Arch. Pharm. Res. Vol. 16, No. 1, pp. 6-12, 1993

The Effects of KR-10876, a New Quinolone Antimicrobial Agent, on the Central Nervous System

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(Received November 17, 1992)

To evaluate KR-10876, a new fluoroquinolone antibacterial agent, its effects on the central nervous system (CNS) were investigated in mice as part of pharmacological study, and the results were compared with those for ciprofloxacin and ofloxacin, two prototypes of quinolone antibacterial agents. All the parameters indicative of CNS function and acute toxicity were measured by close observation of the animals at regular time intervals after oral treatment of test compounds. KR-10876, ciprofloxacin and ofloxacin exerted a dose-dependent effect on the CNS functions studied. KR-10876 did not have any effects on the parameters measured at lower dose (100, 300 mg/kg, p.o.), but at high dose (1,000 mg/kg, p.o.), it caused ptosis, suppressed spontaneous locomotor activity, hypothermia, and prolonged hexobarbital-induced sleeping time. KR-10876 also had a slight effect on motor coordination only at high dose. Simialr to ciprofloxacin and ofloxacin, KR-10876 did not protect mice from pentylenetetrazol-, strychnine-, and electroshock-inducedl convulsions at doses tested. These findings demonstrate that KR-10876 affects CNS functions only at high doses. The rank order for effects is ofloxacin≥KR-10876>ciprofloxacin.

Key words: KR-10876, New fluoroquinolone, Central nervous system, Pharmacology

INTRODUCTION

It is known that quinolone carboxylic acid derivatives have potentials for novel antibacterial agents due to their peculiar antimicrobiological and pharmacokinetic properties. Broad spectrum of antibacterial activity and even distribution in most tissues and body fluids lead this class of compounds to therapeutic applications for many types of infections, including urinary tract infections, gonorrhea, bacterial enteritis, respiratory tract infection, typhoid fever, soft tissue infection, osteomyelitis and tuberculosis (Cohen *et al.*, 1984; Homes *et al.*, 1985; Hooper and Wolfon, 1985; Monk and Campoli-Richand, 1987; Henwood and Monk, 1988; Nenman, 1988; Patou and Reeves, 1988). However, the clinical use of most compounds of this class is limited because of their side effects, especially on the central nervous system (CNS) and cardiovascular system. The adverse effects of these compounds on CNS in humans include headache, dizziness, nausea, vomiting Wijands *et al.*, 1984; Maeson *et al.*, 1984), depression and convulsive seizures (Sipson and Brodie, 1985), and these effects are subserved by their penetrativity through the blood-brain barrier system after oral and i.v. administration (Hashinoto *et al.*, 1975; Tochino *et al.*, 1980). It was also found that quinolones (3-30 mg/kg, i.v.) lowered both systolic and diastolic pressure in anesthetized cats and dogs, probably due to histamine release.

Recently, it has been shown that a new fluroquinolone KR-10876 (structure shown in Fig. 1), being developed by this institute, retains potent broad spectrum antibacterial activities and novel pharmacokinetic properties (Kim *et al.*, 1990) comparable with those of ciprofloxacin and ofloxacin, two prototypes of quinolone antibiotics.

Despite the favorable pharmacological profile of KR-10876, the adverse effects on the central nervous system and in cardiovascular system of most compounds of this class could lead to restriction of the use of these drugs. We therefore tried to further study the pharmacological effects of KR-10876, especially, on CNS and shed some light on the possibility of this compound being developed as a new antimicrobial drug.

