THE EFFECT OF PERPHENAZINE ON EPINEPHRINE-INDUCED CARDIAC ARRHYTHMIAS IN DOGS. II, ANAESTHESIA WITH CYCLOPROPANE, CHLOROFORM, AND TRICHLORETHYLENE[1]

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IN ADDITION to the clinical efficacy of perphenazine (Trilafon®) in alleviating symptoms of anxiety and other manifestations of emotional stress (1–4), this drug exerts a significant depressive effect on epinephrine-provoked myocardial irritability if it is administered before general anaesthesia with Fluothane and the azeotropic mixture of Fluothane and diethyl ether in dogs (5).

A dose level of perphenazine (0.25 mg /kg.) was selected for studying the effect on myocardial irritability that would not alter the pulse rate, blood pressure, or respiratory pattern in the dogs, and, if translated into the dose that would be required for clinical anaesthesia, would not be excessive in man, or exceed the effective therapeutic range for moderate sedation (0 1 mg./kg.).

Further studies in dogs were carried out to determine whether the protection afforded by perphenazine against l'epinephrine-provoked cardiac arrhythmias would apply also to anaesthesia with cyclopropane (25 per cent), chloroform (0 5 per cent), and trichlorethylene (1 per cent), since these agents are known to provoke spontaneous cardiac arrhythmias when inhaled during spontaneous respiration, and cause serious ventricular arrhythmias if l'epinphrine is administered during anaesthesia with these hydrocarbons (6, 7, 8, 9)

METHOD

Thirty-six acute experiments carried out on twenty-nine mongrel dogs are reported These animals varied in weight from 5 5 to 17 kg. (mean, 8 5 kg.). The same technical procedure was followed as was reported in the preceding experiments (5).

The concentration of each anaesthetic agent employed was specially selected, after preliminary trials, in order to produce a stable plane of surgical anaesthesia within a few minutes when the dog's tidal volume and airway pressure were preset on a respirator, and would not cause significant cardiovascular depression or the development of electrocardiographic evidence of spontaneous myocardial irritability while pulmonary ventilation was adequate

Cyclopropane-oxygen (25–75 per cent) was administered through a semi-closed circle system with fresh baralyme in the circuit, employing gas flows of at least 200 ml. cyclopropane and 600 ml. oxygen. Chloroform 0.5 per cent and trichlorethylene 1 per cent were administered from a calibrated Fluotec vaporizer with

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the vaporization setting at 0 5 and 3 per cent respectively (10). At least 7 L. gas/min. flowed through the vaporizer continuously (N_2O, 5, L. + O_2, 2 L.). The concentration, dose and rate of injection of epinephrine (0.02 mg./ml./kg. body weight/sec.) was the same as used previously (5), and was also specially selected in order that the electrocardiogram of the dog would probably show ventricular extrasystoles, ventricular tachycardia, multifocal ventricular extrasystoles, or ventricular fibrillation after 20 min of each of the anaesthetic agents.

Results

Cyclopropane 25 per cent and Oxygen 75 per cent

No significant spontaneous arrhythmias appeared during the 20 minutes of anaesthesia in twelve acute experiments on nine dogs The only alteration that was observed on the electrocardiogram was a slight sinus arrhythmia and a progressive

TABLE I

Effect of Perphenazine on Epinephrine-induced Cardiac Arrhythmias during 25 per cent Cyclopropane-75 per cent O_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	11 0	0 22	2 8	10	7 (Fig 1)
2	6 2	0 12	1 5	3	24
3	7 8	0 16	0	− 2	530–VF
4	9 0	0 18	0	− 4	194–VF
5	8 0	0 16	2 0	− 1	6
6	6 0	0 12	1 5	11	13
1	11 0	0 22	0	− 3	224–VF
3	7 8	0 16	2 0	8	9
4	9 0	0 18	2 3	Tachycardia–Bradycardia	
7	16 0	0 32	4 0	VF–Death*	
8	17 0	0 34	4 2	12	36 (Fig 2)
9	13 2	0 26	3 3	0	0†

*Mechanical difficulty during anaesthesia
†Bradycardia and hypotension after experiment, death in 3 hrs

slowing of the heart rate In seven of the nine dogs, the heart rate slowed to less than half after 20 minutes of cyclopropane, as compared to that in the control period (Fig. 1A, B). In the other two dogs there was little or no change in the heart rate (Fig 2A and B). In six experiments, femoral artery pressures were recorded, but there was no significant alteration before the injection of l'epinephrine.

