SOME CARDIOVASCULAR ACTIONS OF CYCLIZINE, CHLORCYCLIZINE AND HOMCHLORCYCLIZINE

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Antihistamines are known to exert a variety of actions on cardiovascular system (4, 11, 14, 17 and 18), some of which have formed the basis for their clinical trials (5, 6, 10). Hence it wasconsidered of interest to investigate the hitherto unexplored actions of some anti-histamines viz., cyclizine, chlorcyclizine and homchlorcyclizine, on various circulatory parameters. This communication reports the results of such investigations.

MATERIALS AND METHODS

Drugs studied are : cyclizine hydrochloride (1-Diphenyl-methyl-4-methyl piperazine), chlorcyclizine hydrochloride [1-(4-chlorobenzyhydryl)-4-(methyl piperazine)] and homchlorcyclizine dihydrochloride (N-p-chlorobenzyhydryl-N'-methyl homopiperazine). Fresh solutions of 1% concentration were prepared in distilled water. The doses refer to the weight of the salts.

1. Blood pressure, heart rate and splenic volume

Adult mongrel dogs of both sexes weighing between 10 *kg* and 18.9 *kg* were anaesthetized with pentobarbital (Nembutal), 30 *mg/kg* I/V. 12 animals were used for each drug. Systemic blood pressure was recorded from a cannulated carotid or femoral artery. Spleen volume was recorded by an oncometer connected to a tambour. Both the vagi were cut and artificial respiration under positive pressure was instituted after cannulating the trachea to minimise the possibility of respiratory changes influencing cardiovascular system. A femoral vein was cannulated and connected to a burette containing normal saline. The drugs were injected rapidly into the cannulated vein and flushed with 5 *ml* of saline.

In addition, the ability of cyclizine, chlorcyclizine and homchlorcyclizine to modify blood pressure responses to central and peripheral vagal stimulation, carotid occlusion, administration of acetylcholine, adrenaline and noradrenaline was tested. One drug was tried in one animal.

2. Dog heart *'in situ'*

Adult mongrel dogs of both sexes weighing between 12.3 *kg* and 21.0 *kg* were used. They were anaesthetized with pentobarbital (Nembutal) 30 *mg/kg* I/V. Chest was opened in the mid-line and a pericardial cradle was made by suturing the four flaps of the cut pericardium on thoracic wall. Artificial respiration under positive pressure was instituted before opening

the chest. Auricular and ventricular contractions were recorded kymographically by the suspe sion method of Jackson (8) through a system of pulleys and Brodie's heart lever.

3. Isolated frog heart perfusion

The experimental procedure as described by Burn (3) was employed in all essential detai The drugs were studied for their effect on heart rate and contractility.

4. Femoral blood flow

This was measured in dogs weighing between 9 *kg* and 21 kg, anaesthetized with pent barbital, 30 *mg/kg* I/V. The anticoagulant used was heparin, 400 units/*kg* I/V. The l femoral artery was perfused by arterial blood derived from the animals's own cannulated caroti artery. The drug was given directly into the perfused femoral artery and changes in the tim taken by the bubble to cover the distance between the entry and the exit of the flow-meter we measured by a stop watch (13).

RESULTS

When the blood pressure had stabilized for 15 to 20 minutes after the operative procedur drugs were injected.

1. Effect on blood pressure, heart-rate and splenic volume

Cyclizine, chlorcyclizine and homchlorcyclizine in doses of 1 *mg*, 3 *mg* and 5 *mg/kg* cause a fall in mean arterial blood pressure which returned to normal within 2 to 5 minutes. The inte sity of effect was dose dependant. As regards effect on heart rate, cyclizine at all dose level caused an increase in heart rate while chlorcyclizine and homchlorcyclizine caused a decrea in heart rate.

All the three drugs caused a decrease in splenic volume. The results are summarize in Table I.

2. Modification of blood pressure responses to various procedures

Cyclizine (3 *mg/kg* I/V) caused a satistically significant reduction of blood pressur response to peripheral vagal stimulation and to administration of acetylcholine and adrenalin There was no significant change in the response to noradrenaline, central vagal stimulatio and carotid occlusion. Chlorcyclizine (3 *mg/kg* I/V) brought about a reduction in the bloo pressure response to peripheral vagal stimulation while the effect of noradrenaline was augmen ed. These findings are statistically significant. No statistically significant change was observe in the blood pressure response to central vagal stimulation, acetylcholine, adrenaline an carotid occlusion. Homchlorcyclizine (3 *mg/kg* I/V) brought about a statistically significan reduction of blood pressure response to peripheral vagal stimulation and acetylcholine whi modification of blood pressure response to central vagal stimulation, adrenaline, noradrenalin and carotid occlusion was not statistically significant. Results are summarized in Table II an illustrated in figure 1.

