VENTRICULAR ARRHYTHMIAS INDUCED BY AMINOPHYLLINE DURING HALOTHANE ANAESTHESIA IN DOGS

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INTRAVENOUS AMINOPHYLLINE and sympathomimetic amines have been advocated for treatment of asthmatic attacks during anaesthesia.¹⁻⁵ Halothane, an agent which sensitizes the heart to certain sympathomimetic amines, has been shown to be a valuable agent for anaesthetizing patients with an asthmatic history.⁶

The administration of caffeine and theophylline intravenously to dogs anaesthetized with pentobarbital may lead to ventricular arrhythmias in the presence of catecholamines.^{6,7} In clinical use aminophylline has been reported to have produced arrhythmias and cardiac "collapse" when administered intravenously.⁸⁻¹⁰ During the course of animal studies in which sympathomimetic amines and aminophylline were administered during halothane anaesthesia it was noted that a number of animals developed arrhythmias after aminophylline injection.

It was the purpose of this study to determine the incidence and severity of arrhythmias following aminophylline in awake dogs and in dogs anaesthetized with halothane, barbiturates, or ether. The effect of combinations of aminophylline and sympathomimetic amines during halothane anaesthesia has been reported previously.¹¹

METHOD

Adult mongrel dogs premedicated with morphine (0.2 mg./kg) and scopolamine (0.01 mg./kg.) or atropine (0.02 mg./kg.) were induced with thiopental (13.6-20.0 mg./kg.) and suxamethonium 10 mg. and intubated with a cuffed endotracheal catheter. Ventilation was maintained with a Palmer Ideal Pump using sufficient volumes of room air to maintain end tidal P_{O_2} at 34-38 mm. Hg, monitored with an infrared CO_2 -analyser. Two ml. of 1 per cent lidocaine was used in dogs in the unanaesthetized group for placement of femoral catheters. Pentobarbital, chosen as the agent for the group with barbiturate anaesthesia, was given in just sufficient dosage to keep the animals from struggling (22.4-39.1 mg./kg. in 60-90 minutes). Ether and halothane vapourized with oxygen in a "copper kettle" and a "Fluotec" respectively were administered by a non-rebreathing system.

Unanaesthetized Group

Ten premedicated trained dogs were given aminophylline 50 mg./kg. by constant injection within four minutes. Heart rate increased from 110 ± 24.6 to 130 ± 52.6 . Multifocal premature ventricular contractions (M.P.V.C.) lasting several seconds appeared in one animal and sinus tachycardia (S.T.) developed

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TABLE I
ARRHYTHMIAS FOLLOWING AMINOPHYLLINE

Anesthesia group	No. dogs	Arrhythmias				
		None	Sinus tachycardia	Premature ventricular contraction	Ventricular tachycardia	Ventricular fibrillation
Unanesthetized	10	1	8	1	0	0
Barbiturate	9	2	7	0	0	0
Ether	6	1	3	2	0	0
Halothane 3%	6	5	1	0	0	0
Halothane 1%	16	1	3	4	5	3

Arrhythmia listed is the most severe occurring in each animal.

in eight other animals (Table I). Arterial pressure changes following aminophylline were inconsistent, with increases of not over 10 mm. Hg and decreases of not more than 35 mm. Hg (Fig. 1).

Barbiturate Group

When heart rate and arterial pressure became stable (60-90 minutes) after induction with pentobarbital, aminophylline 50 mg./kg. was given to nine dogs. Heart rate increased 81 ± 40.2 from 175 ± 34.3 , and arterial pressure decreased 40 ± 23.9 from 147 ± 2.13 mm. Hg (Fig. 1). Arrhythmias did not occur.

FIGURE 1. Blood pressure level prior to aminophylline is shown in graph A and changes in mm. Hg following aminophylline are shown in graph B. Key: ● = ventricular arrhythmias; ○ = no arrhythmias.

Ether Group

Six dogs were ventilated with 3 per cent ether for 30 minutes and were then given aminophylline 50 mg./kg. Heart rate increased 54 ± 29.2 from 157 ± 36.5 and arterial pressure decreased 32 ± 15.1 from 116 ± 23.9 mm. Hg (Fig. 1). M.P.V.C. appeared for three minutes in one animal and for seven minutes in another (Table I).

Halothane 3 Per Cent Group

Six animals were ventilated with halothane 3 per cent for ten minutes and were then given aminophylline 50 mg./kg. Heart rate increased 23 ± 16.9 from 137 ± 26.5 beats/minute and arterial pressure decreased 33 ± 16.2 from 102 ± 24.0 mm. Hg. Arrhythmias were not found after aminophylline while the animals were being ventilated with 3 per cent halothane. However, when the dogs were subsequently ventilated with room air and were in a lighter plane of anaesthesia, two animals developed unifocal premature ventricular contractions (U.P.V.C.), one developed M.P.V.C., and one other had ventricular tachycardia (V.T.). The above arrhythmias appeared within five minutes after return to ventilation with room air and continued for 15–22 minutes.

