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Drug Dependence Potential of Viloxazine Hydrochloride Tested in Rhesus Monkeys

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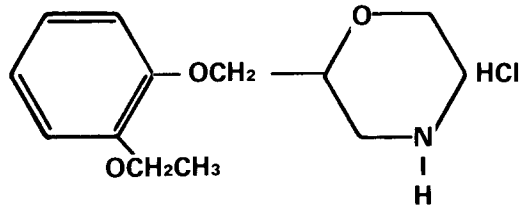
YANAGITA, T., Y. WAKASA AND H. KIYOHARA. *Drug dependence potential of viloxazine hydrochloride tested in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 12(1) 155–161, 1980.—The drug dependence potential of viloxazine was tested in 5 experiments on rhesus monkeys. In gross behavioral observation of normal monkeys the acute CNS effects of the drug were found to be very weak. Decrement of spontaneous motor activity and occasional eye-closing were observed with single doses higher than 16 mg/kg IV, IM and 128 mg/kg PO, while convulsions and death occured at 64 mg/kg IV and IM. Viloxazine did not suppress the morphine and barbital withdrawal signs in monkeys that had been made physically dependent on these drugs and withdrawn. In the test for physical dependence by repeated administration of the drug at 16 mg/kg IM twice daily for 31 days in normal monkeys, no observable withdrawal sign was developed in the naloxone precipitation and natural withdrawal tests. In intravenous self-administration experiments, a weak reinforcing effect was demonstrated in some monkeys, but the effect was extremely weak. Thus, viloxazine was found to be physical dependence-free and its overall dependence potential was regarded as very low.

Viloxazine Dependence potential Physical dependence Self-administration Rhesus monkeys

VILOXAZINE hydrochloride (ICI 58,834, "Vivalan") is an antidepressant developed by ICI Pharmaceutical Division. It is a white crystaline water-soluble compound with the following chemical name and structure (ICI Pharmaceutical Division. Data of VIVALAN for Clinical Investigators. Personal communication. July, 1974):

Chemical name; 2-(2-ethoxyphenoxymethyl) tetrahydro-1,4-oxazine hydrochloride
Structure;



Generic name: viloxazine hydrochloride

It is known that the pharmacodynamic profile of the compound is generally similar to that of the tricyclic depressants but dissimilar in that the compound possesses some anticonvulsant and EEG desynchronizing effects but no anticholinergic and antihistaminic effects [4]. The antidepressant effect of the drug has been clinically demonstrated through many trials, and the early onset of its therapeutic effect as well as its lower incidence of side effects compared to the tricyclic antidepressants such as imipramine have been regarded as clinical advantages of this drug [1, 3, 5, 6].

Concerning the dependence potential of this drug, a preliminary physical dependence study conducted in a limited number of rhesus monkeys found the drug to be physical dependence-free (Greenwood, D. T., *et al.* Evaluation of the dependence liability of ICI 58,834 (viloxazine) hydrochloride, "Vivalan" in the rhesus monkey—A preliminary appraisal. Personal communication. November, 1975). In the present study, the dependence potential of the drug was tested more intensively in rhesus monkeys.

METHOD

Used in the present study were male and female rhesus monkeys (*Macaca mulatta*), imported from India, which were fed with vitamin C (30 mg/monkey) and INAH (75 mg/monkey) with added chow, and conditioned for more than 3 months in group-housing cages.

Viloxazine hydrochloride was dissolved in saline, and various concentrations of the drug solution were used in each experiment.

Gross Behavioral Observation of the Acute Central Nervous System Effects of Viloxazine in Normal Monkeys

Twelve healthy normal adult monkeys housed in group cages received single doses of the drug, following which the animals' gross behavior was observed until the drug effects disappeared using a standardized observational protocol. A closed-circuit television was used as an observation aid, and the monkeys were periodically led from their cages into the aisle individually to examine motor function, muscle rigidity, and rectal temperature. The rectal temperature was determined prior to, and 1 and 2 hours after administration of the