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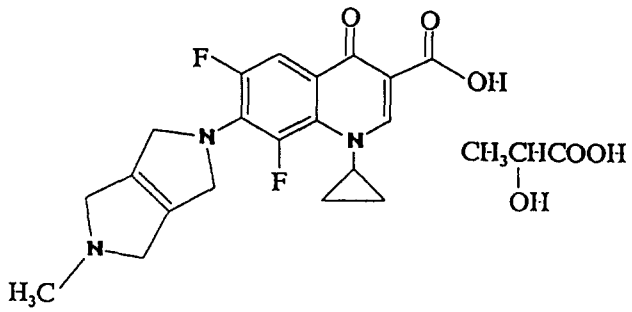

Fig. 1. The Chemical structure of KR-10876, the chemical name of which is 1-Cyclopropyl-6,8-difluoro-7-{7-methyl-3,7-diazabicyclo[3.3.0] Octl(5)en-3-yl}-1,4-dihydro-4-oxoquinoline-3-carboxylic acid lactate.

MATERIALS AND METHODS

Animals

The experiments were performed on male and female ICR mice (20-25 g) and S.D. rats (120-150 g). The animals were purchased 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). Food and water were provided ad lib. Animals were divided into groups at random.

Chemicals

KR-10876, a colorless crystalline powder, was synthesized by this institute. Other drugs, commercially purchased, were: ciprofloxacin·HCl (Sigma). ofloxacin (Hoechst). norfloxacin (Sigma), hexobarbital·Na (Bayer), chlorpromazine·HCl (Fluka), diazepam (Shionogie), fenbufen (Sigma), pentylenetetrazol (Sigma), strychnine·HCl (Sigma). KR-10876, ciprofloxacin·HCl, chlorpromazine·HCl, hexobarbital·Na, strychnine·HCl were dissolved in distilled water, and all the other drugs were suspended in aqueous solution of tween 80 (1%). The test drugs were administered to mice and rats in a volume of 0.1 and 0.5 ml/10 g, respectively.

Acute toxicity

KR-10876, ofloxacin, ciprofloxacin in different dose levels were given once as an oral suspension to both species of animals, 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, 13 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 (weight: 20-25 g) were used in the experiments after 20 h fasting. According to the modified method of Irwin (1964), the behavior of the animals were observed at 0.5, 1, 2, 3, 5 and 24 h after the oral administration of KR-10876, ofloxacin and ciprofloxacin.

Effect on spontaneous motility

Ten groups of 4 female mice (weight: 20-25 g) were used for single dose experiments with KR-10876, ofloxacin, and ciprofloxacin (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 300 min after administration of test drugs.

Effect on motor function (rota-rod test)

Groups of 8 female mice (weight: 25-30 g) were used for single dose experiments with KR-10876, ofloxacin and ciprofloxacin (100-1000 mg/kg, p.o.). The animals which retained on the rotarod for more than 3 min were preselected and randomly distributed to 9 groups. According to the method of Dunhum 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) were counted.

Induction of hexobarbital-induced sleeping time

Groups of 4 female mice (weight: 20-25 g) were used for single dose experiments with KR-10876, ofloxacin and ciprofloxacin (100-1000 mg/kg, p.o.). Hexobarbital·sodium (70 mg/kg) was intraperitioneally injected 30 min after oral administration of test drugs. The duration of a loss of the righting reflex was measured as indicative of the sleeping time.

Protection from pentylenetetrazol-induced convulsions

Groups of 10 female mice (weight: 25-30 g) were used for single dose experiments with KR-10876, ofloxacin and ciprofloxacin (100-1000 mg/kg, p.o.). Test drugs were administered orally 30 min before the injection of the convulsant pentetrazol (100 mg/kg, i.p.) and anticonvulsive activity was determined by measuring loss of clonic seizures and mortality.

Protection from strychnine-induced convulsions

Groups of 10 female mice (weght: 25-30 g) were used for single dose experiments with KR-10876, ofloxacin and ciprofloxacin (100-1000 mg/kg, p.o.). Test drugs were administered orally 30 min before the in-

Table I. LD_{50} values of KR-10876

Species	Sex	Route	LD_{50} (mg/kg)	95% Confidence Limit (mg/kg)
Mouse	Male	p.o.	2140	1596-2521
	Female	p.o.	2042	1941-2774
Rat	Male	p.o.	1056	955-1268
	Female	p.o.	1109	952-1313

jection of the convulsant strychine (2 mg/kg, i.p.) and anticonvulsive activity was determined by measuring loss of tonic seizures and mortality.