TABLE I

Effect of Intravenous Administration of Cyclizine, Cholor-cyclziine and Homchlorcyclizine on heart rate, mean blood pressure and splenic volume

S. No.	Drug	Dose (mg/kg)	Mean Percentage change		
			Heart rate ±S.E. (beats/min.)	Mean blood pressure ±S.E. (mm. Hg.)	Splenic Volume
1.	Cyclizine	1	+17.95±1.01	—33.20±0.05	Decrease
		3	+20.20±1.21	—58.95±3.15	Decrease
		5	+30.50±1.13	—76.70±2.25	Decrease
2.	Chlorcyclizine	1	— 7.57±0.15	—33.03±4.10	Decrease
		3	—11.90±2.10	—67.17±2.35	Decrease
		5	—21.87±1.25	—84.97±2.05	Decrease
3.	Homchlorcyclizine	1	—12.10±2.10	—17.50±0.15	Decrease
		3	—13.90±1.30	—46.80±2.15	Decrease
		5	—19.70±1.05	—73.70±2.45	Decrease

(+) denotes an increase, (—) denotes a decrease
The results are the average of four experiments for each dose.

3. Effect on dog's heart '*in situ*'

Cyclizine, 3 *mg/kg*, exerted a positive inotropic effect while chlorcyclizine and homchlorcyclizine in doses of 3 *mg/kg* elicited negative inotropic responses. Inotropic effects were transient and lasted for 2 to 5 minutes. Results are summarized in Table III.

TABLE III

Effect of Intravenous Administration of 3 mg/kg of Cyclizine, Chlorcyclizing and Homchlorcyclizine on dog's Heart in Situ

S. No.	Drug	No. of observations	Average percentage change in contraction	
			Auricle ±SE	Ventricle ±SE;
1.	Cylizine	3	+51.1±5.25	+36.1±3.33
2.	Chlorcyclizine	3	—33.3±4.19	—30.3±4.23
3.	Homchlorcyclizine	3	—39.1±4.26	—19.1±3.21

(+) denotes an increase (—) denotes a decrease

TABLE II

Effect of Intravenous Administration of 3 mg/kg of Cyclizine, Chlorcyclizine and Homchlorcyclizine on Blood Pressure Response to Central and Peripheral Vagal Stimulation, Acetyicholine, Adrenaline, Noradrenaline and Carotid Occlusion in Dogs

Procedure and drug	No. of observations	Cyclizine: Mean percentage change in B.P. (mm Hg) Before	Cyclizine: Mean percentage change in B.P. (mm Hg) After	Cyclizine: Difference (SE) P	Chlorcyclizine: Mean percentage change in B.P. (mm Hg) Before	Chlorcyclizine: Mean percentage change in B.P. (mm Hg) After	Chlorcyclizine: Difference (SE) P	Homchlorcyclizine: Mean percentage change in B.P. (mm Hg) Before	Homchlorcyclizine: Mean percentage change in B.P. (mm Hg) After	Homchlorcyclizine: Difference (SE) P
Cetral-vagal stimulation	5	*+39.22	+49.22	+10.00 >.05 (4.67)	+45.76	+37.38	—8.48 >.05 (2.40)	+48.94	+56.74	+7.80 >.05 (2.1)
Peripheral vagal stimulation	5	**—70.20	—18.42	—51.78 <.001 (7.52)	—63.92	—30.52	—33.40 <.001 (2.90)	—48.46	—8.68	—39.78 <.02 (11.12)
Acetyl-choline-	5	—48.86	—29.42	—19.44 <.02 (5.47)	—45.90	—34.86	—11.04 >.05 (4.04)	—44.24	—20.26	—23.98 <.001 (3.14)
Adrenaline	5	+47.66	+34.24	—13.42 <.05 (3.98)	+46.14	+40.96	—5.18 >.05 (5.08)	+50.20	+42.82	—7.38 >.05 (5.05)
Noradrena-line	5	+47.56	+41.20	—6.36 >.05 (2.77)	+28.92	+46.10	+17.18 <.05 (5.14)	+33.46	+27.96	—5.50 >.05 (1.8)
Carotid occlusion	5	+37.70	+44.42	+6.72 >.05 (2.44)	+28.56	+24.96	—3.60 >.05 (2.20)	+28.22	+25.14	—3.08 >.05 (0.65)

