

## MYOCARDIAL IRRITABILITY: PHARMACODYNAMIC CONTROL BY MEPAZINE (PACATAL) IN DOGS

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RECENT developments in cardiac surgery have attracted considerable attention to the desirability of pharmacodynamic control of cardiac activity during surgical procedures. The stabilization of the heart action to mechanical, thermic, pharmacologic and metabolic influences, as well as those exerted by electrolytes, must be considered in any study related to this problem. Individuals in the field of surgery and anesthesiology are particularly concerned with the problem of avoiding disturbances of the impulse formation, especially ventricular fibrillation. For that reason the knowledge of drugs which may serve to prevent such disturbances is of utmost importance.

The following report is concerned with findings in a study using the phenothiazine derivative N-methyl-piperidyl-(3)-methyl-phenothiazine (mepazine). This drug, first described in its pharmacologic actions by Nieschulz, Pependiker and Sack (1), has been found in experimental studies with dogs to depress the irritability of the myocardium to mechanical and thermic stimuli (2, 3, 4). These findings have been corroborated in clinical usage related not only to surgical and anesthesiology problems but to disturbances of rhythmicity encountered in myocarditis (5, 6, 7).

The depressant effect on the irritability of the myocardium seemed to be mainly one of a local anesthetic nature which was most apparent after intravenous application of the drug. This action was designated as "intravasal anesthesia of the heart" (Gadermann and Donat) and proved to be superior to the effect obtained with either topical or intravenous administration of procaine (2). This effect seems to be a primary property of mepazine (Pacatal) although depression of myocardial irritability has been reported with other phenothiazine derivatives such as chlorpromazine (8, 9, 10, 11).

It was the purpose of this investigation to determine the protective effects of mepazine on the heart under cyclopropane anesthesia when epinephrine was injected.

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## METHOD

A modification of the method described by Meek, Hathaway and Orth (13) was used. Twenty mongrel dogs, weighing between 6.5 kg. and 18.6 kg. (average weight 10.5 kg.), were anesthetized with cyclopropane-oxygen mixtures and tracheal intubation was performed to insure an open airway. The dogs were then connected through a soda-lime carbon dioxide absorber to an 80-liter bag containing a 33 per cent-35 per cent mixture of cyclopropane in oxygen. After the animals had rebreathed the anesthetic mixture for 30 minutes, epinephrine in a concentration of 0.005 mg./kg. was injected intravenously in approximately four seconds.

Cyclopropane, oxygen and carbon dioxide content of the arterial blood was determined by the method of Orcutt and Waters using the Van Slyke-Neill manometric apparatus (14). The arterial blood samples were drawn as soon after the epinephrine injections as was technically possible (one to five minutes).

Electrocardiograms were taken prior to and during the injection of epinephrine and throughout the subsequent period of irregularities until either ventricular fibrillation occurred or a regular sinus rhythm was re-established. In seven dogs simultaneous kymographic tracings were made of the femoral arterial pressure.

One week after the controls were run, mepazine was administered and the procedure repeated. Gadermann and Donat in earlier work (2) stressed the importance of administering mepazine in divided doses in order to obtain optimal blood concentration. Since no satisfactory method for determining the effective blood level of mepazine was available we decided to follow their recommendations and therefore the drug was given as follows: 2.5 mg./kg. intramuscularly 90 to 135 minutes (average 123 minutes) prior to the injection of epinephrine, 2.5 mg./kg. intravenously both 25 minutes and 5 minutes prior to the injection of epinephrine (total dose 7.5 mg./kg.). The inconsistency of the time of intramuscular injections was the result of unforeseen delays during the procedure. No difference in the effect of mepazine was observed when given within this time span.

To demonstrate the reproducibility of the effects the entire experiment was repeated under the same conditions in dogs numbers 3, 8 and 9. Identical results were obtained. In two dogs (numbers 6 and 7) only the control was repeated; whereas in dogs numbers 1, 2 and 10 the mepazine study was repeated. In dogs numbers 16 to 20 the experiment was done in reverse order administering epinephrine first to the dogs who were given mepazine followed by the control epinephrine test one week later.

Changes in the normal impulse formation with disappearance of sinus rhythm and occurrence of either ventricular or auricular extrasystoles were considered a significant epinephrine effect. Changes in

heart rate alone were not considered as a significant epinephrine effect as long as the sinus rhythm was maintained. Also not considered significant in this study were changes in the S-T interval.

