SUPPRESSION OF CYCLOPROPANE-EPINEPHRINE ARRHYTHMIAS IN DOGS BY FOUR PHENOTHIAZINE DERIVATIVES

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IN ADDITION to the wide use of phenothiazine derivatives in the field of mental disease a number also have been employed successfully as premedicants in general and regional anesthesia (1–3). Pharmacological investigations have demonstrated that certain phenothiazines have a number of actions on the autonomic nervous system which may be related to their use in anesthesia. These actions include ganglionic blockade, adrenergic blockade, antihistaminic, and anticholinergic action (3–9). A point of particular importance in the use of cyclopropane or trichlorethylene as anesthetic agents is the protection afforded by several derivatives against experimental hydrocarbon-epinephrine arrhythmias (3, 4, 6, 10–12).

The present study compares the effectiveness of perphenazine, chlorpromazine, promazine, and mepazine in preventing the arrhythmias resulting from epinephrine administration to dogs under cyclopropane anesthesia.

METHODS

The dogs were anesthetized with thiopental sodium, 25 mg./kg. intravenously, and an endotracheal tube was inserted. Each animal was administered cyclopropane 16 per cent in oxygen delivered at a rate of 600 ml./minute (100 ml. cyclopropane plus 500 ml. oxygen). The excess gas in the rebreathing bag was permitted to escape to the outside atmosphere. Blood pressure was recorded in the femoral artery by a mercury or glass membrane manometer. Polyethylene tubing was placed in the external jugular vein for intravenous injections. A lead 2 electrocardiogram was recorded continuously during infusion of epinephrine on a direct writing instrument.

The procedure for evaluation of the activity of the phenothiazine derivatives was based on that described by Cummings and Hays (13). Epinephrine challenges were started after a forty-five minute period of equilibration on 16 per cent cyclopropane. The initial concentration of epinephrine (Adrenalin) was adjusted for each animal to contain 1 microgm./kg./ml. (1x-epinephrine). This solution was infused

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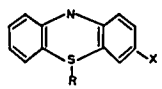
intravenously at a constant rate of 3 ml./minute (3 μg./kg./minute) until the appearance of *multiple ventricular* ectopic beats. Nodal beats or occasional ventricular ectopics were not considered an endpoint and epinephrine administration was continued until multiple ventricular ectopics appeared. Three or four control runs were completed at fifteen minute intervals. The epinephrine solutions were kept in an ice bath during the entire experiment to prevent reduction in potency.

The compounds under study (fig. 1) were injected intravenously after a consistent endpoint for epinephrine was obtained. Dose levels of 0.1, 1.0 or 5.0 mg./kg. were studied in individual animals. The control concentration (1x) of epinephrine was tested fifteen minutes



COMPOUND	X	R
PERPHENAZINE	−Cl	$-CH_2CH_2CH_2-N\langle\rangle N-CH_2CH_2OH$
CHLORPROMAZINE	−Cl	$-CH_2CH_2CH_2-N(CH_3)_2$
PROMAZINE	−H	$-CH_2CH_2CH_2-N(CH_3)_2$
MEPAZINE	−H	$-CH_2-\langle\rangle N-CH_3$

FIG. 1. Phenothiazine derivatives used in this study.

after the phenothiazine derivatives. If an endpoint did not occur with a total of 10 ml., a higher concentration of epinephrine, 10 μg./kg./ml. (10x-epinephrine), was tested in fifteen minutes, also at the rate of 3 ml./minute until the endpoint or a total of 10 ml. had been administered. Finally, if protection was still present, a 1:1000 epinephrine solution (75–100x epinephrine) was used up to total of 10 milliliters.

RESULTS

Effect of Epinephrine Before Phenothiazine Derivative.—The characteristic changes produced by the epinephrine infusion, in the majority of animals, consisted of gradual development of sinus tachycardia, the appearance of occasional ectopic beats or bigeminal rhythm and finally the multiple ectopic activity (figs. 2, 3, 4). A-V dissociation with the development of nodal rhythm occurred in about 30 per cent of the

animals before the ventricular ectopic activity was established. Sinus or nodal bradycardia was observed in a few animals. The electrocardiographic changes which occurred before the multiple ectopic endpoint were consistent within an animal and usually were not altered markedly by the doses of the phenothiazine derivatives that prevented the development of the arrhythmia.

Hypertension was observed in every animal during the control (1x) epinephrine infusions. The blood pressure increased to a maximum of about 250 to 280 mm. of mercury regardless of the control level.