In the three animals which did not receive perphenazine there was a period of at least 3 minutes in which paroxysmal auricular tachycardia, ventricular tachycardia, multifocal ventricular extrasystoles, and ventricular fibrillation appeared on the electrocardiogram after the injection of l'epinephrine The blood pressure rose immediately after injection of l'epinephrine and then fell rapidly to a very low level.

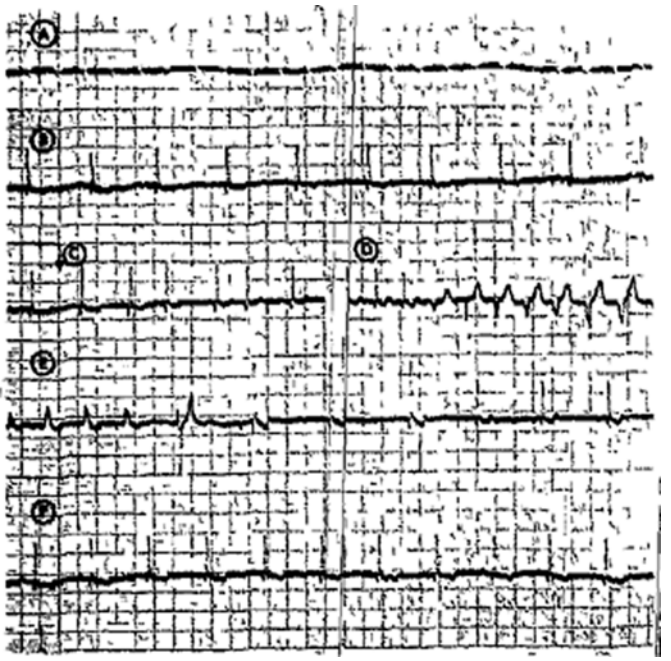

FIGURE 1 Observe bradycardia after 20 min of 25 per cent cyclopropane, and short run of paroxysmal ventricular tachycardia after 0 22 mg l epinephrine in 11 kg dog premedicated with 2 8 mg perphenazine A, control before cyclopropane, slight sinus arrhythmia at 188/min , B after 20 min of 25 per cent cyclopropane, slight sinus arrhythmia at 82/min C, end of injection of l epinephrine, rate increasing; D 9 sec after C, paroxysmal ventricular tachycardia at 180/min , E, 14 sec after C, P waves reappear, F 30 sec after C, slight sinus arrhythmia at 100/min

In the other nine experiments in which perphenazine premedication was administered, the following observations were recorded One dog (no 4) had a brief period of paroxysmal auricular tachycardia, followed by a short run of slow ventricular rhythm, then normal complexes appeared at the rate seen before the injection of epinephrine In another experiment (no 7) there was some mechanical difficulty with the automatic respirator which was ventilating the dog Thus caused signs of obstructive breathing intermittently during the 20 minutes control period When the l'epinephrine was injected, ventricular tachycardia developed immediately and changed abruptly in a few seconds to ventricular fibrillation Another dog (no 9) had no arrhythmias during the experiment, but developed a severe bradycardia and hypotension about 7 minutes after the l'epinephrine injection and discontinuation of cyclopropane Thus rate was regular at between 26–30/minutes for over 2½ hrs , with gradual reduction of the voltage During this time only oxygen was administered with the respirator Spontaneous breathing did not return and the blood pressure became too low to record after 3 hrs When the respirator was disconnected the animal expired promptly This death may have been due to "cyclopropane shock" or to the effects of a relative