Halothane 1 Per Cent Group

Sixteen animals were ventilated with halothane one per cent for fifteen minutes and were then given aminophylline. Heart rate increased 74 ± 16.9 from 134 ± 24.8 (excluding three cases of ventricular fibrillation (V.F.)). The incidence and severity of arrhythmias are shown in Table I. Three dogs developed M.P.V.C. progressing to V.T. and terminating in V.F. Individual data on the dogs in this group is presented in Table II. Arterial pressure decreased 40 ± 16.6 from 131 ± 22.8 excluding the animals with ventricular fibrillation. Arterial pressure changes did not differ significantly ($p < 0.05$) in the animals developing arrhythmias. A myocardial ischaemic E.C.G. pattern appeared in four animals while they were being ventilated with halothane but disappeared following aminophylline. Arrhythmias were induced with less than 25 mg./kg. of aminophylline in ten dogs and less than 37.5 mg./kg. in two others. Ventricular fibrillation developed in one animal when 12.5 mg./kg. was given.

Deepening Level of Anaesthesia during Arrhythmias

Five dogs in the group which developed ventricular arrhythmias and one with S.T. from aminophylline-halothane were ventilated with halothane 3 per cent while arrhythmias were occurring (Table III). Within three minutes on halothane 3 per cent, arrhythmias ceased and the dogs were again ventilated with room air. Several minutes later arrhythmias reappeared in the five animals which had previously had ventricular arrhythmias, starting with U.P.V.C. progressing to M.P.V.C. and occasional bursts of V.T. The animal with S.T. (dog 40) after aminophylline also developed U.P.V.C., M.P.V.C., and V.T. The arrhythmias lasted from one to eighteen minutes, terminating with U.P.V.C. and then normal sinus rhythm (N.S.R.). Halothane 3 per cent was again administered following termination of arrhythmias, and the results are shown in Table III under the second trial. Four of the animals immediately developed arrhythmias lasting for

TABLE II
HEART RATE, ARTERIAL PRESSURE, AND E.C.G. CHANGES FOLLOWING AMINOPIHYLLINE ADMINISTRATION DURING VENTILATION WITH 1 PER CENT HALOTHANE

Dog no.	Wt. (kg.)	Aminophylline (mg./kg.)		Heart rate		Arterial Systolic pressure mm.Hg		E.C.G. changes	Arrhythmia duration (min.)
		Arrhythmia	Total	Before	After	Before	After		
31	9.1	37.5	50	71	240	140	120	V.T.	35
34	12.2	12.2	12.2	215	173	154	140	V.F.	
38	8.9	—	50	164	—	74	—	none	
32	8.6	12.5	50	136	220	120	120	U.P.V.C.	7
33	11.8	37.5	50	127	210	116	84	M.P.V.C.	8
36	11.6	25.0	50	177	240	158	110	U.P.V.C.	>20
37	8.9	12.5	50	186	225	114	98	V.F.	
39	11.8	6.4	21	173	260	176	164	V.F.	
40	10.9	—	50	113	—	122	—	S.T.	
41	8.2	25.0	50	136	260	150	120	V.T.	>20
42	12.5	13.9	50	158	215	154	112	V.T.	>20
43	14.1	—	50	113	—	112	—	S.T.	
44	8.4	12.5	50	117	173	130	100	M.P.V.C.	>20
45	8.6	—	50	177	240	152	—	S.T.	
47	8.6	25.0	50	125	206	150	140	M.P.V.C.	4
48	8.0	25.0	50	200	206	128	84	M.P.V.C.	18

Aminophylline dosage is presented as that which induced arrhythmias and total amounts administered. Heart rates and arterial pressures are shown before, at the time arrhythmias occurred, and during arrhythmias. S.T., sinus tachycardia; U.P.V.C., unifocal premature ventricular contractions; V.T., ventricular tachycardia; V.F., ventricular fibrillation.

TABLE III
EFFECT OF CHANGES IN LEVEL OF ANAESTHESIA ON AMINOPHYLLINE—1 PER CENT HALOTHANE ARRHYTHMIAS

Dog no.	E.C.G. Aminophylline-Halothane (1%)	Halothane 3% ventilation (min.)		Arrhythmia with 3% halothane	Arrhythmia reappearance time with room air ventilation (min.)		Arrhythmia with room air ventilation		Duration of arrhythmia (min.)	
		1	2		1	2	1	2	1	2
40	S.T.	6	5	none	3	2	V.T.	V.T.	1	1
36	U.P.V.C.	5	5	disappeared	1	1	V.T.	V.T.	3	5
33	M.P.V.C.	6	6	disappeared	1	1	U.P.V.C.	M.P.V.C.	3	3
41	V.T.	5	5	disappeared	2	1	V.T.	V.T.	3	4
42	V.T.	5	6	disappeared	.5	.5	V.T.	V.T.	7	4
44	V.T.	6	4	disappeared	1	1	V.T.	V.T.	18	9

Cessation of aminophylline—1 per cent halothane arrhythmias during ventilation with 3 per cent halothane and time of reappearance of arrhythmias during subsequent ventilation with room air. Results repeating 3 per cent halothane-room air ventilation are shown in column 2.

several seconds, which then reverted to N.S.R. When halothane was discontinued and the animals subsequently returned to ventilation with room air, U.P.V.C., M.P.V.C., and occasional bursts of V.T. were found.