Inhibition of electroshock-induced tonic convulsions

Groups of 10 female mice (weight: 25-30 g) were used for single dose experiments with KR-10876, ofloxacin and ciprofloxacin (100-1000 mg/kg, p.o.). Convulsions were induced by applying a single electroshock (50 mA, 0.3 sec) to the ears via bipolar electrodes attached to them.

Test drugs were administered orally 30 min before the application of electroshocks and anticonvulsive activity was determined by measuring loss of tonic extensor seizures.

Interaction with fenbufen for convulsion-inducing effect

Groups of 10 female mice (weight: 20-25 g) were used for the experiment with a single dose only. 10 min after treatment with fenbufen (200 mg/kg, p.o.), animals were given KR-10876, ofloxacin and ciprofloxacin (100-1000 mg/kg, p.o.) and the incidence of convulsion was examined at 0, 30, 60, 120, 180, 360 and 480 min.

RESULTS

Acute toxicity

As shown in Table I, the estimated oral LD_{50} values of KR-10876 were 2140 and 2040 mg/kg for male and female mice, and 1058 and 1109 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, KR-10876 produced the symptoms such as decreased spontaneous activity, ptosis, salivation, hypothermia and tremors. Death occured within 48 h after the oral administration. In survivors, the symptoms disappeared from 1 to 6 hours after the administration. Body weight changes were not noted after the administration of the drug.

Effect on general behavior

As shown in Table II, at low doses tested (100 and

Table II. Effects of KR-10876 on general behavior in mice

Compounds	Vehicle					KR-10876														
Dose (mg/kg, p.o.)	–					100					300					1000				
Time (hr)	0.5	1	2	3	5	0.5	1	2	3	5	0.5	1	2	3	5	0.5	1	2	3	5
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
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
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
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
5. Exophalmos	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	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
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
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
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
10. Diarrhea	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
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
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
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
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
16. Eye lids	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
17. Locomotion	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
18. Respiration rate	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
19. Death	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 man score; max. 8 min. 0 (14-18) and number of animals (19)

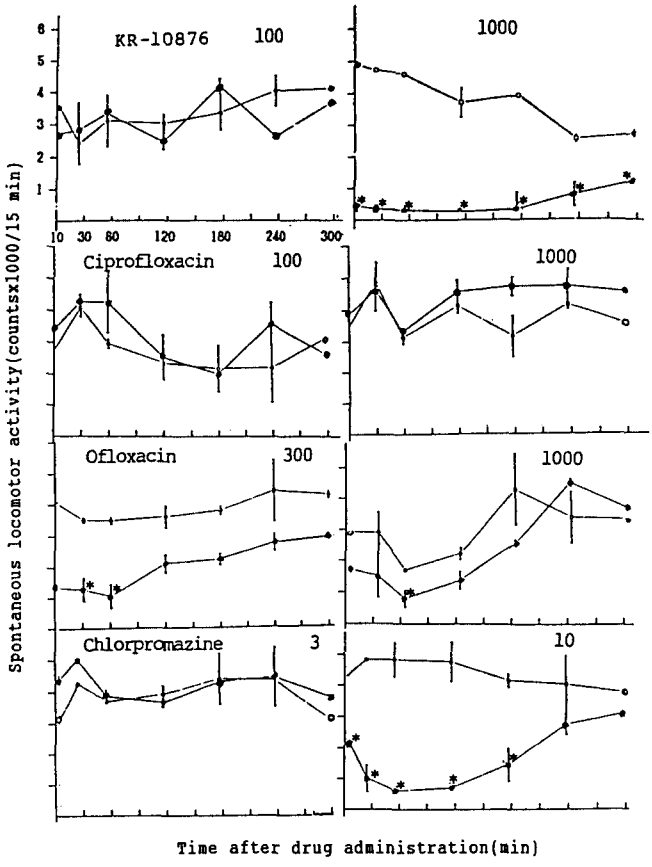

Fig. 2. Time course of changes in spontaneous locomotor activity following oral adminstration (mg/kg, p.o.) of KR-10876, ciprofloxacin, ofloxacin and chloropromazine to mice. Each point is the mean± S.E. (n=4) *p<0.01 (Student's t-test), ○−○ control ●−● Test drug.