TABLE 1

GRADE OF WITHDRAWAL SIGNS IN MORPHINE DEPENDENT MONKEYS

Mild I, II	Intermediate III, IV	Severe V, VI	Very severe VII, VIII
Apprehension, continual yawning, rhinorrhea, lacrimation, hiccup, shivering, perspiration on face, chattering, quarrelling and fighting	Intention tremor, anorexia, pilomotor activity, muscle twitchings and rigidity, holding the abdomen	Extreme restlessness, assumption of peculiar attitudes, vomiting, severe diarrhea, erection and continued masturbation, inflammation of the eyelids and conjunctiva, continual calling and crying, lying on the side with eyes closed, marked spasticity	Docility in the normally excitable animal, dyspnea, pallor, strabismus, dehydration, weight loss, prostration, circulatory collapse, death

drug. The routes and doses of the drug used were as follow: intravenous, at 1, 4, 8, 16, 32, and 64 mg/kg; intramuscular, at 8, 16, 32, and 64 mg/kg; and oral (intragastric), at 12, 64, and 128 mg/kg. At each dose two monkeys were used as a rule, and at least a 1 week interval was allowed between tests which involved repeated employment of the same animals. Saline was given to 2 monkeys in each test as vehicle control, and all observation was conducted under the blind procedure.

Cross-physical Dependence Test by Single-dose Administration of Viloxazine to Morphine- or Barbital-dependent and Withdrawn Monkeys

Eight monkeys which had been made physically dependent on morphine by repeated subcutaneous administration of 3 mg/kg morphine HCl 4 times daily for more than 1 year and then withdrawn for about 11 hours, received single doses of viloxazine at 8 and 16 mg/kg or saline intramuscularly and morphine at 3 mg/kg subcutaneously. The suppressing effects of the drugs on the morphine withdrawal signs were observed in the group cages with occasional leading out into the aisle of individual monkeys for observation of motor function, muscle rigidity, and rectal temperature, as well as for exaggerating the withdrawal manifestation. Two monkeys were employed for each dose including saline as the control. Observation was conducted under the blind procedure, and the severity of the withdrawal manifestation was graded in accordance with Table 1 [7].

The other test used 11 monkeys which had been made physically dependent on barbital by repeated oral (intragastric) administration of 75 mg/kg free base of barbital twice daily for more than 16 weeks and then withdrawn for about 24 hours. The barbital was suspended in 0.5% carboxymethylcellulose. Single doses of viloxazine at 16 and 32 mg/kg, and of sodium pentobarbital at 12.5 mg/kg were intramuscularly administered to the withdrawn monkeys (3 monkeys being employed for each dose) and the severity of the withdrawal manifestation was graded in accordance with Table 2 [8]. Observations of the suppressing effect of the drug on the barbital withdrawal signs were conducted as in the first experiment.

TABLE 2

GRADE OF WITHDRAWAL SIGNS IN BARBITURATE DEPENDENT MONKEYS

Grade	Signs
Mild	apprehension hyperirritability mild tremor anorexia piloerection
Intermediate	aggravated tremor muscle rigidity impaired motor activities retching or vomiting weight loss (10%)
Severe	convulsions delirium (hallucinatory behavior, nystagmus, dissociation from environment) hyperthermia (> 1.5°C)

Test for Physical Dependence by Repeated Aministration of Viloxazine to Normal Monkeys

Viloxazine was intramuscularly administered to 6 normal monkeys, weighing 4.7 to 6.6 kg, at doses of 16 mg/kg every 12 hours for 31 days. On days 14 and 28 of administration, the naloxone precipitation test was conducted by subcutaneous administration of naloxone in single doses at 1 mg/kg. The animals were naturally withdrawn from day 32 and withdrawal observation was conducted for 5 days. During the administration period, the monkeys' physical condition was observed regularly, with the depth of the drugs' gross behavioral effects and the monkeys' body weights and rectal temperatures being determined weekly. During the withdrawal period, observation for withdrawal signs and determination of body weight and rectal temperature were performed daily. Withdrawal observation was conducted under the blind procedure.

