THE EFFECT OF PERPHENAZINE ON EPINEPHRINE-INDUCED CARDIAC ARRHYTHMIAS IN DOGS: I, ANAESTHESIA WITH FLUOTHANE, AND FLUOTHANE-ETHER AZEOTROPE[1]

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A WIDE VARIETY of tranquillizer drugs have been tested clinically for preoperative medication during the past few years (1) Several of these have, in addition to an adequate sedative effect, a potent anti-emetic activity, and appear also to prevent or suppress myocardial irritability during anaesthesia (2, 3, 4).

The problem for the anaethetist has been to find the tranquillizer drug which produces the most predictable type of sedation and perhaps some anti-emetic and anti-arrhythmic effects without greatly disturbing the patient's circulation. One of the many tranquillizer drugs tested was the phenothiazine derivative, perphenazine (Trilafon®) This report deals with the effect of premedication with perphenazine on epinephrine induced arrhythmias in dogs during anaesthesia with Fluothane and the azeotropic mixture of Fluothane and diethyl ether.

METHOD

Thirty acute experiments were carried out on twenty mongrel dogs who varied in weight from 5.5 to 15 kg (mean, 8 0 kg). In alternate experiments the dogs were given 0 25 mg /kg perphenazine intravenously a few minutes preceding the anaesthetic No other premedication was given At least one week was allowed to elapse before an experiment was repeated on a surviving dog.

Each dog was lightly anaesthetized with a "sleep dose" of thiopental (75–175 mg), followed by 20 mg succinylcholine intravenously. A solution of 5 per cent dextrose in water was attached to the intravenous needle to assure adequate hydration and to keep the vein open. A cuffed orotracheal tube was placed in the trachea immediately following induction of anaesthesia This was connected through a non-rebreathing valve, a Fluotec vaporizer, and an anaesthetic machine to a mechanical respirator The latter was adjusted to a rate of 25–30/minutes, with volume set between 150 and 250 ml. and intermittent positive pressures to between 10 and 15 mm. Hg. Anaesthesia with nitrous oxide–oxygen (5:2) was used until the preliminary connection of a Sanborn direct writing visocardiette In SIX experiments, direct femoral artery and vein pressures were measured through an indwelling catheter attached to Statham strain gauges and to a multi-channel oscilloscope with photographic recorder. In other experiments, the femoral artery cannula was attached to a mercury manometer. After control

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tracings were recorded, Fluothane (0.5 per cent) or the azeotropic mixture of Fluothane and diethyl ether (1 per cent) was added from the calibrated Fluotec vaporizer for approximately 25 minutes. This allowed sufficient time for an adequate and stable blood level of the primary anaesthetic and was not long enough for a possible adrenolytic action by Fluothane or the Fluothane-ether azeotrope to become dominant, as is seen with cyclopropane (5). Then l'epinephrine was injected intravenously in a strength of 0 02 mg /ml. at the rate of 1 ml./sec. to a total dose of 0 02 mg /kg The electrocardiograph (lead 2) and blood pressure

TABLE I

EFFECT OF PERPHENAZINE ON EPINEPHRINE-INDUCED CARDIAC ARRHYTHMIAS DURING 0 5 PER CENT FLUOTHANE + N_2O O_2 (5 2) ANAESTHESIA IN DOGS

Dog	Weight (kg)	Dose of epinephrine (mg)	Dose of perphenazine (mg)	Onset of arrhythmia after injection (secs)	Duration of arrhythmia (secs)
1	15 0	0 30	0	6	VF–Death
2	7 1	0 14	0	3	68
3	8 3	0 16	2 0	Tachycardia only	
4	8 0	0 16	2 0	10	32
5	15 0	0 30	0	2	VF–Death
6	6 3	0 12	0	4	VF–Death
2	7 1	0 14	1 8	Tachycardia only	
7	8 2	0 16	2 0	7	63
8	8 4	0 16	0	4	VF–Death
9	8 0	0 16	0	3	46
10	6 3	0 12	1 5	5	27
11	5 5	0 11	1 4	4	57
9	8 0	0 16	2 0	7	21
12	5 5	0 11	0	5	VF–Death
10	6 3	0 12	0	2	112

TABLE II

EFFECT OF PERPHENAZINE ON EPINEPHRINE-INDUCED CARDIAC ARRHYTHMIAS DURING 1 0 PER CENT FLUOTHANE-ETHER AZEOTROPE + N_2O O_2 (5 2) ANAESTHESIA IN DOGS