300 mg/kg, p.o.), KR-10876 did not exert any effect on the general behavior in mice. At a higher dose (1000 mg/kg, p.o.), however, it caused ptosis and suppressed spontaneous locomotor activity. A significant decrease in body temperature was observed at oral doses of 300 and 1000 mg/kg. Ofloxacin at low doses (100 and 300 mg/kg, p.o.) did not show any effect on the general behavior; however, at a higher dose (1000 mg/kg, p.o.), it caused ptosis, suppressed spontaneous locomotor activity, and decreased the body temperature significantly. Unlike KR-10876 and ofloxacin, ciprofloxacin did not have any effect on both the general hehavior and body temperature, at all doses tested (100-1000 mg/kg, p.o.).

Effect on spontaneous motility

As shown in Fig. 2, KR-10876 produced no changes in spontaneous locomotor activity of mice at low doses (30, 100 and 300 mg/kg, p.o.). However, at a higher dose (1000 mg/kg, p.o.), it caused significant decrease ($p<0.01$), which lasted over a varying period of time (10 to 300 min). Ciprofloxacin (100 to 1000 mg/kg, p.o.) did not depress the spontaneous locomotor activity in mice. Ofloxacin induced no changes in spontaneous activities in mice at a low dose (300 mg/kg, p.o.); however, at a higher dose (100 mg/kg, p.o.), a significant decrease ($p<0.05$) was noted over the period of 10 to 60 min ater administration.

Table III. Effects of KR-10876, Ciprofoxacin and Ofloxacin on motor function in mice

Drug	Dose (mg/kg)	Route	n	Incidence of ataxia (number of mice)							
				10 min	30 min	60 min	120 min	180 min	240 min	300 min	24 h
KR-10876	100	p.o.	8	0	0	0	0	0	0	0	0
	300		8	0	0	0	0	0	0	0	0
	1000		8	0	2	2	1	1	0	0	0
Cipro-	100	p.o.	8	0	0	0	0	0	0	0	0
floxacin	300		8	0	0	0	0	0	0	0	0
	1000		8	0	0	0	0	0	0	0	0
Ofloxacin	100	p.o.	8	0	0	0	0	0	0	0	0
	300		8	0	0	0	0	0	0	0	0
	10000		8	2	2	2	1	0	0	0	0
Diazepam	5	p.o.	8	3	1	0	0	0	0	0	0

Table IV. Effects of KR-10876, Ciprofloxacin and Ofloxacin on hexobarbital-induced hypnosis in mice

Drug	Dose (mg/kg)	Route	n	Sleeping time (min) Means± S.E	Control ratio (%)
Control			6	33.5± 4.4	100
KR-10876	30	p.o.	6	40.6± 6.8	121.0
	100		6	36.8± 3.7	109.8
	300		6	43.1± 4.9	128.6
	1000		6	73.3± 12.4*	218.8
Control			6	39.8± 2.1	100
Ciprofloxacin	100	p.o.	6	45.1± 11.0	113.5
	300		6	45.3± 10.3	113.5
	1000		6	43.6± 7.5	109.5
Control			6	37.1± 7.0	100
Ofloxacin	100	p.o.	6	38.3± 9.0	103.2
	300		6	45.0± 13.5	121.2
	1000		6	61.3± 21.3*	165.2
Control			6	39.8± 2.1	100
Chlorpromazine	3		6	64.8± 6.1*	162.8
	10		6	125.5± 10.7*	314.0

*p<0.01 (wilcoxon sign-test)

Effect on motor function

As shown in Table III, KR-10876 and ofloxacin (100 and 300 mg/kg, p.o.) did not affect the motor coordination in mice. Even at a higher dose (100 mg/kg, p.o.), they had little effect on motor coordination. Ciprofloxacin showed no effect on motor coordination at all doses tested (100-1000 mg/kg, p.o.).

