SOME PHARMACOLOGICAL ACTIONS OF CYCLIZINE, CHLORCYCLIZINE AND HOMCHLORCYCLIZINE

By

V.K. PENDSE AND B.R. MADAN

Department of Pharmacology, S.P. Medical College, Bikaner

Three antihistamines namely, cyclizine (1-diphenylmethyl-4-methyl piperazine), chlorcyclizine [1-(4-chlorobenzhydryl)-4-(methyl piperazine)] and homchlorcyclizine (N-*p*-chlorobenzhydryl-N-methyl homopiperazine) have been reported to exert a variety of actions on cardiovascular system (13, 14). In an extension of this work, the actions of these drugs on smooth and skeletal muscles, neuromuscular junction and central nervous system have been investigated and form the basis of this report.

MATERIALS AND METHODS

Fresh solutions of cyclizine, chlorcyclizine and homchlorcyclizine were prepared in distilled water in which these compounds are freely soluble.

In experiments which required intraperitoneal administration of drugs in rats, concentrations of solutions were adjusted so that the volume injected never exceeded 0.1 *ml*/100 *gm*.

I. SMOOTH MUSCLE :

Isolated smooth muscle preparation of rabbit's intestine was set up according to the method described by Burn (2). Ability of antihistamines in concentration of 3 $\mu g/ml$ to antagonise the response induced by 0.15 $\mu g/ml$ of acetylcholine was tested. Also, the influence of the drugs on the spontaneous motility of rabbit's intestine was investigated in doses of 0.1 μg and 3 $\mu g/ml$.

II. SKELETAL MUSCLE :

(1) *Frog's rectus abdominis muscle preparation*

Frog's rectus muscle preparation was set up according to the method described by Burn (2). Control tracings were taken by adding acetylcholine, 1 $\mu g/ml$. Ability of antihistamines to antagonise this response was tested in doses of 0.3 μg and 1 $\mu g/ml$.

(2) *Phrenic nerve-diaphragm preparation*

Three experiments were conducted for each drug in this preparation which was set up according to the method of Bulbring (1).

Muscle contractions due to the direct and indirect (through phrenic nerve) were recorded before and after addition of the drugs. Ability of neostigmine, 3 $\mu g/ml$, to antoganize the blocking effect of antihistamines was also tested.

III. CENTRAL NERVOUS SYSTEM :

(1) *Spontaneous motor activity (SMA)*

For testing effects of drugs on spontaneous motor activity (SMA) of rats, method described by Vad *et al.* (21) was employed with slight modification (19). Fifty-two male albino rats weighing between 105 *gm* and 250 *gm* were used. One rat was tested at a time. Drugs were administered intraperitoneally in doses of 5 *mg*, 10 *mg* and 30 *mg/kg*.

(2) *Conditioned response (CR)*

A group of 30 albino rats of both sexes weighing between 120 *gm* and 180 *gm* were used for training in the Cook's pole-climbing apparatus. During training the buzzer and the shock were simultaneously applied as described by Chittal and Sheth (3). The rats were trained initially three times a day. After a week's training, the buzzer was tried and the shock was applied only when the rat did not climb the pole within three seconds of the buzzer. On the day of the experiment, all the rats were given a trial run before administration of the drugs to ensure uniformity of response. Drugs were administered intraperitoneally in doses of 10 *mg* and 30 *mg/kg*.

(3) *Pentobarbital hypnosis*

Ninety albino rats of both sexes weighing between 100 *gm* and 200 *gm* were randomly divided into seven groups, one group of 30 animals and six groups of 10 animals each. The former served as control and was given distilled water intraperitoneally, the latter groups received antihistamines in doses of 5 *mg* and 10 *mg/kg*. After half an hour, all the animals were given pentobarbital, 20 *mg/kg* intraperitoneally. The time in minutes for loss and subsequent recovery of righting reflex was recorded.

(4) *Anti-tremor activity*

Anti-tremor activity was studied in 38 adult albino rats of both sexes weighing between 60 *gm* and 150 *gm* which were divided into seven groups, one group of 8 animals and six groups of 5 each (6, 7). The control group received only tremorine, 16 *mg/kg* intraperitoneally. Visible fine tremors of head, limbs and body with rigidity, salivation, lacrimation and diarrhoea appeared in 10 to 15 minutes. Antihistamines, 5 *mg* and 20 *mg/kg* intraperitoneally, were administered 30 minutes prior to tremorine in other groups.