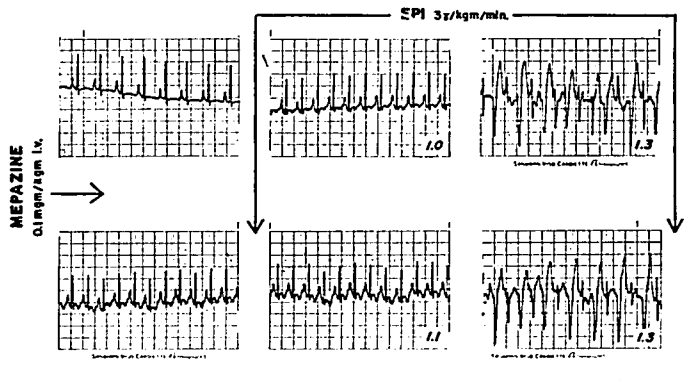


FIG. 2. Effect of mepazine, 0.1 mg./kg. The control electrocardiogram is on the left; the other electrocardiograms are during the period of epinephrine administration. The upper set of electrocardiograms were recorded before the drug and the lower set after the drug. The dose of epinephrine, in μg./kg., which produced the first ectopic beat is given on the records in the center section, while the dose which produced the multiple ectopic beats is given on the records in the left section. Paper speed was 25 mm./second. Note that mepazine did not block the arrhythmia.

Effect of Epinephrine After the Phenothiazine Derivatives.—Although certain doses of these compounds were effective in preventing the development of multiple ectopic beats (figs. 2, 3, 4 and table 1), the other electrocardiographic alterations produced by epinephrine were usually not markedly modified; approximately seventy per cent of the animals showed the same pattern of change after drug as was observed before drug administration. However, this was not always true when higher concentrations of epinephrine were used.

Typical examples of the electrocardiographic changes for a highly effective compound (perphenazine) and a relatively ineffective compound (mepazine) are given in figures 2, 3, and 4. Mepazine, 0.1 mg./kg., afforded no protection in the experiment depicted in figure 2, as

the arrhythmia developed at 1.3 μg./kg. of epinephrine before and after drug. Note the sinus tachycardia before the arrhythmia.

The effectiveness of a low dose of perphenazine (0.1 mg./kg.) is illustrated in figure 3. The original concentration of epinephrine (1 μg./kg.) did not produce an arrhythmia at a total dose of 10 milliliters. However, when the 10x-epinephrine was used, an arrhythmia resulted at a total of 75 μg./kg. compared with a control value of 1.6 μg./kg. It

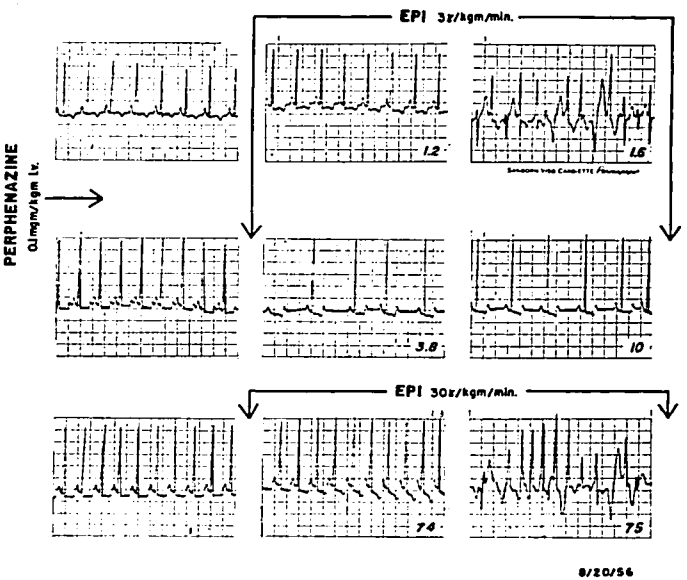


FIG. 3. Effect of perphenazine, 0.1 mg./kg.—blockade of 1x-epinephrine. Remainder of legend as in figure 2. Note the increase in epinephrine dose required to produce the arrhythmia (from 1.6 to 75 μg./kg.).

is interesting to observe that the 1x-epinephrine produced no change in sinus rate before drug and sinus bradycardia after drug. On the other hand, the 10x-epinephrine did not alter the sinus rate. Figure 4 illustrates the effect of 5 mg./kg. of perphenazine. In this case it was necessary to administer a 1:1,000 solution of epinephrine (75–100x) to achieve the endpoint. Sinus tachycardia occurred with epinephrine administration at all times. The extent of the increase in heart rate was related to the rate of epinephrine administration.