*(+) denotes a rise in blood pressure

**(—) denotes a fall in blood pressure

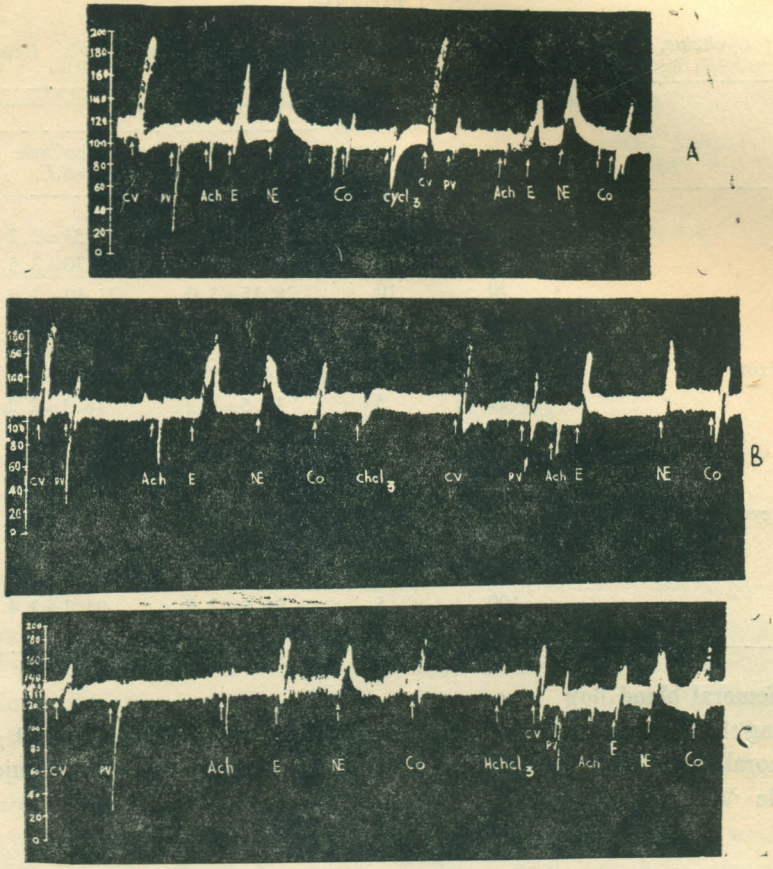

Fig. 1

Effect of antihistamines on blood pressure responeses to various procedures in the anaesthetized dogs. Each strip is from a different animal.

CV	-Central vagal stimulation
PV	-Peripheral vagal stimulation
Ach.	-Acetylcholine
E	-Adrenaline
NE	-Noradrenaline
CO	-Carotid occlusion
$CyCl_3$	-Cyclizine 3 mg/kg
$ChC1_3$	-Chlorcyclizine 3 mg/kg
$Hchcl_3$	-Homchlorcyclizine 3 mg/kg

4. Effect on isolated perfused frog's heart

In doses ranging between 3 μg and 100 μg all the three durgs at all dose levels studied caused a decrease in heart rate and a decrease in amplitude of contractions (Table IV). Recovery was complete every time and duration and intensiy were proportional to the dose.

TABLE IV

Effect of Cyclizine, Chlorcyclizine and Homchlorcyclizine on Perfused Frog's Heart

S. No.	Drug	Dose (in μg)	No. of observations	Percentage Reduction		Recovery (In min.) ±S.E
				Heart rate ±S.E.	Amplitude ±S.E.	
1.	Cyclizine	3	10	10.31±1.7	9.53±2.2	1.9±0.1
		10	10	12.31±1.6	10.70±3.5	3.4±0.2
		30	10	28.35±3.0	27.40±3.6	6.9±0.2
		100	5	100.00±0.0	97.00±1.1	17.8±1.1
2.	Chlorcyclizine	3	5	14.4±1.5	15.1±3.3	4.9±0.3
		10	5	17.5±6.2	18.3±2.2	6.7±0.2
		30	5	24.2±2.4	20.7±3.1	16.6±0.6
		100	5	67.0∓3.5	94.3±1.3	57.4±1.3
3.	Homchlorcyclizine	3	5	12.7±3.6	12.5±1.5	4.4±0.3
		10	5	26.9±7.2	14.2±4.6	13.2±0.8
		30	5	27.5±4.0	52.8±7.5	36.4±1.1
		100	5	95.9±2.6	94.7±3.4	61.8±0.8

5. Effect on femoral blood flow

Following the intra-arterial administration of all the drugs in doses of 10 μg, 30 μg, and, 100 μg/kg femoral blood flow was increased without any change in the systemic arterial blood pressure (Table V) .