## RESULTS

Cyclopropane sensitizes the heart of the dog to intravenously injected epinephrine as shown earlier by Meek and coworkers (13). Using a modification of their technique it was found that following 30 minutes of cyclopropane-oxygen anesthesia, epinephrine in doses of 0.005 mg./kg. given over a period of four seconds intravenously consistently produced significant disturbances of cardiac rhythm (table 1). In all dogs changes in heart rhythm or impulse formation occurred within 11 to 24 seconds after injection of epinephrine and lasted 10 to 62 seconds. In most cases there first appeared sinus tachycardia followed by the appearance of extrasystoles of ventricular or supraventricular origin as well as changes in intraventricular conduction similar to bundle branch block (table 1). In dogs numbers 5, 11, 12 and 17 the extrasystoles progressed to ventricular flutter and fibrillation.

By electrocardiographic comparison the effect of epinephrine on the heart of dogs anesthetized with cyclopropane without and with mepazine was clearly different. In the dogs given mepazine there was either complete absence of arrhythmias or a reduction in both their severity and frequency. In order to illustrate the different degrees of effect or protection these results were classified as +, ++ or +++ (table 1). In adhering to this classification the relative decrease in the severity of arrhythmias is not always evident, as in dogs numbers 4 and 10. In these mepazine-treated animals a marked reduction in the severity of the arrhythmias was obvious; however, the occurrence of occasional extrasystoles demanded classification as +.

From table 1 it is seen that of the 16 surviving dogs no extrasystoles occurred in seven of them (dogs numbers 3, 8, 9, 15, 16, 18 and 19) and they were classified +++. In seven the results were classified ++ because of the appearance of occasional extrasystoles after mepazine. This was in contrast to prolonged sequences of ventricular and supraventricular extrasystoles that occurred in the controls. Included in this group were those showing, after mepazine, intraventricular conduction disturbances similar to bundle branch block (dogs numbers 1, 2, 6). Also in this group one dog (number 17) died from ventricular fibrillation during the control injection which was performed one week after the mepazine study. In the three dogs classified as + there was a significant reduction of the epinephrine-induced arrhythmias after mepazine but there was a disturbance of impulse formation or alteration of the atrioventricular conduction relationship (dogs numbers 4, 13, 14).

An example of full protection (+++) by mepazine is illustrated

in figure 1 (dog 3). After the control epinephrine injection there occurred sequences of ventricular extrasystoles originating mainly from two foci. This was followed by occasional ventricular extrasystoles and disappearance of P waves. After mepazine medication the sinus rhythm remained undisturbed; the only evidence of the epinephrine effect was a sinus tachycardia.

TABLE 1  
PROTECTIVE ACTION OF MEPAZINE ON CYCLOPROPANE-EPINEPHRINE ARRHYTHMIAS  
(Intravenous epinephrine 0.005 mg./kg.)

Dog No.	Duration and Type of Cardiac Arrhythmias				Degree of Protection
	Control (Without Mepazine)		Protection (With Mepazine)		
	Duration (seconds)	Type	Duration (seconds)	Type	
1	48	S.V. Exs.	3	V.C.D., S.A. maintained	++
2	12	S.V. and V. Exs.	7	V.C.D., S.A. maintained	++
3	20	V. Exs.		S.A.	+++
4	62	S.V. and V. Exs.	6	V. Exs.	+
5		V. Fib.			
6	15-20	Occasional V. Exs., no P waves		V.C.D., S.A. maintained	++
7	16	S.V. and V. Exs.		Occasional V. Exs.	++
8	10	S.V. and V. Exs.		S.A.	+++
9	26	V. Exs. and early V. Flutter		S.A.	+++
10	16	S.V. and V. Exs.	6	V.C.D., one V. Exs., S.A. maintained	++
11		V. Fib.			
12		V. Fib.			
13	33	V. Exs.	20	V.C.D. four V. Exs.	+
14	17	V. Exs.	4	V.C.D., occasional V. Exs.	++
15	46	V. Exs., bi- and trigeminy		S.A.	+++
16	44	V. Exs. and V.C.D.		S.A.	+++
17		V. Fib.		Four V. Exs., S.A. maintained	++
18	66	S.V. and V. Exs.		S.A.	+++
19	38	S.V. and V. Exs.		S.A.	+++
20	21	V. Exs. Sinus arrhythmias		One V. Exs. Sinus arrhythmia	++

S.V.—Supra-ventricular.  
V.—Ventricular.  
Exs.—Extrasystoles.  
Fib.—Fibrillation.  
V.C.D.—Ventricular conduction disturbance.  
S.A.—Sinus rhythm.