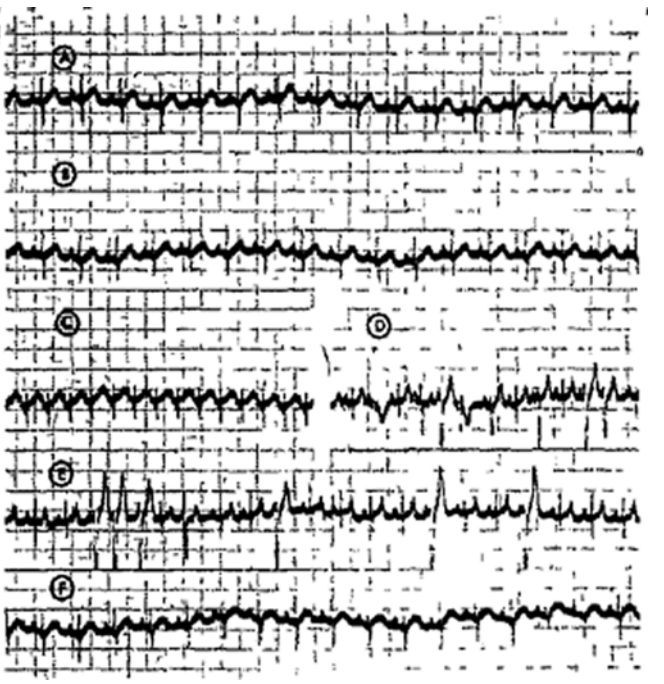

FIGURE 2 Observe that there was no alteration in the heart rate after 20 min of 25 per cent cyclopropane, and short run of ventricular extrasystoles after 0·34 mg l'epinephrine A, control before cyclopropane (after perphenazine), slight sinus arrhythmia at 144/min, B, after 20 min of 25 per cent cyclopropane, unchanged, C, end of injection of l epinephrine, heart rate increased to 230/min D 12 sec after C, multifocal ventricular extrasystoles E 30 sec after C, ventricular extrasystoles followed by normal rhythm, F 60 sec after C normal rhythm rate 150/min

overdose of cyclopropane A response like this was reported by Morris and associates in a similar experiment with chloroform (9)

The other six dogs that received perphenazine had very brief runs of paroxysmal supraventricular tachycardia with a few ventricular extrasystoles (see Figs 1 and 2, C to F)

Chloroform 0·5 per cent with Nitrous Oxide 70 per cent and Oxygen 30 per cent

These experiments were done initially with 1 per cent chloroform, because it was reported that dogs were very much more resistant to chloroform-epinephrine syncope than to that with cyclopropane (6) However, this concentration caused hypotension By trial it was found subsequently that 0·5 per cent chloroform and 70 per cent nitrous oxide with controlled respiration was sufficient to produce a preparation that would respond to epinephrine with ventricular arrhythmias, but would not cause marked alteration of the blood pressure during the preliminary 20 minutes of anaesthesia

TABLE II

EFFECT OF PERPHENAZINE ON EPINEPHRINE-INDUCED CARDIAC ARRHYTHMIAS DURING 0 5 PER CENT CHLOROFORM + 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	11 0	0 22	2 8	3	74 (see Fig 3)
2	9 0	0 18	2 3	9	56
3	6 9	0 14	0	4	144
4	5 9	0 12	0	3	93
5	9 1	0 18	2 3	Tachycardia only	
6	5 0	0 10	1 3	5	16
1	11 0	0 22	0	−1	VF–Death (see Fig 4)
7	6 0	0 12	0	0	264
8	10 4	0 21	2 5	2	46
9	9 0	0 18	2 3	3	18
10	8 0	0 16	0	2	156
5	9 1	0 18	0	−2	290