(5) *Analgesic activity*

Analgesic activity of antihistamines in doses of 5, 10 and 20 *mg/kg* was investigated in 45 albino rats of both sexes weighing between 100 *gm* and 255 *gm*. Five rats were used for each dose. The details of the method have already been described (12).

In addition, 25 albino rats of both sexes weighing between 120 *gm* and 240 *gm* were used for testing the ability of antihistamines to potentiate the effect of morphine. Sub-analgesic dose of morphine, 300 *µg/kg*, was injected intraperitoneally in 10 rats which served as control group. In the remaining animals morphine and drugs under study were given simultaneously.

RESULTS

I. SMOOTH MUSCLE :

Five experiments were conducted for each dose of each drug. All the drugs caused a decrease in normal tone of intestinal muscle. Recovery was complete after washing the preparation with Tyrode's solution. None of the drugs modified acetylcholine-induced contraction of ileal piece.

II. SKELETAL MUSCLE :

(1) *Frog's rectus muscle preparation*

The antihistamines reduced the acetylcholine-induced contraction of rectus abdominis muscle (Table I). Recovery was not complete for one hour when drugs were tried in a dose of 1 *μg/ml.*

TABLE I

Effects of cyclizine, chlorcyclizine and homchlorcyclizine on acetylcholine-induced contraction of the rectus abdominis muscle of frog

S. No.	*Drug*	*Final concentration of drug (μg/ml)*	*No. of observations*	*Mean percentage reduction in acetylcholine response (SE)*
1	Cyclizine	0.3	6	24.9 (0.25)
		1.0	6	64.5 (0.20)
2	Chlorcyclizine	0.3	6	23.3 (0.77)
		1.0	6	64.2 (0.25)
3	Homchlorcyclizine	0.3	6	30.2 (0.68)
		1.0	6	61.0 (1.75)

(2) *Phrenic nerve-diaphragm preparation*

In phrenic nerve-diaphragm preparation, all the drugs in a concentration of 15 *μg/ml* caused inhibition of muscular contraction by 25 to 50% both due to direct and nerve stimulation. The inhibition, which was persistent, was no. reversed by neostigmine.

III. CENTRAL NERVOUS SYSTEM :

(1) *Spontaneous motor activity (SMA)*

Change in SMA depended on the dose of antihistamines. At lower doses, SMA was inhibited while higher doses enhanced SMA (Table II).

TABLE II

Effect of cyclizine, chlorcyclizine and homchlorcyclizine on spontaneous motor activity of rat

Dose (mg/kg)	Drug	Cyclizine		Chlorcyclizine		Homchlorcyclizine	
		Movements per hour ± SE		Movements per hour ± SE		Movements per hour ± SE	
		Control	After injection of drug	Control	After injection of drug	Control	After injection of drug
5		200±3.77 (6)	57±1.66	381±4.92 (5)	141±5.91	246±1.25 (8)	78±3.00
10		415±3.33 (7)	144±3.19	183±3.52 (5)	610±3.88	129±6.50 (5)	184±6.60
20		266±3.34 (6)	759±2.22	199±2.25 (5)	317±2.25	126±7.40 (5)	252±2.35

Figures in parentheses represent number of animals employed.

(2) *Conditioned response (CR)*

All the three drugs did not show any effect on CR. At 30 *mg/kg*, the antihistamines exhibited toxic symptoms in the form of piloerection and fine tremors (Table III).

TABLE III

Effect of cyclizine, chlorcyclizine and homchlorcyclizine on conditioned reflex in rats

S. No.	Drug	Dose (mg/kg)	No. of animals		Toxicity
			Used	Avoided response	
1	Cyclizine	10	5	0	
2	Cyclizine	30	5	0	Piloerection, fine tremors.
3	Chlorcyclizine	10	5	0	
4	Chlorcyclizine	30	5	0	Piloerection, fine tremors.
5	Homchlorcyclizine	10	5	0	
6	Homchlorcyclizine	30	5	0	Piloerection, fine tremors.