Dog	Weight (kg)	Dose of epinephrine (mg)	Dose of perphenazine (mg)	Onset of arrhythmia after injection (secs)	Duration of arrhythmia (secs)
1	8 2	0 16	0	11	87
2	9 5	0 19	0	12	103
3	7 0	0 14	0	7	49
4	5 5	0 11	0	7	58
5	7 0	0 14	0	5	136
6	6 1	0 12	0	6	90
7	8 0	0 16	0	5	88
8	8 1	0 16	2 0	8	VF–Death*
1	8 2	0 16	2 0	25	46
2	9 5	0 19	2 3	17	31
3	7 0	0 14	1 8	9	5
4	5 4	0 11	1 4	23	41
5	7 0	0 14	1 8	17	60
6	6 1	0 12	1 5	14	36
7	8 0	0 16	2 0	18	42

*Severe hypoxia during anaesthesia

recordings were taken continuously from a time just before injection of l'epinephrine was begun until either a normal sinus rhythm reappeared on the ECG, or until fatal ventricular fibrillation was obvious In three experiments with Fluothane, electrical defibrillation and manual cardiac systole through a thoracotomy was attempted for resuscitation

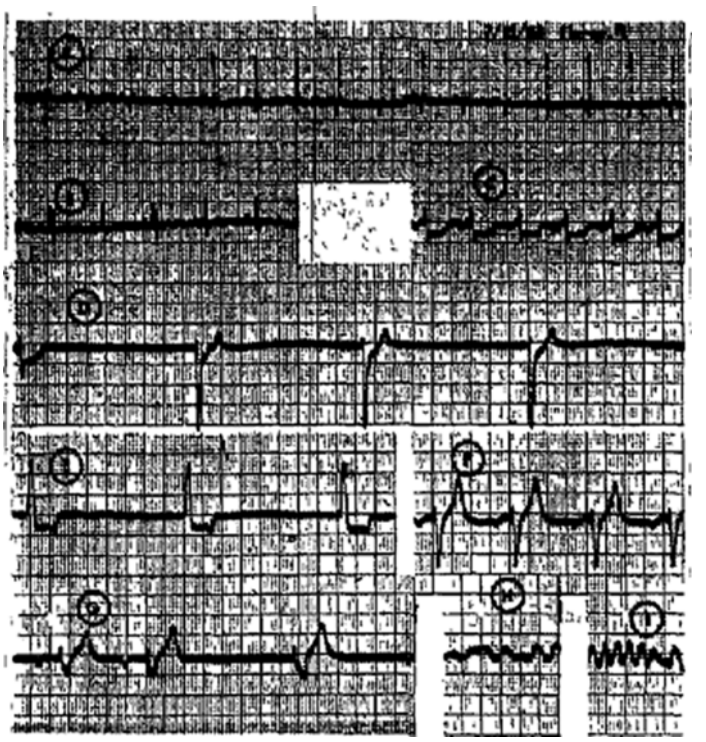

FIGURE 1 Observe that ventricular fibrillation developed when 0 3 mg epinephrine was injected in 15 sec after 25 min of anaesthesia with 0 5 per cent Fluothane A 10 15 AM, 15 min after induction of anaesthesia with 150 mg thiopental, 20 mg succinylcholine and N_2O O_2 (5 2) respiration controlled, B 10 39 AM 24 min anaesthesia with 0 5 per cent Fluothane + N_2O O_2 (5 2), C 10 40 AM, 7 sec after injection of epinephrine—pacemaker displaced D 10 41 AM Ventricular pacemaker, E 10 42 AM Bundle branch block supraventricular conduction F 10 44 AM, intraventricular conduction defect, G 10 45 AM intraventricular conduction defect H 10 47 AM ventricular fibrillation, I 10 50 AM ventricular fibrillation

RESULTS

The onset and duration of arrhythmias with Fluothane and the azeotropic mixture of Fluothane and diethyl ether are tabulated in Tables I and II Example of the responses with and without perphenazine are shown in Figures 1, 2, 3, and 4

Injection of perphenazine did not cause any evident change in the electrocardiographic tracing or in the blood pressure Injection of epinephrine caused a sharp rise in blood pressure which fell rapidly within a few minutes in the surviving animals, and fell precipitously in the animals who developed ventricular fibrillation The blood pressure response was not inverted as is seen with chlorpromazine (2)