DISCUSSION

Positive inotropic and chronotropic activity of methylxanthine derivatives has been recognized since the past century,¹² and more recently has been demonstrated by other investigators.¹³⁻¹⁴ Ventricular arrhythmias have been described as occurring with toxic doses of methylxanthines¹² or with smaller doses in combination with sympathomimetic amines.⁶⁻⁷ In another study arrhythmias did not develop in dogs pretreated with reserpine or in "spinal" animals with intravenous caffeine or theophylline 50-200 mg./kg. until the animals were subsequently given epinephrine 5 µg./kg.⁷ It was concluded that methylxanthines sensitize the myocardium to epinephrine and that the presence of catecholamine is necessary for development of cardiac arrhythmias with doses of methylxanthines as large as 200 mg./kg. We have also shown that with halothane anaesthesia ventricular arrhythmias were more severe when administration of the sympathomimetic amines ephedrine and isoproterenol were preceded by aminophylline.¹¹ The above data suggest that arrhythmias with halothane and aminophylline in the present studies may be related to the presence of catecholamine. Sympathoadrenal stimulation, however, has been shown to be weak with halothane when compared to ether and cyclopropane.¹⁵⁻¹⁷ In addition, cardiovascular responses^{18,19} and contractile responses of excised aortic tissue²⁰ to catecholamine have been reported to have diminished during halothane anaesthesia. Halothane, however, has the property of cardiac sensitization to certain sympathomimetic amines. Sensitization of the heart to arrhythmias by agents which produce myocardial depression has been a subject of concern.²¹ In the present studies the apparent protection afforded by deep halothane anaesthesia to aminophylline-induced arrhythmias seems paradoxical but may parallel the decreased cardiac or vascular tissue responses¹⁸⁻²⁰ to catecholamines as reported by other investigators.

Termination of arrhythmias by deepening the level of anaesthesia with halothane has been reported by Muir *et al.*²² who found arrhythmias in cats breathing halothane 1 per cent but a sudden cessation when the concentration was increased to 2-3 per cent. Appearance of arrhythmias was associated with hypercarbia, and cessation also followed return of arterial P_{CO_2} to normal. Purchase has reported that cardiac arrhythmias during halothane anaesthesia in cats were terminated temporarily by an increase in the concentration of inspired halothane but reappeared within five minutes.²³ Disappearance of arrhythmias seems unrelated to a reduction in arterial pressure or an alteration in blood gases. Johnstone reported that arrhythmias did not occur in deeply anaesthetized and well-ventilated patients but were provoked in lightly anaesthetized subjects by carbon dioxide retention, intravenous injections of atropine, or surgical stimulation.²⁴ Black *et al.*,²⁵ on the other hand, found that the threshold at which hypercarbia induced arrhythmias in humans was not consistently influenced by the depth of halothane anaesthesia.

A significant difference in the level of blood pressure was noted between the 1 per cent and 3 per cent halothane groups prior to the administration of aminophylline ($0.01 < p < 0.02$). It could not, however, be concluded from our studies that the level of blood pressure influenced the incidence or severity of arrhythmias. Although limitation of blood pressure rise after sympathomimetic amines during hydrocarbon anaesthesia has been shown to prevent arrhythmias,^{26,27} arrhythmias have also been reported during falls in blood pressure.²⁸⁻³⁰

SUMMARY

Intravenous administration of aminophylline to dogs anaesthetized with 1 per cent halothane resulted in ventricular arrhythmias in 12 of 16 animals (ventricular fibrillation in three animals). Halothane-aminophylline arrhythmias disappeared when the animals were ventilated with 3 per cent halothane but reappeared when the animals were subsequently ventilated with room air. Arrhythmias did not occur when aminophylline was given to animals ventilated with 3 per cent halothane or to dogs anaesthetized with pentobarbital. Following administration of aminophylline one out of ten unanaesthetized dogs and two of six animals ventilated with 3 per cent ether developed short periods of multifocal premature ventricular contractions. A possible explanation of the data obtained is presented.

RÉSUMÉ

L'administration d'aminophylline par voie endoveineuse à des chiens anesthésiés avec 1 pour cent de fluothane a entraîné des arythmies ventriculaires chez 12 des 16 animaux et une fibrillation ventriculaire, chez trois. Les arythmies fluothane-aminophylline sont disparues lorsque, subséquemment, nous avons ventilé les animaux avec l'air de la pièce. Nous n'avons pas observé d'arythmies lorsque nous avons donné l'aminophylline à des animaux ventilés avec 3 pour cent d'halothane ou à des chiens anesthésiés avec du pentobarbital. A la suite de l'administration d'aminophylline un sur dix des chiens non anesthésiés et deux sur six des animaux ventilés avec 3 pour cent d'éther ont présenté de courtes périodes de contractions ventriculaires prématurées multifocales. Nous présentons une explication possible des résultats obtenus.

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