(3) *Pentobarbital hypnosis*

The sleeping time due to pentobarbital was prolonged by the prior administration of all the drugs (Table IV).

TABLE IV

Effect of cyclizine, chlorcyclizine and homchlorcyclizine on pentobarbital sleeping time in rats

S. No.	*Drug*	*Dose (mg/kg)*	*No. of animals*	*Mean sleeping time (in minutes) ±(SE)*	
1	Control	–	30	57.5	(0.42)
2	Cyclizine	5	10	139.2	(0.32)
3	Chlorcyclizine	5	10	81.3	(0.84)
4	Homchlorcyclizine	5	10	138.5	(0.42)
5	Cyclizine	10	10	92.7	(0.59)
6	Chlorcyclizine	10	10	113.2	(0.47)
7	Homchlorcyclizine	10	10	119.8	(0.36)

(4) *Anti-tremor activity*

None of the drugs had any protective action against the tremorine-induced tremors (Table V).

TABLE V

Effect of cyclizine, chlorcyclizine and homchlorcyclizine on tremorine-induced tremors in rats

S. No.	*Drug*	*Dose (mg/kg)*	*No. of animals employed*	*No. of animals protected from*	
				Tremor	*Salivation*
1	Tremorine (Control)	..	8	0	0
2	Cyclizine	5	5	0	0
		20	5	0	0
3	Chlorcyclizine	5	5	1	1
		20	5	0	0
4	Homchlorcyclizine	5	5	0	0
		20	5	0	0

(5) *Analgesic activity*

None of the drugs had any analgesic activity of its own, nor was there potentiation of morphine analgesia.

DISCUSSION

Cyclizine, chlorcyclizine and homchlorcyclizine have been found in this study to inhibit the tone of rabbit's intestine. This appears to be a direct relaxant action on the smooth muscle and is in agreement with the observations of previous workers for other antihistamines (8, 11).

Antagonism to the acetylcholine-induced contracture of the frog's rectus muscle and inhibition of contractions of diaphragm by direct and indirect (through phrenic nerve) stimulation indicate that both the muscular and neuromuscular apparatuses are involved. Block of the latter is persistent and is neither antagonized nor aggravated by neostigmine. Such a neostigmine-resistant neuromuscular block has been reported previously by Choksey and Jindal (4) for other antihistamines. Since cyclizine, chlorcyclizine and homchlorcyclizine have been reported to possess local anaesthetic activity (13), they may be interfering with the release of acetylcholine as has been described by Paton and Zaimis (17, 18).

While the antihistamines are inactive on CR, tremorine-induced tremors and pain-threshold, they influence the SMA which is depressed in small doses and augmented in large doses. However, at all dose levels, they invariably potentiate pentobarbital hypnosis. Although no attempt has been made to elucidate the mechanism of this action, it is pertinent to mention that these drugs lower normal body temperature in rats and mice (9, 16); and hypothermic agents are known to enhance the sleeping time due to barbiturates (5, 10, 15, 16).

SUMMARY

Cyclizine, chlorcyclizine and homchlorcyclizine were studied for their actions on smooth and skeletal muscles, neuromuscular transmission and central nervous system.

They inhibit the tone of rabbit's intestine. While no antagonism is exhibited to the acetylcholine-induced contraction of the smooth muscle of intestine, they depress the contraction of the frog's rectus muscle produced by acetylcholine.

In rat's phrenic nerve diaphragm preparation, these antihistamines induce a persistent neuromuscular blockade which is neither potentiated nor antagonized by neostigmine. It is perhaps due to interference with the release of acetylcholine at neuromuscular junction.

While spontaneous motor activity is decreased in small doses and enhanced in large doses, there is invariably a potentiation of pentobarbital hypnosis in rats. These drugs do not exert any influence on conditioned response, tremorine-induced tremors and pain-threshold in rats.

ACKNOWLEDGEMENT

Grateful acknowledgement is made to Burroughs Wellcome & Co., Bombay, India, for the generous supply of cyclizine and chlorcyclizine and to Abbott Laboratories, North Chicago, Illinois, for homchlorcyclizine.

REFERENCES

1. Bulbring, E. Observations on isolated phrenic nerve diaphragm preparation of rat. *Brit. J. Pharmacol.* **1**:38, 1946.