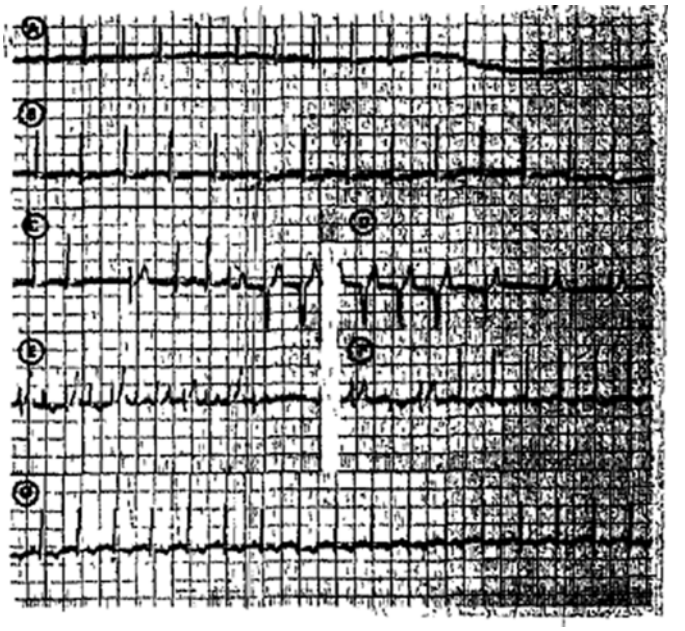

FIGURE 3 Observe slight bradycardia after 20 min of 0 5 per cent chloroform and ventricular arrhythmias after 0 22 mg epinephrine in 11 kg dog premedicated with 2 8 perphenazine A, control before chloroform, rate 136/min , B, after 20 min 0 5 per cent chloroform, rate 120/min , C, end of injection of l'epinephrine, onset of A–V dissociation, D, 30 sec after C, A–V dissociation, E, 45 sec after C, multifocal ventricular extrasystoles, F, 73 sec after C, normal sinus rhythm reappears, G, 90 sec after C, normal sinus rhythm, rate 140/min

No spontaneous cardiac arrhythmias appeared in the twelve acute experiments in the ten dogs, either during induction of anaesthesia or during the 20 minutes prior to administration of l'epinephrine Each of the dogs had a slight reduction in the heart rate within about 5 minutes after beginning the chloroform The reduction of heart rate was not progressive during the 20 minutes of anaesthesia (see Figs 3 A–B, and 4 A–B)

In the six experiments in which the animal received perphenazine, a brief run of increased heart rate, followed by atrioventricular rhythm, nodal and ventricular extrasystoles and slow ventricular rhythm were observed In only one of these animals did the arrhythmias persist for more than 1 minute (see Fig 3)

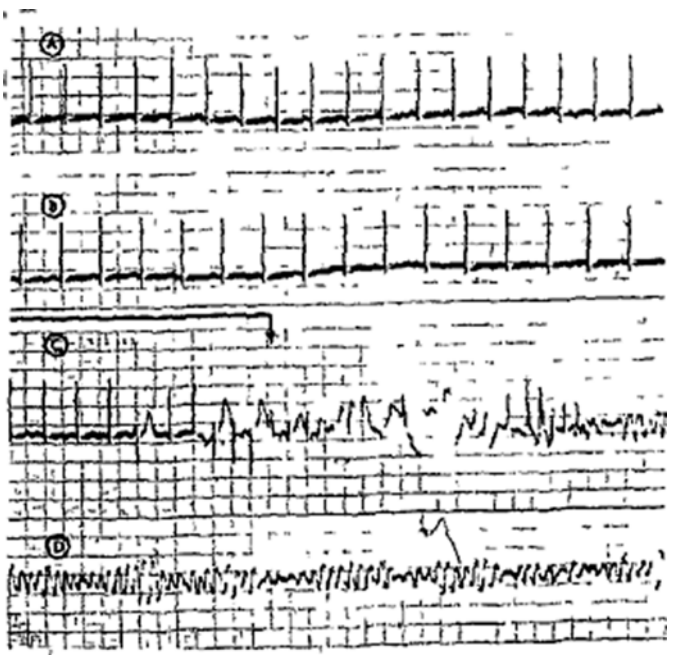

FIGURE 4 Observe slight bradycardia after 20 min of 0 5 per cent chloroform and telescoping of progression of arrhythmias to ventricular fibrillation when epinephrine (0 22 mg) was administered in the unpremedicated dog (same animal as in Fig 3)

In the other six experiments, in which no perphenazine was given, the animals developed bursts of supraventricular tachycardia, ventricular tachycardia, and multifocal ventricular extrasystoles In five of these experiments the arrhythmias persisted for at least 90 seconds and showed the appearance of a "prefibrillation phase" One animal abruptly developed ventricular fibrillation 4 seconds after the injection of l'epinephrine (see Fig 4)

Trichlorethylene 1 per cent with Nitrous Oxide 70 per cent and Oxygen 30 per cent

No significant spontaneous arrhythmias appeared during the 20 minutes of anaesthesia in twelve acute experiments on ten dogs There was also no significant alteration in the heart rate or blood pressure In the six experiments in which

TABLE III

EFFECT OF PERPHENAZINE ON EPINEPHRINE-INDUCED CARDIAC ARRHYTHMIAS DURING 1 PER CENT TRICHLORETHYLENE + 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 6	0 17	2 2	6	18
2	7 0	0 14	1 8	7	27
3	6 0	0 12	0	3	163
4	5 5	0 11	0	7	221
5	8 3	0 16	2 0	Tachycardia only	
6	6 8	0 14	1 8	14	55
7	8 0	0 16	0	4	VT & VF–13 min (intermittently)
2	7 0	0 14	0	3	VF–Death
8	6 4	0 13	1 6	5	66
9	11 2	0 22	2 8	8	124 (Fig 5)
5	8 3	0 16	0	6	VF–Death
10	8 2	0 16	0	3	182 (Fig 6)