Intravenous Cross Self-administration of Viloxazine with Lefetamine and Saline in Experienced Monkeys

Each monkey was restrained by a stainless steel free-jointed arm and harness in an individual cage. An intravenous catheter delivering drug solution from an automatic drug-infusion machine was implanted through the jugular vein. Food and water were made freely available so that the animal could live in the cage as long as necessary [2]. When the monkey pressed a lever switch in the cage, a predetermined volume of solution was delivered through the catheter, thus allowing the monkey to self-administer the drugs. Six monkeys were trained to self-administer lefetamine, a standard reinforcing drug, at a unit dose of 0.1 mg/kg 4 hours daily from 11 a.m. to 3 p.m. The drug solution was then replaced with saline, and the test was initiated when the monkeys began to discriminiate lefetamine from saline by responding at a higher rate for the lefetamine. The test consisted of 4-hour daily sessions conducted over 3 consecutive days. In each session the agent was tested at a certain fixed unit dose. Each test was started with lefetamine at 0.1 mg/kg/injection, followed by saline, and then by fixed unit doses of viloxazine. This 3-session cycle was repeated for various unit doses of viloxazine in 6 monkeys. The infusion volume and the speed were always 0.25 ml/kg and 23 sec/ml, and the unit dose was regulated by adjusting the concentration of the drug solution. The unit dose of lefetamine was constantly fixed at 0.1 mg/kg. Viloxazine was tested at unit doses of 1.0, 0.25, 0.06, and 0.015 mg/kg (0.015 mg/kg in one monkey only). In each session, the self-administration rate for viloxazine was recorded and compared with those for lefetamine and for saline.

Continuous Intravenous Self-administration of Viloxazine in Experienced Monkeys

The apparatus and general method of this experiment are similar to those described in the previous experiment, but here the animals were allowed to daily self-administer the drug solution at all times around the clock.

The test was started with saline for 1 to 2 weeks until the daily self-administration rate became low (less than 10/day) and stable. At that point, saline was replaced with the viloxazine solution. The volume, speed, and regulation of the unit dose at each injection were as previously described. At first, viloxazine was tested at a unit dose of 4 mg/kg for 14 days. If no frequent intake was observed during this period, the unit dose was either increased or decreased based on the results of observation and the experiment continued.

When monkeys were found not to self-administer the drug at a rate higher than for saline, timer-programmed administration of the drug at 4 mg/kg every 2 hours was conducted for 14 days. During this period the animals were also allowed to self-administer the drug at the same unit dose by lever pressing, and the influence of programmed administration on self-administration of the drug was observed both during and following this period.

When monkeys were found to self-administer the drug at a meaningful rate for 4 weeks or longer, a withdrawal test was conducted for 2 days while the lever pressing rate and gross behavioral changes were observed. Upon termination of the experiment, all monkeys were tested again with saline for 7 days or longer. Throughout the experiment the animals' gross behavior was checked daily, and when animals were found to manifest some drug effects, further careful observation was performed with the same methods described previously in the section on gross behavioral observation of the acute CNS effects. The experiment was conducted in 2 experienced monkeys on the first run, and after the preliminary results had been obtained with the first 2 monkeys, the choice of naive or experienced monkeys as the second pair was to be decided according to the results. In the present experiment, a second pair of experienced monkeys was added and the second run was conducted similarly to the first.

RESULTS

Gross Behavioral Observation of the Acute Central Nervous System Effects of Viloxazine in Normal Monkeys

Intravenous administration of single doses of viloxazine at 4 and 8 mg/kg did not produce any observable effects in monkeys (Table 3). At 16 and 32 mg/kg, 1 out of 2 monkeys in each group showed a slight depression of spontaneous motor activity and awareness while the others did not show any observable change. At 64 mg/kg, 2 out of 2 monkeys convulsed immediately after administration and died by respiratory arrest within a few minutes.

In intramuscular administration of the drug, 8 mg/kg did not produce any observable effects. At 16 mg/kg a slight depression was observed in 1 monkey for about 1 hour. At 32 mg/kg both monkeys showed depression for about 3 hours, and one showed motor impairment. At 64 mg/kg, 2 out of 2 monkeys died with convulsions 10 to 20 minutes after administration.

In oral administration of the drug by the gavage doses up to 64 mg/kg produced no observed effects. About 4 hours after administration of 128 mg/kg, 3 out of 3 monkeys manifested depression and motor impairment and 1 monkey convulsed when chased into the aisle. The depressant effect continued for about 6 hours.