DISCUSSION

Cyclizine, chlorcyclizine and homchlorcyclizine produce a fall of blood pressure. Factors responsible for the hypotensive action of a drug are many, only a few of which have been elucidated in this study. All the drugs cause an increase in the femoral blood flow which represents a direct vasodilator action since it is not accompanied by any change in the other circulatory parameters (13). Vagolytic action of a drug causes an increase in heart rate. However, chlorcyclizine and homochlorcyclizine, which induce a peripheral vagal blockade, exert a negative chronotropic effect in the intact anesthetized dog. This may be attributable to their direct depressant effect on the sinoatrial node as is also evidenced by the results obtained in the perfused frog's heart preparation. Cyclizine, which shares the inhibitory actions of other antihistamines on the amphibian heart, brings about an increase in the rate and amplitude of myocardial contractions in the intact dog. While the effect on the rate appears to be the result of its ability to block the vagus, the changes in contractility may not be interpreted as the direct positive inotropic effect of the drug on the dog's heart since extracardiac factors may increase recordings of contractile force exclusive of any direct myocardial stimulation by a drug (2, and 12). No attempt has been made in this study to determine the nature of these extracardiac actions.

TABLE V

Effect of Cyclizine , Chlorcyclizine and Homchlorcyclizine on Femoral Blood Flow of Dog

S. No.	Drug	Dose (μg/kg) intra-arterially	No. of observations	Time for bubble to flow, mean ±S.E. (in seconds)		Mean percentage increase in flow ±S.E.
				Before the drug	After the drug	
1.	Cyclizine	10	5	16.8±1.6	11.6±1.2	30.95±25
		30	5	17.8±1.5	10.8±1.4	37.39±2.8
		100	5	17.4±1.7	9.6±1.3	48.67±1.8
2.	Chlorcyclizine	10	5	19.6±3.1	12.2±0.9	34.94±4.8
		30	5	20.2±2.8	10.0±0.9	49.27±2.6
		100	5	20.6±2.6	8.8±0.9	56.97±9.8
3.	Homchlorcyclizine	10	5	21.2±2.5	12.2±1.0	41.56±2.2
		30	5	22.4±2.9	10.0±1.2	55.04±2.1
		100	5	22.4±2.9	8.0±1.1	64.02±1.8

Central vasomotor mechanisms do not seem to be involved in causing a fall of blood pressure since the blood pressure responses to carotid occlusion and central vagal stimulation are not significantly modified by antihistamines. Peripheral adrenergic blockade by cyclizine as evidenced by the reduction of the responses of blood pressure to adrenaline is in corroboration of the findings of previous workers (1, 9, 15). Homchlorcyclizine does not have any significant effect on the blood pressure responses to adrenaline and noradrenaline. While chlorcyclizine does not modify the action of adrenaline on blood pressure, it causes a statistically significant increase in the noradrenaline-induced pressor effect. Such selective augmentation of noradrenaline response has been reported previously for mepyramine (7) and BP 400 (14). The basic mechanism for this differential action on the response to catecholamine remains elusive.

Effects of various antihistamines on peripheral cholinergic mechanisms are interesting. Cyclizine and homchlorcyclizine block or reduce the vasodepressor effects of peripheral vagal stimulation and acetylcholine administration. Chlorcyclizine shares the property of other two antihistamines in antagonizing the effects of peripheral vagal stimulation. However, it does not appreciably reduce the vasodepressor action of acetylcholine injection. This may be attributable to the fact that the site of block may be central to the site of action of acetylcholine-presumably by interference with the release of acetylcholine (16).

SUMMARY

Some cardiovascular actions of cyclizine, chlorcyclizine and homchlorcyclizine have been investigated. All the drugs cause hypotension, peripheral vagal blockade, direct femoral vascular dilatation and depression of the force of contraction of perfused frog's heart. While

cyclizine brings about an increase in the rate and force of contraction of dog's heart 'in situ chlorcyclizine and homchlorcyclizine exhibit negative inotropic and chronotropic effects.

The blood pressure responses to central vagal stimulation, carotid occlusion and to t administration of catecholamines and acetylcholine are modified differently by the antihist mines. Cyclizine reduces the response to acetylcholine and adrenaline. Chlorcyclizine e hances the pressor effect of noradrenaline. Homchlorcyclizine antagonizes the effect of acety choline. The responses of blood pressure to other procedures are not modified significant by these drugs. These results have been discussed in the light of findings obtained by othe workers.

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