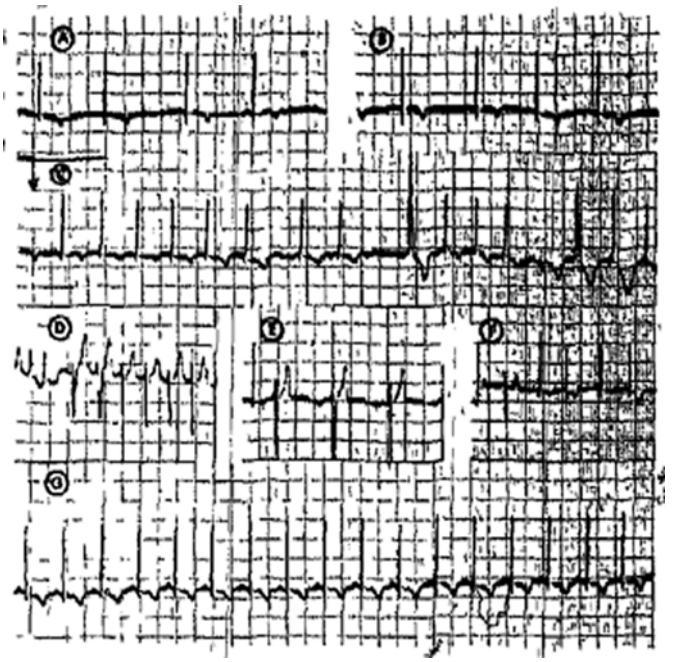

FIGURE 5 Observe ventricular arrhythmias after l'epinephrine A, control before trichlorethylene, sinus arrhythmia @ 82; B, after 20 min 1 per cent trichlorethylene, sinus arrhythmia @ 84, C, end of injection of l'epinephrine (0 22 mg), immediate increase in heart rate, and appearance of ventricular extrasystoles, D, E, F 30, 40 and 120 sec after C, ventricular extrasystoles, G, 130 sec after C, sinus rhythm

perphenazine premedication was given, there were no arrhythmias in one, and up to 2 minutes of intermittent ventricular arrhythmias in the other five after the injection of epinephrine (see Fig 5)

In the other six experiments, the animals did not receive perphenazine Three of them developed ventricular fibrillation—two of these died quickly, while the other alternated between ventricular tachycardia, multifocal ventricular extrasystoles, and ventricular fibrillation for 18 minutes The other three had long runs of ventricular arrhythmias that appeared at times to change to fibrillation, but they each reverted to a slow ventricular rhythm, which gradually accelerated until a near normal rate and configuration reappeared (see Fig 6)

