COMPARISON OF VASOPRESSOR RESPONSES IN THE PRESENCE OF PHENOTHIAZINE DERIVATIVES

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PHENOTHIAZINE compounds are used extensively in medicine and are of importance to anesthesiologists as adjuvants in anesthetic management and for problems incident to their use when patients receiving these compounds must undergo surgery. Their value is determined by the ratio of desirable to undesirable properties of the individual agents.

Early uses of phenothiazine derivatives were for their antihistaminic properties [1, 2] and as an adjunct to hypothermia.[3, 4] The effects of particular interest to anesthesiologists are as follows:

Nervous system. The sedative and tranquilizing actions of phenothiazines make them desirable for preanesthetic medication. They afford psychic sedation, reduce the total amount of narcotics and anesthetic agents needed, and decrease secretory activity.[5-10] Unfortunately, these same depressant properties may prolong postoperative awakening time.

An important and desirable activity is their antiemetic property. Although there are varying reports of effectiveness, promethazine, mepazine and chlorpromazine are all capable of reducing the incidence of postoperative nausea and vomiting to less than 10 per cent.[5-8]

Depression of the ascending reticular system results in a reduction of central reflex activity, including the normal response to stress.[11, 12] The full implications of this effect have not been established.

The parasympatholytic activity of phenothiazines is often desirable, especially for reduction of secretions and obtundation of vagal reflex activity.[6, 9, 13]

The sympatholytic and adrenolytic effects of these drugs on the autonomic system, which normally serves a protective function in maintaining circulatory homeostasis, are undesirable in the presence of hemorrhagic or neurogenic shock.[14-18]

Cardiovascular system. There is a reduction of myocardial irritability by these drugs, due partly to their local anesthetic action. When this action is desirable mepazine offers the most promise.[19-22]

Hypotension is often seen when chlorpromazine is administered, and to a less degree with other phenothiazines.[6-9, 18] The appearance of hypotension is alarming but more distressing is the inability to combat this hypotension with standard vasopressors.[10, 14-18, 22, 23]

This study was initiated in order to better understand and to be able to better treat hypotension following phenothiazine administration. The phenothiazines studied were promethazine (Phenergan), mepazine (Pacatal) and chlorpromazine (Thorazine) and the vasopressors utilized were epinephrine, norepinephrine (Levophed), methoxamine (Vasoxyl) and phenylephrine (Neosynephrine).

METHOD

Ten mongrel dogs weighing 8.5 to 16.5 kg. (average 11.5 kg.) were anesthetized with 2.5 per cent pentobarbital administered intravenously during the 1½–4 hour procedure (average total dosage for each dog was 33.5 mg./kg.). An oral intubation of the trachea was performed and the animals allowed to breathe room air via the endotracheal catheter. Direct blood pressure was obtained by arterial cannulation. Respiration was monitored with a thoracic bellows attachment. Blood pressure and respiration were recorded on an ink-writing kymograph.

Experiments consisted of four parts with each dog serving as its own control. In the first or control part of the experiment the anesthetized dog was given 4 vasopressors (epinephrine, norepinephrine, phenylephrine, methoxamine) at 15 minute intervals. This

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TABLE 1

ARBITRARILY VARIED ORDER OF ADMINISTRATION OF PHENOTHIAZINE DERIVATIVES AND VASOPRESSORS

Dog No.	Order of Phenothiazines Given			Order of Vasopressors Given			
	Promethazine	Mepazine	Chlorpromazine	Epinephrine	Norepinephrine	Methoxamine	Phenylephrine
112	3	1	2	1	2	3	4
113	3	1	2	1	2	3	4
114	3	1	2	4	3	2	1
115	3	1	2	4	3	2	1
116	2	3	1	4	1	2	3
117	1	2	3	4	1	2	3
122	1	2	3	2	4	1	3
124	1	3	2	3	4	1	2
125	3	2	1	2	1	4	3
127	2	1	3	3	4	1	2

was immediately followed by the second part wherein one of the three phenothiazines (promethazine, mepazine, or chlorpromazine) was administered intravenously and the injection of the vasopressors repeated.

Seven to nine days later the animal was returned to the laboratory, anesthetized and prepared, as previously mentioned. Another of the phenothiazine drugs was administered and the action of the vasopressor agents studied. Seven to nine days later the procedure was repeated with the remaining phenothiazine derivative.