2. Burn, J.H. Practical Pharmacology. Blackwell Scientific Publications Ltd., Oxford. 1952.

3. Chittal, S.M. and U.K. Sheth. Effect of drugs on conditioned avoidance response in rats. *Arch. Int. Pharmacodyn.* **144**:471, 1963.

4. Choksey, H.K. and M.N. Jindal. Mechanism of neuromuscular blockade by some antihistaminic compounds. *Arch. Int. Pharmacodyn.* **157**:339, 1965.

5. Courvoiser, S., J. Founel, R. Ducrot, M. Kolsky and P. Koetschet. Proprietes pharmacodynamiques du chlorhydrate de chloro-3(dimethylamino-3' propyl)-10 phenothiazine (4.560 RP); etude experimental d'un nouveau corps et dans l'hibernation artificielle. *Arch. Int. Pharmacodyn.* **92**:305, 1953.

6. Everett, G.M. Tremor produced by drugs. *Nature* (London). **177**:1238, 1956.

7. Everett, G.M. Animal and clinical pharmacologic techniques in drug evaluation, edited by Nodine and Siegler. Year Book Medical Publishers, Inc., Chicago. 359, 1964.

8. Halpern, B.N. Les antihistaminiques de synthese. Essais de chimiotherapie des etats allergiques. *Arch. Int. Pharmacodyn.* **68**:339, 1942.

9. Kimura, E.T., P.R. Yong and R.K. Richards. Pharmacologic properties of N-*p*-chlorobenzhydryl-N'-methyl homopiperazine dihydrochloride (Homchlorcyclizine; S.A.-97), a serotonin antagonist. *J. Allergy.* **31**:237, 1960.

10. Kopera, J. and A.K. Armitage. Comparison of some pharmacological properties of chlorpromazine, promethazine, and reserpine. *Brit. J. Pharmacol.* **9**:392, 1954.

11. Loew, E.R. Pharmacology of antihistamine compounds. *Physiol. Rev.* **27**:542, 1947.

12. Madan, B.R., J.D. Sharma and D.S. Vyas. Some neuropharmacological actions of librium. *Ann. Biochem. Exp. Med.* **22**:221, 1962.

13. Madan, B.R. and V.K. Pendse. Antiarrhythmic, anticonvulsant and local anaesthetic activity of cyclizine, chlorcyclizine and homchlorcyclizine. *Indian Heart. J.* 1969 (in press).

14. Madan, B.R. and V.K. Pendse. Some cardiovascular actions of cyclizine, chlorcyclizine and homchlorcyclizine. *Indian Physicol. J. Pharmacol.* 1969 (in press.)

15. Malhotra, C.L., P.K. Das and N.S. Dhalla. Some neuropharmacological actions of hersaponin—an active principle from *Herpestis monniera* Linn. *Arch. Int. Pharmacodyn.* **129**:290, 1960.

16. Norton, S., K.I. Kolville, A.E. Light, A.L. Wnuck, R.V. Farelli and E.J. de-Beer. Pharmacologic properties of cyclizine hydrochloride (Marezine). *J. Pharmacol. Exp. Ther.* **112**:297, 1954.

17. Paton, W.D.M. and E.J. Zaimis. Actions and clinical assessment of drugs which produce neuromuscular block. *Lancet.* **2**:568, 1950.

18. Paton, W.D.M. and E.J. Zaimis. Actions of d-tubocurarine and of decamethonium on respiratory and other muscles in cat. *J. Physiol.* **112**:311, 1951.

19. Pendse, V.K. Pharmacological actions of cyclizine, chlorcyclizine and homchlorcyclizine with special reference to central nervous system. Thesis, M.Sc. (Medicine) Pharmacology. University of Rajasthan, 1967.

20. Swinyard, E.A., H.H. Wolf, G.B. Fink and L.S. Goodman. Some neuropharmacological properties of thioridazine hydrochloride (Mellaril). *J. Pharmacol. Exp. Ther.* **126**:312, 1959.

21. Vad, B.G., D.S. Shrotri and J.H. Balwani. A new technique for recording spontaneous motor activity. *Indian. J. Physiol. Pharmacol.* **7**:153, 1963.