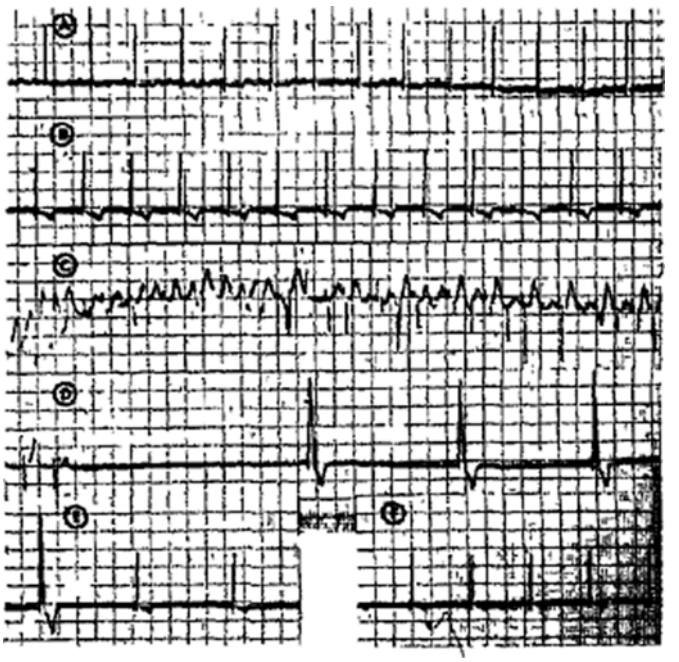

FIGURE 6 Observe prefibrillation phase of ventricular arrhythmias appearing shortly after injection of epinephrine A, control before trichlorethylene, rate 115/min , B, after 20 min 1 per cent trichlorethylene rate 108/min , C, 3 sec after injection of 1 epinephrine (0 16 mg)—brief appearance of ventricular fibrillation, then multifocal ventricular extrasystoles D, 166 sec after C, slow ventricular rhythm E 180 sec after C, return of sinus rhythm F 240 sec after C, sinus rhythm rate 90/min

DISCUSSION

The demonstration of a protective action against experimentally provoked cardiac arrhythmias by epinephrine has been carried out with many drugs, employing a variety of techniques (11) These have led to wide variations in experimental observations and in opinions expressed regarding the conclusions that may be drawn

The procedure employed in the present study was selected in order to eliminate as many variable factors as possible A small amount of thiopental was given intravenously in order to prepare the animal quickly, and to avoid a stormy induction of anaesthesia Respiratory tidal volume and airway pressure

were regulated in order to assure that pulmonary ventilation would be adequate at all times, and that the desired concentration of the primary anaesthetic would be delivered to the lungs and would establish a surgical plane of anaesthesia in a few minutes The liquid anaesthetics were delivered from a calibrated Fluotec vaporizer, which is temperature compensated, in order that variation in the concentration of these agents would be avoided even if the animal should take a deep breath, and to eliminate the possibility of sudden wide changes in the depth of anaesthesia The specific concentrations of the anaesthetics which were selected were chosen because they did not cause marked hypotension (or hypertension) during the initial 20 minutes of anaesthesia which were required to prepare the animal for the acute experiment

A fixed concentration and rate of injection were decided upon for the intravenous administration of l'epinephrine, with total dose dependent upon body weight This method was used rather than administering l'epinephrine until a particular cardiac response might be observed because the latter technique eliminates the factors of rate and dose and renders comparison of response with different anaesthetic agents more difficult

A light level of chloroform anaesthesia was chosen because deep chloroform anaesthesia depresses all functions of the heart, lowers the blood pressure, and perhaps reduces the susceptibility to the peculiarly lethal effect of l'epinephrine In fact, under deep chloroform, l'epinephrine may be an effective restorative of a rapidly succumbing circulation (12, 13) This is probably true also with Fluothane and the azeotropic mixture of Fluothane and diethyl ether (5) On the other hand, with artificial respiration, a high concentration of cyclopropane was used because this abolishes or minimizes the incidence of spontaneous arrhythmias, but also increases the susceptibility to ventricular arrhythmias provoked by l'epinephrine (14)

It was stated that, clinically, spontaneous cardiac arrhythmias have been noticed frequently during trichlorethylene anaesthesia either by palpation of the pulse or by the electrocardiograph (7, 8) In these early reports, the concentration of the inhaled vapour probably exceeded 2 per cent, or the arrhythmias were transient and appeared only during induction of anaesthesia (15) Serious ventricular arrhythmias may occur spontaneously only under deep anaesthesia with trichlorethylene, when rapid shallow breathing occurs, and causes hypoxaemia (16) In the animal studies reported here, no spontaneous arrhythmias were observed during the initial 20 minutes of anaesthesia in distinction to what has been observed by others (8, 9) This may be explained by the fact that induction of anaesthesia was always smooth, and pulmonary ventilation was supported sufficiently to maintain normal respiration When l'epinephrine was injected, however, these animals appeared to be far more susceptible to ventricular fibrillation than with any of the other agents studied

Perphenazine was observed to exert a protective action on the heart against ventricular arrhythmias, without apparent potentiation of the effect of the primary anaesthetics, and without altering the pulse rate or the blood pressure of the dogs, although the arrhythmias were not eliminated

The complete elimination of cardiac arrhythmias with perphenazine may be possible by greatly increasing the dose or by altering the amount of anaesthetics administered. However, the first manoeuvre would cause potentiation of the anaesthetics, and induce undesirable lowering of the blood pressure and possibly myocardial depression, while the second manoeuvre would alter grossly the optimum experimental procedure, and detract from the validity of any conclusions that may be drawn from the observations.