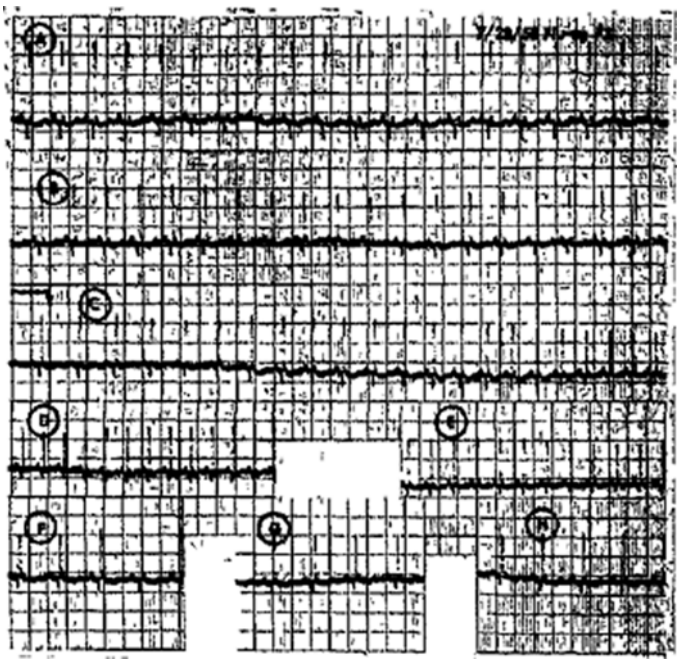

FIGURE 2 Observe that injection of epinephrine caused only a brief period of sinus tachycardia after perphenazine premedication and 23 min of anaesthesia with 0 5 per cent Fluothane A 10 45 A M , 5 min after induction of anaesthesia, and before injection of perphenazine B 10 48 A M , 2 min after injection of 2 0 mg perphenazine intravenously 10 49 A M Fluothane 0 5 per cent added from calibrated Fluotec vaporizer C 11 12 A M , showing end of injection of 8 ml (0 16 mg) l epinephrine and development of sinus tachycardia D 11 18 A M , sinus tachycardia, E 11 27 A M , sinus tachycardia, F, G, H 11 28 11 29 11 30 A M , normal rhythm Respirator and anaesthesia discontinued 11 30 A M , dog raised head, 11 36 A M

Of the eight dogs given 0 5 per cent Fluothane, five developed ventricular fibrillation (see Fig 1) In only one of three of these were resuscitative measures of help for a short time Two of the three surviving dogs had a variety of auricular and ventricular conduction disturbances including auriculo-ventricular nodal and ventricular extrasystoles, auriculo-ventricular block, and a very slow ventricular rhythm These arrhythmias were indicative of a near lethal effect of epinephrine, as is seen with chloroform and cyclopropane (6) The three survivors were subsequently given perphenazine premedication and Fluothane anaesthesia, and had

no serious arrhythmias with epinephrine (see Fig. 2) None of the seven dogs that received perphenazine premedication before 0 5 per cent Fluothane anaesthesia developed ventricular fibrillation or died

Serious ventricular arrhythmias were observed after epinephrine in the seven dogs under anaesthesia with 1 per cent Fluothane-ether azeotrope (Fig 3)