In addition to producing blockade of the arrhythmic effects of epi-

nephrine these phenothiazine derivatives also produced reversal of the hypertensive effect. However, there is an important distinction in the dosage of compound required to block these two actions of epinephrine. Considerably higher doses of each compound were required to reverse the hypertension than to block the arrhythmia (tables 1 and 3).

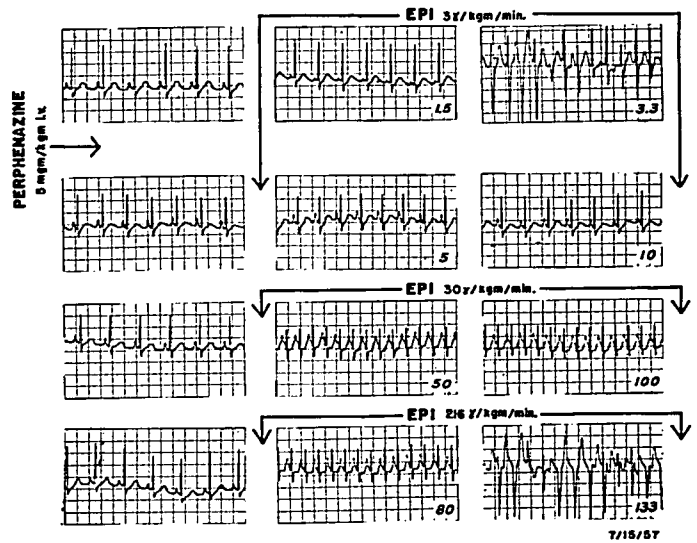


FIG. 4. Effect of perphenazine, 5.0 mg./kg.—blockade of 1x- and 10x-epinephrine. Remainder of legend as in figures 2 and 3.

Comparison of Compounds—Antiarrhythmic Action.—In general, perphenazine was the most active compound, chlorpromazine and promazine were somewhat intermediate and mepazine was much less active (fig. 5). If the activity of perphenazine was assigned the value of 100, chlorpromazine and promazine would range between 30 and 50, and mepazine between 5 and 10. These values are based on the ratio of $\frac{\text{epinephrine dosage after drug}}{\text{epinephrine dosage before drug}}$ (fig. 5).

The compounds can be compared in another way by considering the number of animals protected against the various concentrations of epinephrine. Perphenazine, at 0.1 mg./kg., prevented the arrhythmic effect of the 1x-epinephrine in 75 per cent of the animals, and at 5 mg./

TABLE 1

PROTECTION AGAINST ARRHYTHMIC EFFECT OF VARIOUS CONCENTRATIONS OF EPINEPHRINE

Dose (mg./kg.)	Compound	Epinephrine* Concentration: Relative to Control			
		1x Number protected / Number Test	10x Number protected / Number Test	75–100x Number protected / Number Test	Remarks 10x
0.1	Perphenazine	3/4	0/3	—	
	Chlorpromazine	2/4	0/3	—	2/3 VF
	Promazine	1/2	0/1	—	
	Mepazine	0/2	0/1		1/1 VF
1.0	Perphenazine	3/3	1/3	0/3	
	Chlorpromazine	3/3	1/3	0/3	
	Promazine	3/3	0/2	—	2/2 VF
	Mepazine	1/3	0/2	—	1/2 VF
5.0	Perphenazine	3/3	3/3	2/3	
	Chlorpromazine	1/1	1/1	0/1	
	Promazine	2/2	2/2	1/2	
	Mepazine	4/4	0/4	1/1	1/4 VF

* Maximum volume administered at each concentration 10 ml. unless arrhythmia appeared at smaller volume.
VF = venticular fibrillation.

kg. all animals were protected against the 10x-epinephrine and 2 out of 3 against 75–100x epinephrine. Chlorpromazine and promazine were slightly less effective than perphenazine at 0.1 mg./kg. and almost equally effective at 1 and 5 mg./kg. With mepazine, 5 mg./kg. were required to protect against the lowest concentration of epinephrine. It will be noted in table 1 that ventricular fibrillation resulted with

