14. Abdominal tone	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
15. Tail elevation	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
16. Eye lids	8.0	8.0	8.0	8.0	8.0	8.0	4.0	4.0	4.0	8.0	8.0	8.0	4.0	4.0	4.0	4.0	8.0	8.0	2.0	2.0	2.0	2.0	2.0	4.0
17. Locomotion	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
18. Respiration rate	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
19. Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Each number represents the number of positive/tested (1-13), the mean score; max. 8 min. 0 (14-18) and number of animals (19)

Table V. Effects of IY-80843 on body temperature

Sex	Drugs (mg/kg P.O)		Rectal temperature(℃) after administration						
			0 min	30 min	60 min	120 min	180 min	240 min	480 min
Male	Control		37.90± 0.63	37.05± 0.26	37.28± 0.13	37.28± 0.26	36.75± 0.25	36.70± 0.82	36.55± 0.21
	IY-80843	30	38.22± 0.40	37.30± 0.65	37.30± 0.84	37.43± 0.52	37.33± 0.42	37.03± 0.31	36.90± 0.32
		100	37.18± 0.77	35.10± 0.32**	34.75± 0.34**	34.20± 0.57**	33.48± 0.79**	33.95± 0.06**	35.05± 0.47**
		300	33.95± 0.26	34.05± 0.29**	33.18± 0.17**	32.48± 0.22**	31.25± 1.64**	33.28± 4.36**	31.40± 1.82**
Female	Control		37.93± 0.19	37.22± 0.51	37.35± 0.26	37.10± 0.12	36.98± 0.22	36.88± 0.22	37.35± 0.17
	IY-80843	30	37.95± 0.33	36.97± 0.21	36.95± 0.17*	36.93± 0.32	36.78± 0.41	36.80± 0.22	37.08± 0.22
		100	38.00± 0.29	35.28± 0.22**	34.80± 0.45**	33.95± 0.34**	34.33± 0.24**	34.63± 0.41**	36.70± 0.42*
		300	37.80± 0.28**	34.65± 0.70**	33.55± 1.03**	32.30± 1.74**	33.18± 2.60*	33.60± 3.60	35.43± 1.66*

*: Significantly different from control group($P<0.05$, n=4) using T-test
**: Significantly dirrerent from control group($P<0.01$, n=4) using T-test

(Table II+III).

Effect on general behavior

As shown in Table IV, IY-80843 produced ptosis and the decrease in spontaneous locomotor activity in mice at all doses tested (30-300 mg/kg, p.o.) throughout the period of 8 h observation.

The significant decrease in body temperature was observed at oral doses of 100 and 300 mg/kg in male and female mice (Table V).

Effect on spontaneous motility

As shown in Fig. 1, IY-80843 produced no changes in locomotor activity of mice at the lowest tested dose (50 mg/kg, p.o.). However, at higher doses (100 and 300 mg/kg, p.o.), it caused significant decrease of spontaneous locomotor activity ($p<0.01$), which lasted over varying periods of time (10 to 150 min, 10 to 420 min).

Effect on hexobarbital-induced sleeping time

As shown in Table VII, IY-80843 prolonged the sleeping time in female mice significantly ($p<0.05$) at all doses tested (10-100 mg/kg, p.o.).

Effect on motor function (rota-rod test)

In general, IY-80843 (30-300 mg/kg, p.o.) did not affect the motor coordination in mice: 1 of 8 animals (300 mg/kg, p.o.) showed signs of disturbance in motor performance at 2-3 h after drug administration (Table VI).