Effect on hexobarbital-induced sleeping time

Table V. Effects of various fluoroquinolone-derivatives on convulsion induced by pentylenetetrazol

Compound	Dose (mg/kg, p.o.)	Pentylenetetrazol (150 mg/kg, i.p)				
		Convulsions (No)	TE-time (min)	Death (No)	Death time (min)	Lethality (%)
Control	0	10/10	<1.0	10	3.5± 1.9	100
Ciprofloxacin	1000	10/10	1.5± 0.5	10/10	5.7± 2.6	100
	300	10/10	<1.0	10/10	3.0± 1.3	100
	100	10/10	<1.0	10/10	3.7± 2.2	100
Ofloxacin	1000	10/10	<1.0	10/10	4.0± 1.8	100
	300	10/10	<1.0	10/10	3.4± 2.1	100
	100	10/10	<1.0	10/10	2.9± 2.7	100
KR-10876	1000	10/10	<1.0	10/10	1.0	100
	300	10/10	<1.0	10/10	1.0	100
	100	10/10	<1.0	10/10	1.0	100
Diazepam	1	6/6	<1.0	6/6	3.6± 1.4	100
	3	6/6	<1.0	0/6	–	0
	10	1/10	6.0	0/10	–	0

Table VI. Effects of various fluoroquinolone-derivatives on convulsion induced by pentylenetetrazol

Compound	Dose (mg/kg, p.o.)	Strychnine (2 mg/kg i.p)				
		Convulsions (No)	TE-time (min)	Death (No)	Death time (min)	Lethality (%)
Control	0	8/8	3.5± 0.5	8/8	3.5± 0.5	100
Ciprofloxacin	1000	10/10	3.7± 0.4	10/10	3.7± 0.4	100
	300	10/10	4.4± 0.6	9/10	4.4± 0.6	90
	100	10/10	5.0± 1.3	8/10	5.0± 1.3	80
Ofloxacin	1000	10/10	3.9± 0.9	10/10	3.9± 0.9	100
	300	10/10	2.9± 0.5	10/10	2.9± 0.5	100
	100	10/10	4.0± 0.8	10/10	4.0± 0.8	100
KR-10876	1000	10/10	4.5± 0.8	10/10	4.5± 0.8	100
	300	10/10	4.8± 0.7	10/10	4.8± 0.7	100
	100	10/10	4.1± 0.7	10/10	4.1± 0.7	100
Diazepam	5	8/8	5.8± 0.9	7/8	5.8± 0.9	87.5
	20	5/8	7.6± 0.5	1/8	24.0	12.5

KR-10876 and ofloxacin (30, 100, and 300 mg/kg, p.o.) showed no effect on sleepintg time; however, at a higher dose (1000 mg/kg, p.o.), they prolonged the sleeping time significantly ($p<0.01$). Unlike KR-10876 and ofloxacin, ciprofloxacin did not affected the sleeping time at all doses tested (100, 300 and 1000 mg/kg, p.o.) as shown in Table IV.

Protection from pentylenetetrazol-induced convulsions

KR-10876, ofloxacin and ciprofloxacin (100, 300 and 1000 mg/kg, p.o.) did not protect pentetrazol-induced convulsions in mice as shown in Table V.

Protection from strychnine-induced convulsions

KR-10876, ofloxacin and ciprofloxacin (100, 300 and 1000 mg/kg, p.o.) did not protect strychnine-induced convulsions in mice as shown in Table VI.