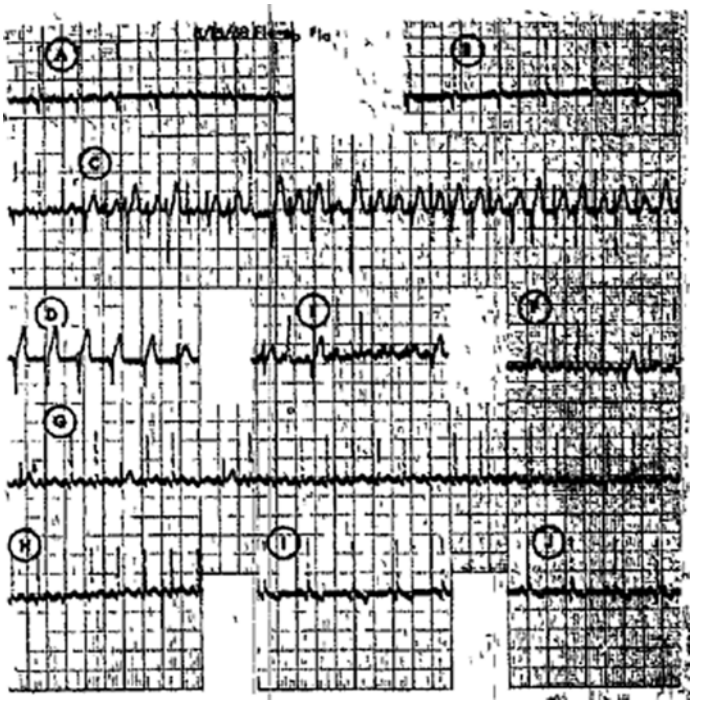

FIGURE 3 Observe multifocal ventricular extrasystoles after 0 16 mg l epinephrine and following 25 min of anaesthesia with 1 per cent Fluothane-ether azeotrope A 2 40 P M, 8 min after induction of anaesthesia, 2 45 P M Fluothane-ether azeotrope 1 per cent added, B 3 09 P M anaesthesia for 24 min, observe slightly reduced heart rate, C 3 10 P M, note onset of multifocal ventricular extrasystoles eleven seconds after injection of epinephrine D C + 30 sec, nodal rhythm, E C + 60 sec, nodal escape, F C + 85 sec, nodal escape, G 3 16 P M sinus tachycardia, H 3 21 P M, sinus tachycardia, I 3 29 P M, normal rhythm, J 3 32 P M, normal rhythm, Respirator and anaesthesia discontinued, 3 30 P M, Dog raised head, 3 34 P M

Three dogs developed a brief run of ventricular flutter and fibrillation on the electrocardiograph tracing, but each animal survived the experiment (In a previous report (7), nine of eleven dogs survived in similar experiments) In the dogs that were given perphenazine premedication, the onset of the arrhythmias was slower and they were of shorter duration (Fig 4) One dog in the latter group had an episode of severe hypoxia during anaesthesia when the oxygen tank ran out, and in spite of the previous administration of perphenazine, it developed ventricular fibrillation after epinephrine

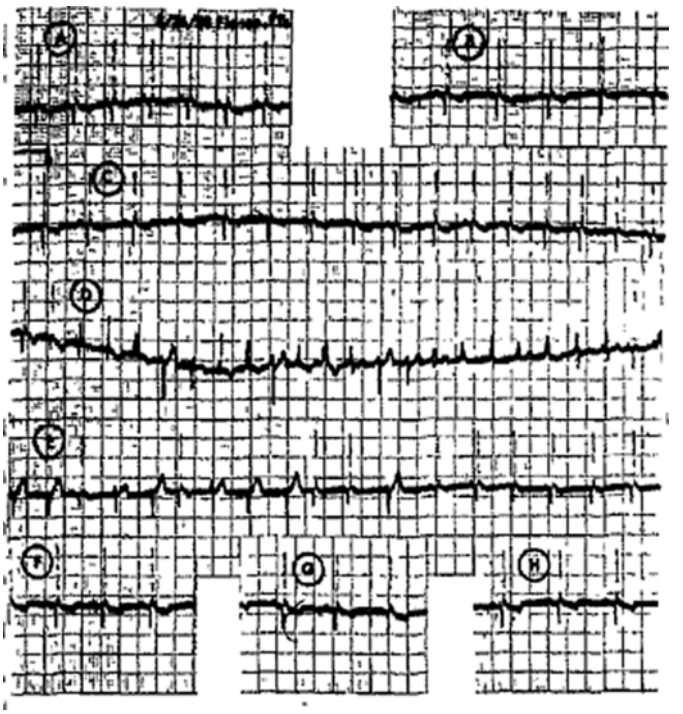

FIGURE 4 Observe short period of multifocal beats and nodal escape after perphenazine premedication and 25 min of anaesthesia with 1 per cent Fluothane-ether azeotrope A 10 55 a m 7 min after perphenazine and induction of anaesthesia, B 11 20 A M, anaesthesia for 24 min, heart rate slowed, C D, E 11 21 A M, after end of injection of epinephrine, note arrhythmia beginning 25 sec after end of injection of epinephrine which lasted 46 sec F, G, H 11 31, 11 35, 11 40 A M, normal sinus rhythm Respirator and anaesthesia discontinued, 11 40 A M, dog raised head, 11 43 A M

DISCUSSION

The causes of cardiac arrhythmias during clinical anaesthesia are undoubtedly secondary to hypoxia and hypercarbia This assertion applies whether the asphyxia is induced primarily by the anaesthetist, by the action of the anaesthetic drugs on the vital organs—principally, the contractile and conductive tissue of the heart—or, not infrequently by the administration of supportive drugs, especially the vasopressor catecholamines