+++—Sinus rhythm maintained.  
++—Occurrence of occasional ventricular extrasystoles.  
+—Marked reduction of intensity and duration of disturbances.

Figure 2 (dog 15) demonstrates, in addition to the electrocardiogram, a kymographic tracing of the arterial blood pressure in a case of full protection (+++). This illustration is especially interesting because it demonstrates the ability of peripheral arterioles to constrict following the epinephrine injection in contrast to what is usually seen following chlorpromazine administration.

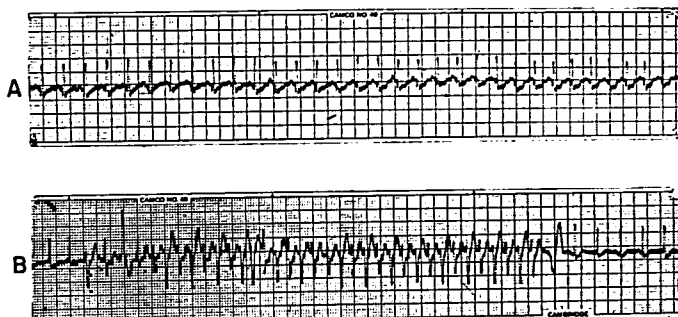


FIG. 1. Electrocardiographic tracing (dog 3, 9.0 kg.) during cyclopropane-oxygen anesthesia with intravenous epinephrine, 0.095 mg./kg. (A) With mepazine and (B) without mepazine. Protection +++.

Satisfactory but not complete protection (++) by mepazine against the epinephrine-induced arrhythmias is demonstrated in figure 3 (dog 17). After mepazine had been given, the electrocardiographic tracings

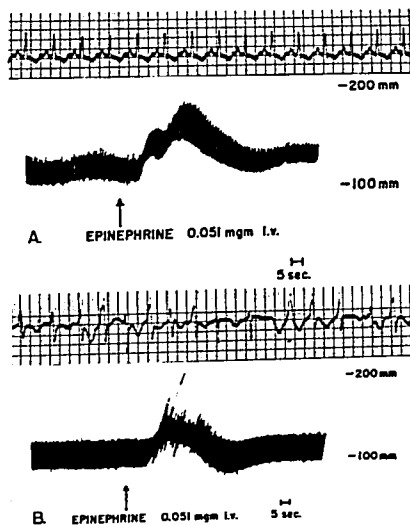


FIG. 2. Electrocardiographic and kymographic tracings (dog 15, 10.2 kg.) during cyclopropane-oxygen anesthesia with intravenous epinephrine, 0.005 mg./kg. (A) With mepazine and (B) without mepazine. Protection +++.

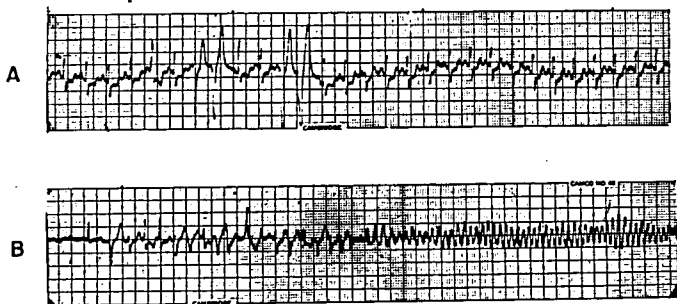


FIG. 3. Electrocardiographic tracings (dog 17, 6.6 kg.) during cyclopropane-oxygen anesthesia with intravenous epinephrine, 0.005 mg./kg. (A) With mepazine and (B) without mepazine. Protection ++.

were unchanged except for four ventricular extrasystoles, hence the classification as ++. One week later, without mepazine medication, a brief run of ventricular extrasystoles occurred followed by ventricular fibrillation and immediate death of the animal.