Table VII. Effects of various fluoroquinolone-derivatives on electroshock-induced convulsion

Compound	Dose (mg/kg, p.o.)	Electroshock (20 mA, 0.3 sec)
		Convulsions (No.)
Control	0	5/5
Ciprofloxacin	100	5/5
	1000	5/5
Ofloxacin	100	5/5
	300	5/5
	1000	5/5
KR-10876	100	5/5
	300	5/5
	1000	5/5

Protection from electroshock-induced convulsions

KR-10876, ofloxacin and ciprofloxacin (100, 300 and

Table VIII. Interaction of quinolones and fenbufen for convulsion-inducing effect in mice

Compound	Dose (mg/kg, p.o.)	Convulsions occurrences (min)							Convulsions (No)
		0	30	60	120	180	360	480	
Fenbufen (FNB)	200								0/10
Ofloxacin	100								0/10
	300								0/10
	1000								0/10
	300+FNB200					1			1/10
	1000+FNB200					4	2		6/10
Ciprofloxacin	100								0/10
	300								0/10
	1000								0/10
	300+FNB200		1	2					3/10
	1000+FNB200		7	2					9/10
Norfloxacin	300								0/10
	1000								0/10
	300+FNB200		9	1					10/10
	1000+FNB200		9	1					10/10
KR-10876	100								0/10
	300								0/10
	1000								0/10
	300+FNB200								0/10
	1000+FNB200								0/10

Tble IX. Summary of effects of KR-10876 and reference drugs on the central nervous system

Items	Animals	Dose (mg/kg)	Route	KR-10876	Ofloxacin	Ciprofloxacin
General behavior	mouse	100-1000	p.o.	+	+	−
Locomotor activity				↓	↓	−
Motor function				(↓)	↓	−
Hexobarbital-induced sleeping				+	+	−
Rectal temperature				↓↓	↓	−
Anticonvulsant activity						
Pentylenetetrazol convulsion				−	−	−
Strychnine convulsion				−	−	−
Maximale electroconvulsion				−	−	−
Interaction with fenbufen for convulsion-inducing effect				−	++	++

++=marked effect, +=Present, ( )=week or transient effect
↓↓ or ↑↑=marked decrease (inhibition) or increase (stimulation) compared to control
↓ or ↑=decrease (inhibition) or increase (stimulation) compared to control

1000 mg/kg, p.o.) did not inhibit tonic extension hind limbs in mice as shown in Table VII.

Interaction with fenbufen for convulsion-inducing effect

Concomitant administration of fenbufen (200 mg/kg, p.o.) and various quinolones in mice produced convulsive seizures as shown in Table VIII. Potency rank order for producing convulsions was norfloxacin>ciprofloxacin>ofloxacin.

The incidence of convulsions in mice following the concomitant use of fenbufen (200 mg/kg, p.o.) and two reference quinolones of varing doses was as follows: 10 of 10 mice (norfloxacin 300, 1000 mg/kg, p.o.). 3 of 10 (ciprofloxacin 100 mg/kg, p.o.), 1 of 10 (ofloxacin 300 mg/kg, p.o.), 6 of 10 (ofloxacin 1000 mg/kg, p.o.). KR-10876 (100, 300 and 1000 mg/kg, p.o.), however, did not cause convulsions after a concomitant use with fenbufen (200 mg/kg, p.o.).

CONCLUSIONS

The pharmacological effects of KR-10876 on the central nervous system were studied in animals, comparing results with those for other quinolone antibacterial agents such as ofloxacin and ciprofloxacin.

As summarized in Table IX, at low doses (100, 300 mg/kg, p.o.), KR-10876 and ofloxacin did not alter the CNS function in mice but at higher dose (1000 mg/kg, p.o.) they caused ptosis, suppressed spontaneous locomotor activity and hypothermia, and prolonged hexobarbital linduced sleeping time, with a slight effect on moter coordination. Ciprofloxacin, however, showed no significant effects on the CNS even at high dose (1,000 mg/kg, p.o.). With a concomitant use of fenbufen (200 mg/kg), ciprofloxacin and ofloxacin produced convulsions, but KR-10876 did not.

These results suggest that KR-10876 affects the function of the central nervous system only at higher dose and it does not interact with fenbufen in inducing convulsion *in vivo*. Thus, it is likely that KR-10876 induces no serious side effects on the central nervous system, and its profile of pharmacological action is, in part, similar to that of ofloxacin.

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