Vasopressors were given in the following amounts: epinephrine 0.005 mg./kg., norepinephrine 0.005 mg./kg., phenylephrine 0.01 mg./kg. and methoxamine 0.1 mg./kg. Solutions were so prepared that 1 ml. of solution contained the dose of vasopressor for one kilogram of dog. This was injected intravenously at a rate of 1 ml./sec. Fifteen minutes were allowed between injections. This is sufficient time for epinephrine and norepinephrine to be destroyed in the body;[24] however, the effect of methoxamine and phenylephrine is more prolonged.[25, 26] To eliminate errors the order of administration of vasopressors and phenothiazine derivatives was arbitrarily varied (table 1).

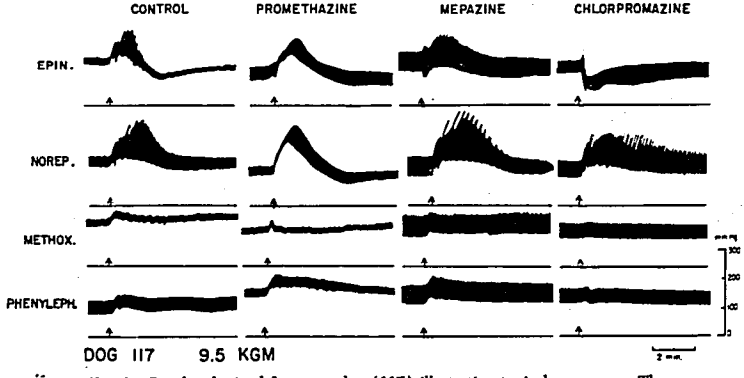


FIG. 1. Results obtained from one dog (117) illustrating typical responses. The phenothiazine derivatives were administered at weekly intervals.

TABLE 2

AVERAGE CHANGE IN SYSTOLIC BLOOD PRESSURE (MM. HG) FOLLOWING INTRAVENOUS INJECTION OF VASOPRESSORS IN CONTROLS AND IN THE PRESENCE OF THE PHENOTHIAZINE DERIVATIVES STUDIED

	Control		Promethazine		Mepazine		Chlorpromazine	
	Average	Extremes	Average	Extremes	Average	Extremes	Average	Extremes
Epinephrine	117.5	70–150	88.0	50–150	99.5	30–175	−49.0	−25 to −65
Norepinephrine	119.5	80–145	114.0	40–155	138.0	100–175	123.0	55–160
Methoxamine (Vasoxyl)	48.0	20–95	21.0	5–35	18.5	10–30	7.5	0–10
Phenylephrine (Neosynephrine)	48.0	20–80	37.0	20–70	20.5	10–35	10.0	−15 to +20

All phenothiazines were given in two doses of 5 mg./kg. each and injected intravenously in 10 seconds. Fifteen minutes after the first phenothiazine injection a vasopressor was given. Fifteen minutes later, a second vasopressor was given. This was followed after 15 minutes by the second dose of phenothiazine (5 mg./kg.) and the two remaining vasopressors were given at 15 minute intervals. This method of administering the phenothiazine compounds is based on preliminary work showing that the maximal effects following intravenous administration of mepazine (5 mg./kg.) and chlorpromazine (5 mg./kg.) lasted approximately 40 minutes. We were unable to determine such a period for promethazine and assumed its maximal intravenous effects were still present for 40 minutes, which is within the period of effective clinical action of this drug.

RESULTS

The consistency of responses was remarkable in all dogs studied. An example of the results (fig. 1) illustrates all kymograph tracings obtained from one dog.

Effect on blood pressure. To compare the vasopressor effect, the peak rise in systolic pressure from control level was measured. Since the effect of each dog's individual response was present in all parts of the experiment, data were averaged (table 2) and are demonstrated graphically (fig. 2).

The effective blood pressure raising ability of epinephrine was slightly diminished in the presence of promethazine and mepazine. The epinephrine "reversal effect" in the presence of chlorpromazine was seen in all dogs.

The effective blood pressure raising ability of norepinephrine was not appreciably diminished in the presence of promethazine, mepazine or chlorpromazine. There was a slight increase in pressor response in the presence of mepazine and chlorpromazine, probably due to a depression of baroreceptor reflexes.