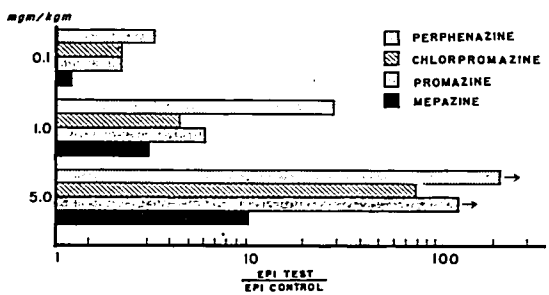


FIG. 5. Comparison of effect of perphenazine, chlorpromazine, promazine, and mepazine at various doses. The logarithmic scale on the bottom indicates the ratio of $\frac{\text{epinephrine dose after compound}}{\text{epinephrine dose before compound}}$

10x-epinephrine in a few of the experiments in animals treated with chlorpromazine, promazine or mepazine. The fibrillation occurred immediately after ectopic activity started. In untreated animals the incidence of fibrillation wtih 1x-epinephrine was 2 of 60 animals and at 10x-epinephrine 3 out of 7. Again, the fibrillation occurred with the onset of ectopic activity.

After observing that the initial ectopic activity occasionally led to ventricular fibrillation even though epinephrine had been discontinued, it was of interest to determine the effects of higher doses of epinephrine. Therefore, the administration of epinephrine was continued beyond the ectopic beat endpoint in a number of control and drug treated

TABLE 2

"REVERSAL" OF EPINEPHRINE HYPERTENSION

Dose (mg./kg.)	Compound	Epinephrine Concentration: Relative to Control		
		1x Number Reversal / Number Test	10x Number Reversal / Number Test	75–100x Number Reversal / Number Test
0.1	Perphenazine	0/4	0/3	
	Chlorpromazine	0/3	0/3	
	Promazine	0/2	0/1	
	Mepazine	0/2	—	
1.0	Perphenazine	1/3	0/3	0/2
	Chlorpromazine	1/3	0/3	—
	Promazine	1/3	0/3	—
	Mepazine	0/3	0/1	—
5.0	Perphenazine	3/3	3/3	0/3
	Chlorpromazine	1/3	0/2	0/2
	Promazine	2/2	0/2	0/2
	Mepazine	1/3	0/4	0/1

animals. The results on 7 control and 36 treated animals indicate that if fibrillation did not occur at the onset of ectopic activity with 10x-epinephrine it would not occur even though the epinephrine administration was continued until a total of 10 ml. was given. Further, if fibrillation did not occur with 10x-epinephrine it did not occur with 75–100x epinephrine.

"Reversal" of Epinephrine Hypertension.—The data summarized in table 2 demonstrate that perphenazine at 5 mg./kg. produced "reversal" of hypertensive action of 1x and 10x-epinephrine solutions. Chlorpromazine and promazine, at 5 mg./kg., produced some reversal of the 1x-epinephrine but did not block the hypertensive action of 10x-epinephrine. Mepazine was the least active having slight blocking effect at the 5 mg./kg. dose and none at 1 mg./kg.

Discussion

Perphenazine, chlorpromazine, promazine, and mepazine afford some degree of protection against cyclopropane-epinephrine arrhythmias. The order of effectiveness among the compounds appears to be related to the order of adrenergic blockade based on "reversal" of the pressor effect of epinephrine. Perphenazine was most active; chlorpromazine and promazine had about thirty to fifty per cent the activity of perphenazine and mepazine from five to ten per cent.

Some investigators have suggested that the arrhythmia provoked by sympathomimetic amines in cyclopropane anesthetized animals was associated with the pressor action (14–16). However, recent work by Cummings (13) indicated that the pressor action was not necessary since isoproterenol, which has a depressor action, produced arrhythmias in such animals. He suggested that the positive inotropic action of certain adrenergic drugs is associated with production of arrhythmia. Our data indicate that blockade of the pressor action of epinephrine is not a prerequisite for blockade of the arrhythmia.

Summary

Perphenazine, chlorpromazine, promazine and mepazine protected dogs against cyclopropane-epinephrine arrhythmias. Perphenazine was most active; chlorpromazine and mepazine had 30–50 per cent the activity and mepazine 5–10 per cent the activity of perphenazine.

These compounds reversed the pressor action of the epinephrine but at considerably higher doses than those required to prevent the arrhythmia.

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ANNUAL SESSION

AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

The 1958 Annual Meeting of the American Society of Anesthesiologists (Preliminary Program, Sept.–Oct. 1958 Issue, page 709) and the Ninth Annual Refresher Course Program (July–Aug. 1958 Issue, page 585) were canceled because of a hotel employees strike at the Penn-Sheraton Hotel, Pittsburgh, Pennsylvania, headquarters for the 1958 Annual Meeting.

A limited Annual Session was rescheduled for November 17–21, 1958, at the Palmer House, Chicago.