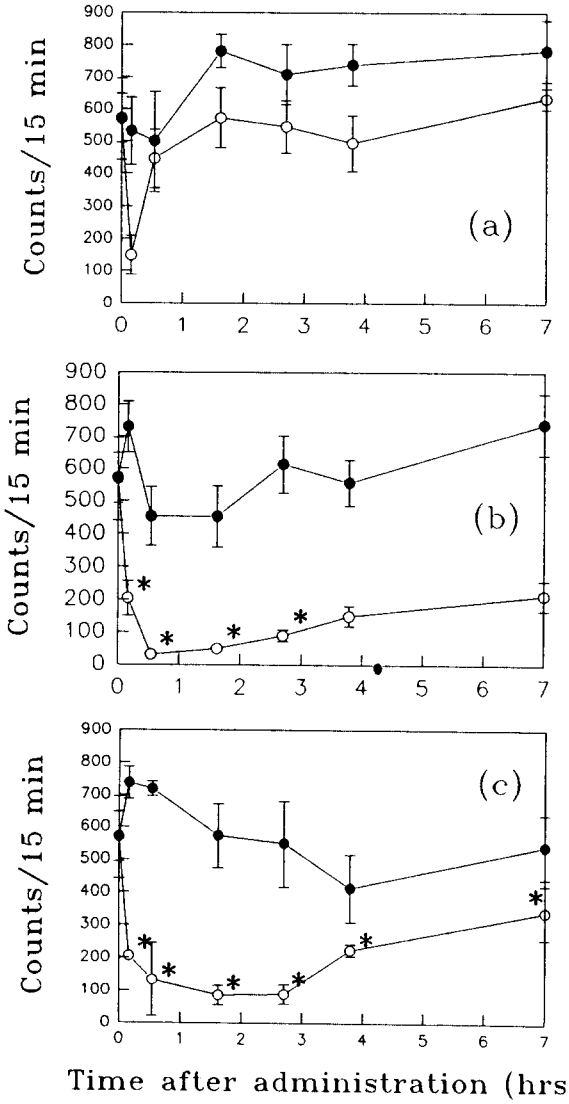

Fig. 1. Time course of changes in spontaneous locomotor activity following adminisration of IY-80843 to mice. Each point is the mean ± SEM (n=4). *P<0.01 (student' t-test) ●—● Control, ○—○ IY-80843, (a) 50 mg/kg, (b) 100 mg/kg, (c) 300 mg/kg

Effect on blood pressure in SHRs

Fig. 2 shows the time course effects of IY-80843 on systolic blood pressure (SBP) and heart rate (HR) in SHRs, an animal model for human essential hypertension. Basal value of mean SBP and HR in the groups treated with the vehicle and IY-80843 at 30 and 100 mg/kg p.o. were:SBP, 203± 2.8, 211± 1.8 and 204± 5.2 mmHg and HR, 358± 9.5, 397± 8.5 and 405± 15.1 beats/min., respectively.

IY-80843 (30 and 100 mg/kg) given in single oral doses, caused a dose-dependent decrease in SBP. The hypotensive effects at each dose were gradual in onset and time-dependent with the maximal effects reached around 4 h after dosing (the maximal % decrease in SBP:28± 3.6 and 43± 4.5% at low and high doses, res-

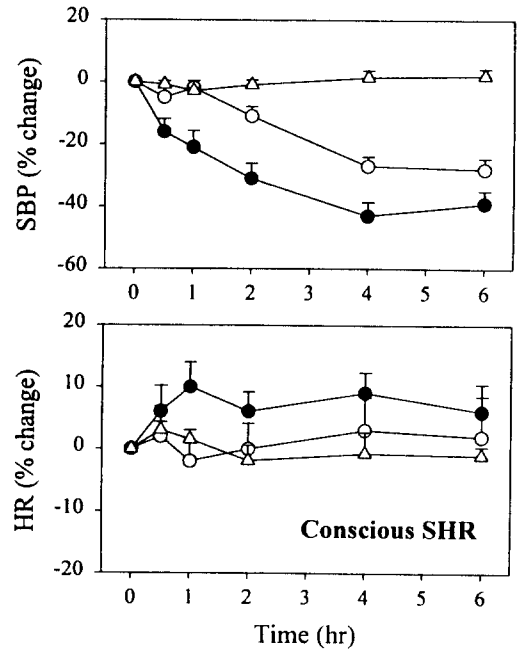

Fig. 2. Effects of IY-80843 on systolic blood pressure(SBP) and heart rate(HR) in conscious SHRs after oral administration. Data are mean percentage change from predrug values ± SEM (n=4-6). Vehicle (△) and IY-80843, 30 mg/kg (○) and 100 mg/kg (●).

Table VI. Effects of IY-80843 on motor function in mice

Drugs	Dose (mg/kg)	Route	n	Incidence of ataxia (number of mice)					
				30 min	60 min	120 min	180 min	240 min	300 min
Control	0	p.o.	8	0	0	0	0	0	0
IY-80843	30	p.o.	8	0	0	0	0	0	0
	100		8	0	0	0	0	0	0
	300		8	0	0	1	1	0	0