Cross-physical Dependence Test by Single-dose Administration of Viloxazine to Morphine- or Barbital-dependent and Withdrawn Monkeys

When morphine-dependent monkeys had been withdrawn for about 11 hours from the last dose, such intermediate-grade withdrawal signs as apprehension, tremor, piloerection, holding of the abdomen, restlessness, unusual body posture, vocalization, quarrelling, and abdominal muscle rigidity were observed in all monkeys. Viloxazine showed no suppression effect on these signs at intramuscular single doses of 8 and 16 mg/kg. Morphine at 3 mg/kg SC suppressed most of these signs (Table 4).

When barbital-dependent monkeys were withdrawn for about 24 hours, 9 out of 11 monkeys manifested such intermediate-grade withdrawal signs as hyperirritability, tremor, muscle rigidity, motor incoordination, and restlessness while the other 2 monkeys further manifested convulsions. Single-dose administration of viloxazine at 16 and 32 mg/kg, IM to these monkeys did not produce any suppression of these signs, but provoked convulsions in both monkeys of the 32 mg/kg group. Sodium pentobarbital at 12.5 mg/kg IM suppressed the signs considerably (Table 5).

Test for Physical Dependence by Repeated Administration of Viloxazine to Normal Monkeys

Viloxazine was repeatedly administered to 5 normal

TABLE 3

GROSS BEHAVIORAL OBSERVATION OF ACUTE CNS EFFECTS OF VILOXAZINE IN NORMAL RHESUS MONKEYS

Drug	Route	Dose (mg/kg)	No. of monkeys	Major signs	Time course (hr) Onset	Duration
Viloxazine	IV	4.0	2	None	—	—
		8.0	2	None	—	—
		16.0	2	Occasional eye-closing Decrease of spontaneous motor activity Holding abdomen	1/2	1/2
		32.0	2	Ibid	1/2	1/2
		64.0	2	Died after convulsions	immediate	
	IM	8.0	2	None	—	—
		16.0	2	Occasional eye-closing Decrease of spontaneous motor activity	1/6	1
		32.0	2	Occasional eye-closing Decrease of spontaneous motor activity Holding abdomen Nearly falling from the pearch	1/3	3
		64.0	2	Died after convulsions	1/3	
	PO	32.0	2	None		
		64.0	2	None		
		128.0	3	Decrease of spontaneous motor activity Impaired motor activity Convulsed after chasing	4	10

monkeys at doses of 16 mg/kg IM twice daily for 31 days. During the administration period a slight suppression of spontaneous motor activity and awareness was observed for about 4 hours following each injection. No indication of the development of tolerance to the effect was observed throughout the period. Body weight and rectal temperature did not show any meaningful change. Naloxone precipitation tests were conducted on days 14 and 28 of administration, but no withdrawal signs were observed. The animals were naturally withdrawn from day 32 for 5 days, during which time the body weight showed a very slight decrease, body temperature showed no meaningful change, and no withdrawal sign was observed (Table 6).

Intravenous Cross Self-administration of Viloxazine with Lefetamine and Saline in Experienced Monkeys

All 6 monkeys self-administered lefetamine at high rates, and the daily average of all lefetamine sessions for each monkey was 149.3 to 289.2 injections per 4 hours (Table 7). Although there were individual differences in the rate, the rates for each monkey were quite stable. All monkeys took saline at low rates. The rates for viloxazine were slightly higher on the average in 6 monkeys, but the rates were still considerably lower than those for lefetamine, and further, no dose-related increase in rate was observable from the results.

TABLE 4

ATTEMPTED SUPPRESSION OF MORPHINE WITHDRAWAL SIGNS BY SINGLE DOSE ADMINISTRATION OF VILOXAZINE IN PHYSICALLY DEPENDENT AND WITHDRAWN MONKEYS*

Drug	Dose (mg/kg)	Route	No. of animals	Grade of withdrawal signs before administration† ( ) No. of animals	Suppression of withdrawal signs ( ) No. of animals	Note
Control (Saline)	0.2 ml	IM	2	Intermediate (2)	None (2)	
Viloxazine (3.2%)	8.0	IM	2	Intermediate (2)	None (2)	
	16.0	IM	2	Intermediate (2)	None (2)	
Morphine (1.5%)	3.0	SC	2	Intermediate (2)	Incomplete (2)	Apprehension and intension tremor still observed

*Physical dependence produced by subcutaneous administration of morphine at doses of 3.0 mg/kg every 6 hours for longer than 1 year, withdrawn for about 11 hours.