The effective blood pressure raising ability of methoxamine was diminished by all pheno-

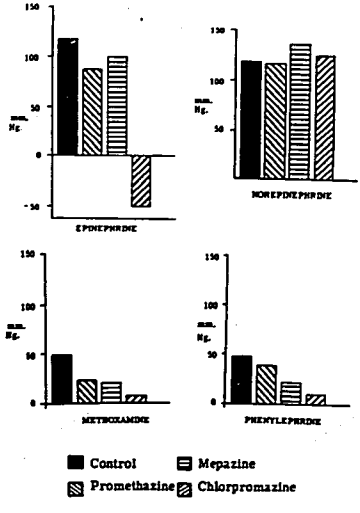


FIG. 2. Average blood pressure raising ability of epinephrine, norepinephrine, methoxamine and phenylephrine in controls and in the presence of promethazine, mepazine and chlorpromazine.

TABLE 3

AVERAGE DURATION OF ACTION (MINUTES) OF VASOPRESSORS IN CONTROLS AND IN THE PRESENCE OF THE PHENOTHIAZINE DERIVATIVES STUDIED

	Control		Promethazine		Mepazine		Chlorpromazine	
	Average	Extremes	Average	Extremes	Average	Extremes	Average	Extremes
Epinephrine	5.8	3.0–10.0	6.4	2.5–15.0	5.1	2.8–8.2	5.9	1.0–10.0
Norepinephrine	5.3	3.0–8.0	5.1	3.0–9.3	5.6	3.5–7.3	6.7	3.8–9.3
Methoxamine (Vasoxyl)	13.9	4.2–15.0	9.4	0.8–15.0	6.8	0.5–15.0	1.5	0.0–4.0
Phenylephrine (Neosynephrine)	9.7	3.7–15.0	9.9	1.8–15.0	8.3	1.0–15.0	1.6	0.5–4.2

thiazine derivatives, particularly chlorpromazine. The ability of phenylephrine to raise blood pressure was also diminished by all phenothiazines particularly chlorpromazine.

Duration of action. Both the pressor and secondary depressor response to these drugs was studied, the time being determined by the return of systolic blood pressure to preinjection levels.

The duration of action of epinephrine and norepinephrine was not appreciably affected by the phenothiazines studied. The average duration of action of methoxamine and phenylephrine was reduced in the presence of mepazine and markedly in the presence of chlorpromazine. Promethazine did not decrease the duration of phenylephrine activity but did decrease that of methoxamine (table 3 and fig. 3).

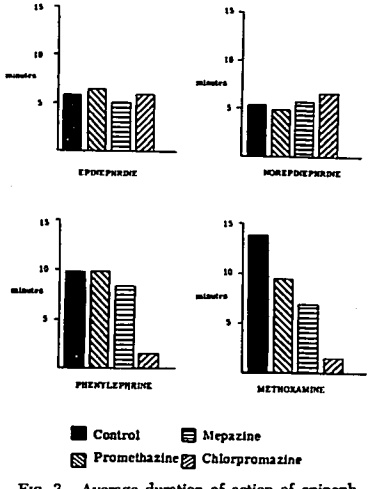


FIG. 3. Average duration of action of epinephrine, norepinephrine, methoxamine and phenylephrine in controls and in the presence of promethazine, mepazine and chlorpromazine.

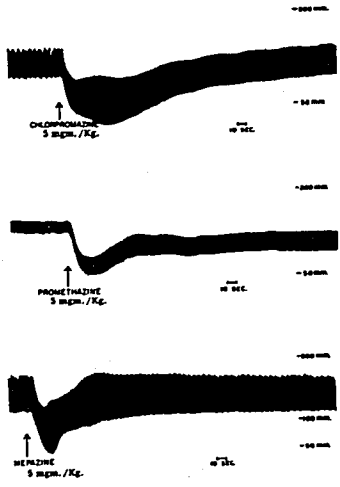
The intravenous administration of all phenothiazines produced a sudden although transient fall in arterial blood pressure and a tachypnea which persisted even after the pressure returned to preinjection levels. The most rapid return of blood pressure to preinjection level was usually seen with mepazine (fig. 4).