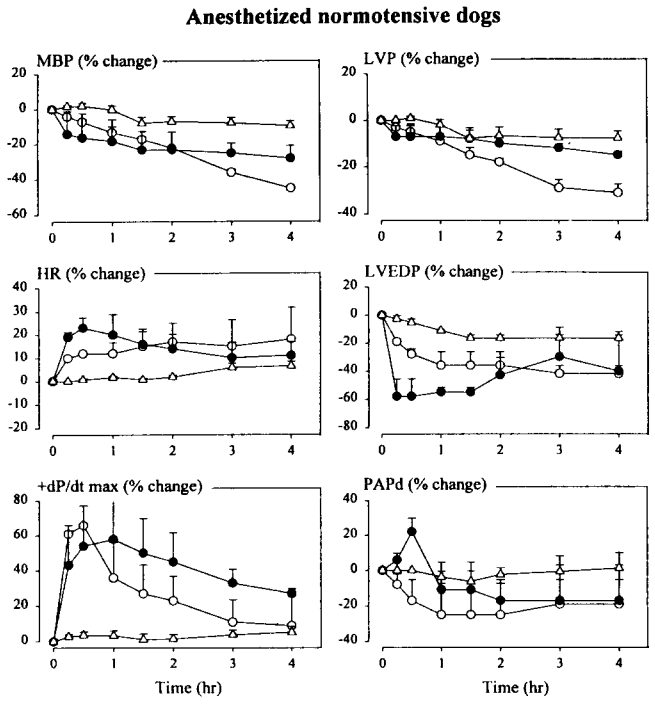

Fig. 3. Effects of IY-80843 on mean blood pressure (MBP), heart rate (HR), $+dp/dt_{max}$, left ventricular pressure (LVP), left ventricular end-diastolic pressure (LVEDP) and pulmonary arterial diastolic pressure (PAPd) in anesthetized mongrel dogs after intraduodenal administration. Data are mean percentage change from predrug values ± SEM (n=2-4), Vehicle (△) and IY-80843, 10 mg/kg (○) and 30 mg/kg(●).

pectively). IY-80843 had no effect on HR at a dose of 30 mg/kg but, at a higher dose (100 mg/kg), it produced a slight increase (<10%) in HR that was sustained during the period of hypotension.

Hemodynamic studies in anesthetized dogs

Fig. 3 shows the effects of IY-80843 on various hemodynamic parameters in anesthetized dogs. Basal values of various parameters in the groups of anesthetized dogs treated with vehicle and IY-80843 at 10 and 30 mg/kg i.d. were shown in Table VIII. IY-80843 (10 and 30 mg/kg, i.d.) evoked dose-related and time dependent falls in MAP up to 2 hour after dosing, although the dose-dependency were not clear thereafter. The onset of hypotensive effects was more rapid at the higher dose. The observed % changes from predose basal values were in the range of 30-40% at 4 h after dosing. The falls in MAP were accompanied by very similar dose-dependent reflex increase in HR, during the early phase of hypotensive effect. The reflex tachycardia was in the range of 19-23% increase from predose values at doses tested. Significant increases in $+dp/dt_{max}$ were observed at both doses administered; the effect reached the maximum (58-66%) between 0.5 and 1 hour after dosing, which was gradually decreased thereafter. IY-80843 caused a gradual but significant time-dependent reduction in LVP (the maximal effect: 15-30% decrease), although not dose-dependent, with LVEDP(the maximal effect: 40-60% change) on a dose-dependent decrease. With regard to the diastolic pulmonary arterial pressure (PAPd), the tendancy toward a sustained decrease was noted for at least 4 hours (the maximal effect: 20-25% decrease from basal values).

Table VII. Effects of IY-80845 on hexobarbital-induced hypnosis in mice

Drugs	Dose (mg/kg)	Route	n	Sleeping time(min) Means± S.E	Control ratio(%)
Control			6	43.5± 3.4	100
IY-80843	10	P.O	6	66.3± 4.2*	152
	30		6	110.0± 2.4**	252
	100		6	207.2± 12.8**	476
Control			6	33.2± 2.4	100
Diazepam	1	P.O	6	60.8± 4.8*	183
	5		6	129.8± 13.3**	390

(Kruskal Wallis-test using Scheffe's procedure)
*: Significantly different from control group(P<0.05)
**: Significantly different from control group(P<0.01)

Table VIII. Basal values of MBP, HR, +dp/dtmax, LVP, LVEDP and PAPd in groups of anesthetized dogs treated with vehicle and IY-80843 at 10 and 30 mg/kg i.d