†Graded following Table 1.

TABLE 5

ATTEMPTED SUPPRESSION OF BARBITAL WITHDRAWAL SIGNS BY SINGLE DOSE ADMINISTRATION OF VILOXAZINE IN PHYSICALLY DEPENDENT AND WITHDRAWN MONKEYS*

Drug	Dose (mg/kg)	Route	No. of animals	Grade of withdrawal signs before administration† ( ) No. of animals	Suppression of withdrawal signs ( ) No. of animals	Duration of complete suppression (hr)	Note
Control (Saline)	0.5 ml	IM	2	Intermediate (2)	None (2)		
Viloxazine (3.2%)	16.0	IM	3	Intermediate (2) Severe (1)	None (3)		
	32.0	IM	3	Intermediate (3)	None (3)		
Sodium pento-barbital (2.5%)	12.5	IM	3	Intermediate (2) Severe (1)	Incomplete (2) Complete (1)	0.5–1	Aggravated tremor still observed

*Physical dependence produced by oral administration of barbital at doses of 75 mg/kg every 12 hours for longer than 16 weeks, withdrawn for about 24 hours.
†Graded following Table 2.

TABLE 6

ATTEMPTED DEVELOPMENT OF PHYSICAL DEPENDENCE BY REPEATED INTRAMUSCULAR ADMINISTRATION OF VILOXAZINE* IN NORMAL MONKEYS

Monkey	Body weight (kg)				Grade of withdrawal signs		
	Initial	14th day	28th day	Withdrawal period†	Naloxone test (1.0 mg/kg, SC) 14th day	Naloxone test (1.0 mg/kg, SC) 28th day	Natural withdrawal test for 5 days
No. 943 (female)	4.7	4.9	4.8	4.6	None	None	None
No. 951 (female)	5.0	5.0	4.7	4.6	None	None	None
No. 618 (male)	5.1	5.2	5.2	5.0	None	None	None
No. 937 (male)	5.2	5.4	5.4	5.3	None	None	None
No. 961 (male)	6.6	6.5	6.7	6.6	None	None	None

*Dosing schedule: 16 mg/kg, IM twice daily for 31 days.
†Minimum body weight during the 5-day withdrawal period.

TABLE 7

INTRAVENOUS CROSS SELF-ADMINISTRATION OF VILOXAZINE WITH LEFETAMINE AND SALINE IN RHESUS MONKEYS

Monkey		Average daily (4 hr) number	Percent ratio of self-administration rate, lefetamine as 100%				
		Lefetamine 0.1/kg/inj	Saline 0.25 ml/kg/inj	Viloxazine 1.0 mg/kg/inj	Viloxazine 0.25 mg/kg/inj	Viloxazine 0.06 mg/kg/inj	Viloxazine 0.015 mg/kg/inj
No. 848 (male)	4.7 kg	186.1	11.5	12.5	11.7	10.2	—
No. 788 (male)	3.5 kg	289.2	6.2	12.4	7.3	5.6	—
No. 753 (male)	3.9 kg	190.3	5.6	10.5	5.9	14.6	—
No. 768 (male)	4.6 kg	247.8	6.5	17.9	8.1	24.9	7.3
No. 862 (male)	2.8 kg	167.4	4.3	5.4	10.0	3.6	—
No. 780 (female)	4.1 kg	149.3	16.3	14.3	14.3	27.3	—
Mean ± SD		—	8.4 ± 4.6	12.3 ± 4.2$^{N.S.}$	9.6 ± 3.1$^{N.S.}$	14.4 ± 9.9$^{N.S.}$	—

N.S.: not significant against saline.