Complications. Of the ten dogs reported in this series none died during the experiment, but two died within 12 hours following the completion of the experiment. Autopsies revealed pneumonia and atelectasis, believed to be a result of respiratory depression incident to combined effects of pentobarbital and phenothiazine drugs.

DISCUSSION

Peripheral vasoconstriction is a result of increased autonomic tone and/or localized reactivity to humoral agents. The effectiveness of norepinephrine, methoxamine and phenylephrine in raising the blood pressure is based in large measure on their ability to constrict the arteriolar vascular bed.[27-29] Epinephrine's effectiveness, however, is based on three mechanisms—direct myocardial stimulation, increased heart rate, and selective peripheral vasoconstriction.[30, 31] Shifts in circulating blood volume are not known to be important in the pressor activity of these compounds.[32, 33]

Depression of the central and peripheral sympathetic nervous system by the phenothi-



DOG NO. 117, Wt. 9.5 Kg., Nembutal Anesthesia

FIG. 4. Typical blood pressure responses in one animal to intravenous administration of (from top to bottom): chlorpromazine, promethazine, mepazine. Injections were made at one week intervals.

azines is known,[32, 34] but this would not interfere with the action of exogenous vasopressors.

The pressor response to epinephrine was only slightly reduced by mepazine and promethazine. A reversal or fall in pressure was consistently observed with chlorpromazine. This is not believed to be primarily a direct cardiac effect since a decreased myocardial excitability to epinephrine is seen with mepazine as well as with chlorpromazine.[21, 22] Epinephrine has a dual action on the vascular bed, causing constriction in skin and viscera and dilatation in vessels of the heart and skeletal muscles. An early explanation of "epinephrine reversal" was based on the possibility of two kinds of receptors in vessel walls. Normally, the receptors for constriction masked those for dilatation, but in the presence of a reversing agent, the constricting receptors were blocked, resulting only in dilation.[35] Another explanation is based on the crucial molecular attachment of epinephrine to the receptor. If the reversing agent interferes with the normal alignment of the epinephrine molecule so that it attaches only partially or abnormally, the effect is inactivation of the receptor.[36] Since the duration of action of epinephrine was not decreased by chlorpromazine we believe that there is no chemical antagonism between these compounds. The epinephrine-reversal effect appears to be the result of direct alteration of the peripheral receptor response by chlorpromazine.

Norepinephrine, methoxamine and phenylephrine have a constrictive effect on peripheral vessels.[24-29] These drugs appear to have minor direct cardiac effects other than the chronotropic property of norepinephrine, which is usually masked by the carotid sinus reflex.[24] While the pressor effect of norepinephrine is unaltered, that of both methoxamine and phenylephrine is diminished in the presence of promethazine, mepazine and chlorpromazine. Norepinephrine differs from these other two vasopressors in that it occurs naturally in the body and it is known to be the principal neurohormone produced by the sympathetic nervous system.[37] Although little is known about vasopressor receptors, the alignment of the vasopressor molecule to the receptor is probably crucial. The interference by phenothiazine derivatives, particularly chlorpromazine, on the blood pressure raising ability of synthetic vasopressors is probably due to an alteration of the receptor, but this does not appear to affect the attachment of norepinephrine.

While the duration of action of norepinephrine is unchanged by the phenothiazine derivatives studied, the action of methoxamine and phenylephrine is shortened by mepazine and chlorpromazine. Promethazine diminished the duration of action of methoxamine but not phenylephrine.

The depressant action of the phenothiazine derivatives on the pressor effect of the synthetic vasopressors is in this order of increasing severity: promethazine, mepazine, chlorpromazine.

SUMMARY

The effects of promethazine, mepazine and chlorpromazine on vasopressor response were compared in dogs. Epinepherine, norepineph-

rine, methoxamine and phenylephrine were the vasopressors studied.

Norepinephrine pressor effect was not diminished nor was its duration of action in the presence of promethazine, mepazine or chlorpromazine.

Epinephrine pressor effect was not appreciably diminished nor was its duration of action by promethazine or mepazine. In the presence of chlorpromazine there was a reversal of pressor effect although the duration of action was unaltered.

The pressor effect of methoxamine and phenylephrine was diminished and the duration of action was reduced by mepazine and particularly by chlorpromazine. Promethazine diminished the pressor effect of methoxamine and phenylephrine and shortened the duration of action of methoxamine but not that of phenylephrine.

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