Parameter	Vehicle	IY-80843	
	(n=2)	10 mg/kg (n=2)	30 mg/kg (n=2)
MBP (mmHg)	111± 7.1	130± 12.4	118± 3.5
HR (bpm)	158± 8.2	156± 2.8	185± 21.2
$+dp/dt_{max}$ (mmHg/S)	2825± 175	2800± 71	2700± 354
LVP (mmHg)	135± 5.4	170± 14.1	160± 7.1
LVEDP (mmHg)	9.0± 0.4	8.0± 1.1	4.5± 0.4
PAPd (mmHg)	10.8± 0.7	7.0± 0.7	6.0± 2.1

DISCUSSION

In this study, the general pharmacological evaluation of IY-80843 on the central nervous and cardiovascular systems were studied in various species of animals. As summarized in Table IX, IY-80843 caused ptosis, decrease of spontaneous locomotor activity, hypothermia, prolonged hexobarbital-induced sleeping time in mice and hypotensive effects in SHRs and dogs.

The potentiation of sleeping time is most likely due to inhibition of the metabolism of hexobarbital since most H_2-receptor antagonists are known to inhibit microsomal drug metabolism. Based upon these studies, IY-80843 appears to exert effects on central nervous and cardiovascular systems, probably via a mechanism related to H_2-receptor antagonism, as reported for

Table IX. Summary of effects of IY-80843 on the central nervous and cardiovascular systems

Items	Animals	Route	Dose (mg/kg)	Symptoms
General behavior	Mouse	p.o.	30~100	Ptosis, Decrease of spontaneous locomotor activity
Rectal temperature	"	p.o.	100~300	Hypothermia
Locomotor activity	"	p.o.	100~300	Decrease of spontaneous locomotor activity
Hexobarbital-induced sleeping	"	p.o.	10~100	Prolongation of sleeping time
Blood pressure	SHR	p.o.	30~100	Hypotension
	Dog	i.d.	10~ 30	Hypotension

most H_2-receptor antagonists(Guay *et al.*, 1986; Smith *et al.*, 1987; Epstein *et al.*, 1985; Bemis *et al.*, 1989). However, the potential side effects of IY-80843 on the central nervous and cardiovascular systems would be limited to doses at least several times higher than its ED_{50} values for target effects in rat (10 mg/kg, p.o. unpublished data).

REFERENCES CITED

Bemis, K., Bendele, A., Clemens, J., Deldar, A., Gidda, J. General pharmacology of nizatidine in animals. Arzneim.-Forsch. 39(1) Nr.2 (1989).

Chiverton, SG., Hunt, R.H. Medical regimens in short and long-term ulcer management. *Clin. Gastroenterol.* 2, 255-676 (1988).

Domschke, S., Domschke, W. New histamine H_2-receptor antagonist. *Hepato-Gastroenterology* 27(3), 163-168 (1980).

Dunham, N. W. and Miya, T. S. A note on a simple apparatus of detecting neurological deficit in rats and mice. *J. Amer. pharm. Ass.* 10, 208-209 (1957).

Epstein, CM., Klopper, J. Ranitidine headache. Headache. 25, 392-393 (1985).

Guay, DRF., Metzke, GR. Hypotension after intravenous cimetidine in intensive care unit patients. *Anesthesiology* 65, 130 Letter. (1986).

Irwin, S., In Nodine, J. H. and Siegler, P. E.(Eds) Animal and clinical Pharmacologic techniques in Drug Evaluation. Yearbook Medical publishers, Chicago, 1964, pp. 36-54.

Ireland, A., Gear, P., Colin-Jones, DG., Goldding PL. Ramage JK. Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcer. Lancet II, 274-275 (1984).

Kim, Y. I., Kim, D. Y., Song, Y. H. N-methoxyphenyl Alkyl-N'-Imidazolylphenyl amidine derivatives. Korean patent. Registration No. 94-1776 (1994).

Sabbatini, F., Lazzaroni, M., Petrillo, M., Piai, G. Comparative study of mifentidine and ranitidine in the short-term treatment of duodenal ulcer. *Eur. J. Clin. Parmacol.* 39, 515-517 (1990).

Smith, C., Bardgett, D., Hunter, J. Hemodynamic effect of intravenous administration of cimetidine or ranitidine in the critically ill patient. *Br. J. Anesthesiol.* 59, 1397-1402 (1987).

Susumu, O. and Yoichi, N. Effects of famotidine, a histamine H_2-receptor antagonist, on gastric secretion and gastric and duodenal lesions in rats. *Parmacometrics*, 27(3), 563-569 (1984).

Susumu, O., Hamyo, K. and Hiroshi, O. Effects of a new histamine H_2-receptor antagonist, ranitidine, on experimental acute gastric and duodenal ulcers. *Folia pharmacol.* Japan 77, 397-406 (1981).