The group of dogs for which the protective effect of mepazine was designated as + (dogs 4, 13, 14) is characterized by a consistently pronounced disturbance of cardiac rhythmicity when unprotected by the drug. Figures 4 and 5 (dog 4) illustrate that mepazine did not

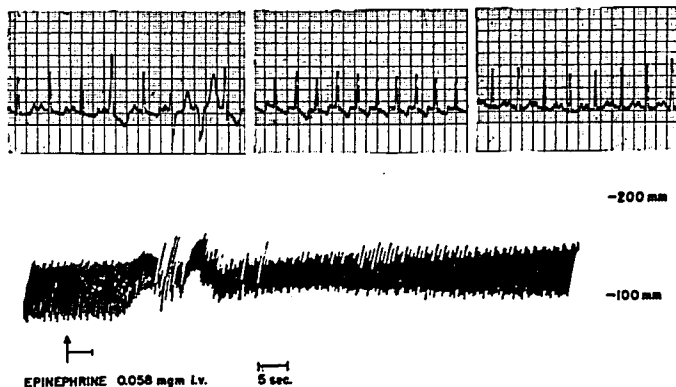


FIG. 4. Electrocardiographic and kymographic tracings (dog 4, 11.5 kg.) during cyclopropane-oxygen anesthesia with intravenous epinephrine 0.005 mg./kg.—with mepazine. Protection +.

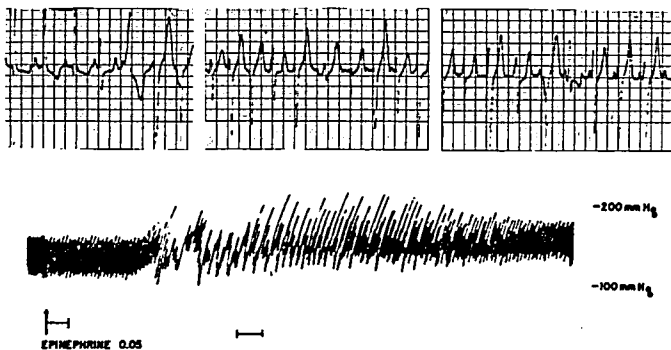


FIG. 5. Electrocardiographic and kymographic tracings (dog 4, 11.5 kg.) during cyclopropane-oxygen anesthesia with intravenous epinephrine, 0.005 mg./kg. intravenously—without mepazine.

completely abolish the occurrence of extrasystoles, but duration and intensity of the epinephrine effect were significantly reduced (table 1).

Arterial cyclopropane concentrations varied as shown in table 2. However, the concentration of cyclopropane in some instances was

TABLE 2  
BLOOD ANALYSIS IN VOLUME PER CENT: CYCLOPROPANE-OXYGEN ANESTHESIA

Dog Number	Without Mepazine			With Mepazine		
	C <sub>2</sub> H <sub>6</sub>	O <sub>2</sub>	CO <sub>2</sub>	C <sub>2</sub> H <sub>6</sub>	O <sub>2</sub>	CO <sub>2</sub>
1	12.44	23.38	46.9	13.03	21.09	46.6
2	11.23	21.94	33.7	11.42	18.51	39.2
3	9.88	17.55	41.3	9.27	12.35	47.2
4	14.87	20.73	39.2	13.14	10.86	51.2
5	—	—	—	—	—	—
6	14.54	14.77	40.5	11.00	13.50	44.8
7	13.52	16.06	56.6	11.24	15.16	46.6
8	11.60	12.30	49.8	10.43	12.09	51.2
9	15.20	13.85	48.6	—	—	—
10	16.09	14.95	43.0	14.66	18.07	54.5
11	—	—	—	—	—	—
12	—	—	—	—	—	—
13	17.22	16.80	50.3	14.20	18.75	41.3
14	13.40	18.65	53.4	11.89	14.23	43.7
15	15.03	18.31	42.2	8.50	16.49	35.44
16	11.87	11.11	46.9	16.42	16.49	44.0
17	—	—	—	18.47	18.63	57.3
18	11.36	9.84	47.3	11.46	14.42	43.6
19	9.00	14.30	47.5	11.85	11.03	52.7
20	7.58	7.97	55.8	11.02	9.52	45.4

Samples drawn at the approximate time of epinephrine injection (see METHOD).

greater in the mepazine series and in other instances was greater in the controls. Therefore, the protection as seen cannot be attributed to varying depths of anesthesia.