Perphenazine (Trilafon®) has a tranquillizing effect which is more effective than the neurosedative type of drugs, has no marked hypnotic effect, and is not as potent as the powerful psychosedatives Its anti-emetic properties appear to be highly predictable in about one-fifth to one-tenth the dosage used with chlorpromazine Although the dose tested in these experiments was not large for dogs, perphenazine had a very effective anti-arrhythmic action without causing inversion of the blood pressure response to l'epinephrine

Pulmonary ventilation was controlled mechanically in these experiments because it was observed both in other experiments and during clinical anaesthesia that nodal rhythm, ventricular extrasystoles, and ventricular tachycardia were far more likely to develop during spontaneous breathing (with the associated respiratory acidosis) than when pulmonary ventilation was provided adequately by manually or mechanically augmenting the respiration (7, 8). It was found also that during spontaneous respiration it was not possible to maintain a surgical depth of anaesthesia with the lower concentration settings on the Fluotec vaporizer. Mechanical control of respiration, therefore, assured that a stable blood level of the anaesthetic vapours was readily established, and that the effects of asphyxia could not be a factor in this study.

Although Fluothane and the Fluothane-ether azeotrope may have a specific effect on myocardial conductivity and excitability which can increase the incidence of cardiac arrhythmias, these agents have many very desirable qualities. They should be administered, therefore, with the respect and caution they deserve, rather than with fearful trepidation. When serious arrhythmias exist preoperatively, it is perhaps helpful to administer an agent such as perphenazine, which will prevent the aggravation of such cardiac disturbances, and then proceed to administer these agents while making sure the pulmonary ventilation is adequate at all times In this way, arrhythmias will be avoided, or if they do occur, will be of a mild nature with no great clinical import.

During these experiments fatal ventricular fibrillation was provoked by epinephrine very readily with 0.5 per cent Fluothane, but not with the 1 per cent Fluothane-ether azeotrope. These experiments confirm, perhaps, the clinical observation that spontaneous arrhythmias are far less frequent with the azeotrope (7). Premedication with perphenazine provided protection with both agents as long as respiratory depression or hypoxia was not permitted to occur.

Summary

Thirty acute standard experiments were carried out on twenty dogs during anaesthesia with 0.5 per cent Fluothane and 1 per cent Fluothane-ether azeotrope with N_2O:O_2 (5:2) to determine whether perphenazine would prevent serious or fatal ventricular arrhythmias, provoked by a lethal dose of l'epinephrine, after approximately 25 min. of anaesthesia Pulmonary ventilation was controlled mechanically in a non-rebreathing system during each experiment to assure that respiratory acidosis or hypoxia would not be a factor in assessing the validity of the results, to assure that the concentration set on the Fluotec vaporizer would be delivered effectively to the dog's lungs and to assure a stable blood level of the anaesthetic agents. It was found that l'epinephrine was far more likely to cause death with 0.5 per cent Fluothane than with 1 per cent Fluothane-ether azeotrope. Perphenazine was effective in preventing death with Fluothane, and in reducing the duration and severity of arrhythmias with both Fluothane and the Fluothane-ether azeotrope.

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RÉSUMÉ

Nous avons fait trente expériences chez vingt chiens soumis à l'anesthésie avec 0 5% et 1% de Fluothane-éther azéotrope et $N_2O:O_2$ (5:2) pour rechercher si la perphenazine pourrait prévenir les arythmies ventriculaires sérieuses ou fatales apparaissant à la suite de l'administration d'une dose mortelle d'épinéphrine après environ 25 minutes d'anesthésie Au cours de chacune des expériences, nous avons contrôlé mécaniquement la ventilation pulmonaire avec un système sans réinspiration pour être assurés que l'acidose respiratoire et l'hypoxie soient exclues comme facteurs influençant les résultats et pour être assurés également que la concentration indiquée sur le vaporisateur Fluotec soit bel et bien livrée dans les poumons du chien maintenant un niveau sanguin stable d'agents anesthésiques. Nous avons observé que l'épinéphrine était aussi capable de causer la mort avec 0 5% de Fluothane qu'avec 1% de Fluothane-éther azéotrope. La perphenazine a réussi à prévenir la mort avec le Fluothane et à réduire la durée et la sévérité des arythmies aussi bien avec le Fluothane qu'avec le mélange Fluothane-éther azéotrope

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