It appeared from these studies that perphenazine was more potent than chlorpromazine in reducing the duration and severity of cardiac arrhythmias provoked by l'epinephrine, and had no significant effect on the pressor response to l'epinephrine at the dose level tested (17, 18, 19).

Summary and Conclusions

The effect of 25 per cent cyclopropane, 0.5 per cent chloroform with 70 per cent nitrous oxide and 1 per cent trichlorethylene with 70 per cent nitrous oxide on the heart rate was observed during thirty-six acute experiments in dogs in which pulmonary ventilation was regulated, and the concentrations of the inhaled anaesthetics were accurately controlled. There was marked slowing of the heart rate with cyclopropane, slight slowing with chloroform, and little or no change with trichlorethylene. There was no significant difference in the heart rate in the animals that were premedicated with perphenazine 0.25 mg/kg, as compared to the unpremedicated animals.

Sensitization to epinephrine-provoked cardiac arrhythmias by a standard concentration and rate of injection (0.02 mg/ml/sec.) were observed, when the total dose was regulated according to the animals' weight. It was found that ventricular fibrillation was less likely to occur when epinephrine was injected during anaesthesia with 0.5 per cent chloroform than with 25 per cent cyclopropane, or with 1 per cent trichlorethylene. In a similar study with Fluothane and the azeotropic mixture of Fluothane and diethyl ether, the cardiac response to epinephrine with 0.5 per cent Fluothane was similar to that with 25 per cent cyclopropane, and the 1 per cent of the azeotropic mixture was similar to that with 0.5 per cent chloroform.

Premedication with perphenazine (0.25 mg./kg.) caused a significant reduction in the severity and duration of the cardiac arrhythmias provoked by epinephrine if pulmonary ventilation was adequate throughout the experiment, but did not cause reversal of the pressor response. It was suggested that the elimination of epinephrine-provoked cardiac arrhythmias by perphenazine would require such alteration in the depth of anaesthesia or dose of perphenazine as would reduce the validity of the results of these experiments for practical application.

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RÉSUMÉ

Nous avons étudié l'effet sur le rythme cardiaque de 25 pour cent de cyclopropane, de 0.5 pour cent de chloroforme avec 70 pour cent de protoxide d'azote et de 1 pour cent de trichlorethylène avec 70 pour cent de protoxide d'azote chez trente-six chiens dont la ventilation pulmonaire était maintenue et dont les concentrations d'agents anesthésiques inhalés étaient précisement contrôlées. Nous avons observé un ralentissement marqué du cœur avec le cyclopropane, un léger ralentissement avec le chloroforme et peu ou pas de changement avec le trichlorethylène Chez les animaux prémédiqués avec de la perphénazine 0.25 mg./kg., nous n'avons pas observé de différence dans le rythme cardiaque comparativement aux animaux non prémédiqués.

Nous avons observé une sensibilisation à provoquer des arythmies cardiaques par l'épinéphrine à une concentration et à une vitesse d'injection standard (0.02 mg./ml. sec.) lorsque la dose totale était calculée d'après le poids des animaux. Nous avons observé que la fibrillation ventriculaire était moins exposée à survenir lorsque l'épinéphrine était injectée durant l'anesthésie avec 0.5 pour cent de chloroforme que durant l'anesthésie avec 25 pour cent de cyclopropane ou avec 1 pour cent de trichlorethylène. A la suite d'une étude semblable avec le Fluothane et le mélange azéotrope Fluothane et éther diéthylique, nous avons noté que la réponse cardiaque à l'épinéphrine avec 0 5 pour cent de Fluothane était semblable à celle observée avec 25 pour cent de cyclopropane et que celle de 1 pour cent du mélange azéotrope était semblable à celle de 0.5 pour cent de chloroforme.

La prémédication avec de la perphénazine (0 25 mg./kg.) a entraîné une réduction importante de la sévérité et de la durée des arythmies cardiaques provoquées par l'épinéphrine à la condition que la ventilation pulmonaire soit adéquate durant toute l'expérience, mais elle n'a pas inversé l'effet presseur. Il nous a semblé que l'élimination par la perphénazine des arythmies ventriculaires provoquées par l'épinéphrine nécessiterait une telle profondeur d'anesthésie ou des doses telles de perphénazine que la valeur pratique des résultats de ces expériences serait bien diminuée.

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