Studies of the arterial blood pressure were carried out simultaneously with electrocardiographic control in seven of the test animals. In five of the seven dogs, following mepazine administration, the systolic blood pressure was lowered 15 to 30 mm. of mercury (average 23 mm. of mercury), while no change was noted in the remaining two. The drop in blood pressure immediately followed the intravenous injection and was both brief and transient, returning to the preinjection level within eighty seconds (average 60 seconds). With the intravenous injection of epinephrine, a notable rise of the arterial blood pressure occurred in both the control dogs and in those treated with mepazine. Thus, the blood pressure raising power of epinephrine was not significantly impaired by the presence of mepazine.

#### DISCUSSION

To accurately interpret the mepazine effect demonstrated in this study it is necessary to discuss briefly the mechanisms through which epinephrine, during cyclopropane anesthesia, can cause an increase of myocardial irritability with all degrees of cardiac arrhythmias including ventricular fibrillation. As has been shown earlier in dogs (15) impulses which apparently originate in the mesenteric vascular bed, travelling by visceral afferent fibers through the spinal cord to a brain center above the pons and returning to the heart by way of the cardiac sympathetics, can increase the irritability of the heart. In the presence of this increased myocardial irritability a small dose of epinephrine when injected intravenously causes marked cardiac arrhythmias through direct stimulation of the heart.

Since no chemical antagonism between mepazine and epinephrine has been demonstrated, protection against the epinephrine effect as observed with mepazine in the dogs of this series is explainable by (a) depression of sympathetic impulses, (b) a direct effect on the heart itself or (c) adrenolytic activity. All mechanisms are possible.

Mepazine is known to reduce or abolish either impulses or impulse transmission of various nervous structures (16, 17) including both the sympathetic and the parasympathetic divisions of the autonomic nervous system. A suppression or blockage of extracardiac efferent sympathetic impulses may be, at least in part, responsible for its action of controlling myocardial irritability.

Secondly, a direct action of mepazine on the heart resulting in myocardial depression is quite possible. Experimental studies (18) have not only confirmed earlier investigations with chlorpromazine (8) and mepazine (1) but have also proven a local anesthetic effect of mepazine on the cardiac receptors. The local anesthetic property of



mepazine affecting such structures appeared to be considerably stronger than that of equal doses of procaine (2). A specific property of mepazine is its depressant effect on the conduction system in the heart. No such effect was found with identical doses of chlorpromazine (19).

Phenothiazine compounds such as chlorpromazine are known to cause unpredictable and sometimes marked depressant effects on the arterial blood pressure in both animals and humans (8, 20, 21, 22). When adrenergic substances are used to counteract a decrease in blood pressure occurring in conjunction with phenothiazine medication, the reactivity of the arterial system may be altered. This results in either marked reduction or disappearance of their vasoconstrictor action or a reverse effect with further lowering of the arterial blood pressure (23, 24, 25). Mepazine has been shown to affect arterial blood pressure only insignificantly when used for preanesthetic medication in human subjects (12). In this study, with mepazine given intravenously, a transient drop of the arterial blood pressure was frequently noted. However, in contrast to chlorpromazine, a known adrenolytic agent, the power of epinephrine to increase blood pressure remained unaltered or was only insignificantly reduced. From this one can conclude that the adrenolytic action of mepazine, if present, is considerably less than chlorpromazine.

Therefore, the prevention of cyclopropane-epinephrine arrhythmias by mepazine is felt to be due either to the local anesthetic effect on the myocardium or the depressant effect on myocardial conduction or, more likely, some degree of both. Supportive evidence for this conclusion is the protection against hyperirritability under other conditions such as mechanical irritation of the myocardium during surgical manipulations or thermic stress produced in hypothermia (5, 6, 7).

#### SUMMARY AND CONCLUSIONS

The effect of the phenothiazine compound N-methyl-piperidyl-(3)-methylphenothiazine (mepazine) on myocardial irritability was investigated. To produce myocardial hyperirritability, epinephrine was injected intravenously during cyclopropane-oxygen anesthesia. In control dogs epinephrine in a standard dose of 0.005 mg./kg. given intravenously over a period of four seconds always resulted in the occurrence of cardiac arrhythmias including, in four dogs, ventricular flutter and fibrillation.

When mepazine was administered to each dog a week later and the experiment repeated under identical conditions, there was complete absence or a marked reduction of such arrhythmias. Consequently it is believed that mepazine provides a specific protection of the heart against such arrhythmias by reducing myocardial irritability.

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