TABLE 8

INTRAVENOUS CONTINUOUS SELF-ADMINISTRATION OF VILOXAZINE IN RHESUS MONKEYS

Monkey	Naive or experienced	Average daily number of self-administration: Saline 0.25 ml/kg /inj. for 7 days	4 mg/kg/ inj. for 14 days	8 for 14 days	1 for 14 days	4 for 14 days	4 for 14 days	4 program† for 14 days	4 for 14 days	4 for 14 days	Saline for 2 days	4 for 14 days	1 for 14 days	Saline for 7 days	
No. 761 female 3.2 kg	experienced*	4.0	3.8	2.4	—	—	—	1.3	1.0	—	—	—	—	1.0	(1st day 4) (2nd day 2)
No. 857 male 4.3 kg	experienced*	2.9	4.1	6.6	—	—	—	—	10.6	11.3	(1st day 16) (2nd day 0)	10.7	38.9	15.7	(1st day 39) (2nd day 23)
No. 858 male 3.9 kg	experienced*	4.4	8.6	—	1.8	6.6	3.1	1.9	4.0	—	—	—	—	15.1	(1st day 15) (2nd day 29)
No. 256 female 5.4 kg	experienced*	0.28	0.07	—	—	—	—	0	0	—	—	—	—	0.28	(1st day 1) (2nd day 1)

*Previously experienced with intravenous self-administration of other drugs and rested from the experiment for longer than 1 month.
†Programmed administration of doses of 4 mg/kg every 2 hours added to the self-administration.

Continuous Intravenous Self-administration of Viloxazine in Experienced Monkeys

Two monkeys, Nos. 761 and 857, were tested first. Both monkeys showed low rates for saline (Table 8). When they were tested with viloxazine at a unit dose of 4 mg/kg, the rate remained low. Two weeks later the unit dose was doubled to 8 mg/kg. This time No. 857 showed some increase in rate during 2 weeks of observation, so the observation was further continued by decreasing the unit dose again to 4 mg/kg. Four weeks later a 2-day withdrawal test with self-administration of saline was conducted in this monkey during which the monkey took saline 16 times on the 1st day and nil on the 2nd day. No withdrawal sign was observed in this test. When the self-administration of viloxazine was resumed, the monkey took the drug at a rate similar to the previous rate. Finally the unit dose was decreased to 1 mg/kg at which the intake increased by nearly 4 times. The monkey was tested with saline again, and took it 39 times on the 1st day and 23 times on the 2nd day, and an average of 15.7 times per day over 7 days. No withdrawal sign was observed in this period. No. 761 and the other 2 experienced monkeys which were newly added to the experiment did not take the drug at any meaningful rate, so timer-programmed administration of the drug at 4 mg/kg every 2 hours was performed for 2 weeks leaving the self-administration schedule intact. Still no active intake was observed during or after this 2-week period. No. 857 occasionaly vomitted as he took the drug at relatively high doses, but otherwise no observable drug effects were noted during the experiment.

DISCUSSION

The acute effects of viloxazine on the gross behavior of rhesus monkeys were extremely weak, with the minimal effective doses being determined as 16 mg/kg by the intravenous and intramuscular routes and 128 mg/kg by the oral route. The central nervous system effects observed in the gross behavior were very weak in comparison with other psychotropic agents and no effect which seemed to be specific to viloxazine was observed in normal rhesus monkeys. Motor impairment and convulsions can be attributable to its acute toxic effects.

Viloxazine was found to be physical dependence-free in the experiments. This conclusion was readily reached due to the clear-cut nature of the experimental results. Although observation was limited to the gross behavioral effects, development of tolerance seems unlikely.

Contrary to this, some positive but weak reinforcing effect was observed in both self-administration experiments. But in the cross self-administration experiment the effect varied from one monkey to the other and from one unit dose to the other, with no dose-related increases of the self-administration rate being observed in the individual or group results. In the continuous self-administration experiment only 1 out of 4 monkeys took the drug at a meaningful rate, but even here the total daily intake was relatively low because the daily dose level was approximately 40 mg/kg on the average for each period, which was less than 3 times the aforementioned minimal effective dose. All these findings indicate that the reinforcing effect of viloxazine is extremely weak if present at all. Since viloxazine does not possess any noteworthy acute gross-behavioral effects or physical dependence potential, and since its reinforcing effect is very weak, the overall dependence potential of the drug can be regarded as very low.

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