VENTRICULAR ARRHYTHMIAS DURING HALOTHANE ANAESTHESIA EFFECT OF ISOPROTERENOL, AMINOPHYLLINE, AND EPHEDRINE*

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HALOTHANE has been reported as a valuable agent for anaesthetizing patients with asthma or for terminating asthmatic attacks during surgery.¹⁻⁵ If the asthmatic attack persists despite the use of halothane anaesthesia, other therapeutic agents such as sympathomimetic amines (ephedrine or isoproterenol) and aminophylline are often administered. Epinephrine in therapeutic dosage is contraindicated during halothane anaesthesia because ventricular fibrillation has been reported.^{6,7} The authors have recently had severe bronchospasm develop in a 48 year-old asthmatic patient during halothane anaesthesia. Aminophylline 250 mg given intravenously and subsequently followed by isoproterenol 2 c.c. of 1:150 solution by aerosol did not improve the bronchospasm. Shortly after intravenous administration of ephedrine (10 mg) the patient developed tachycardia, the rate of which could not be counted by oesophageal stethoscope. The arrhythmia reverted to normal before an electrocardiogram could be procured.

Ephedrine⁸ and aminophylline⁹ given intravenously during halothane anaesthesia in dogs have been reported to induce ventricular arrhythmias, but data on isoproterenol is lacking. Aminophylline given intravenously to unanaesthetized subjects has been reported to have resulted in cardiac collapse.^{10,11} Other reports suggest that the effects of catecholamines and aminophylline are synergistic and may lead to death in humans^{12,13} and also in mice.¹³ The cause of death was not determined. Aramine has been reported to have induced ventricular fibrillation in a patient postoperatively. On perusal of the report¹⁴ we noted that caffeine sodium benzoate was given just before the Aramine. Adrenaline with caffeine^{15,16} or theophylline¹⁶ in dogs has been reported to have resulted in ventricular arrhythmias including ventricular fibrillation.

Positive inotropic and chronotropic effects are well documented with isoproterenol, ephedrine, and the xanthines (caffeine, theophylline, and aminophylline).¹⁷ Although halothane is a cardiac depressant,¹⁸ it sensitizes the heart, producing arrhythmias with certain sympathomimetic amines.^{4,6,8}

The available evidence suggests that combinations of aminophylline and certain sympathomimetic amines administered during halothane anaesthesia may be synergistic in their effect upon the heart, causing a greater incidence of arrhythmia than each administered individually. It is, therefore, the purpose of this study to determine the incidence and severity of arrhythmia when isoproterenol or ephedrine is administered during halothane anaesthesia and also with the administration of aminophylline prior to the sympathomimetic amines.

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METHODS

Adult mongrel dogs premedicated with morphine 0.02 mg/kg and atropine 0.2 mg/kg were induced with thiopental 9.2–19.4 mg/kg and suxamethonium 10 mg and intubated with cuffed endotracheal catheters. Ventilation was maintained with a Palmer's "Ideal" pump with sufficient volumes of room air to maintain an end-expiratory P_{CO_2} at 36–38 mm Hg. End-expiratory P_{CO_2} was monitored with a Beckman LBI infra-red carbon dioxide analyzer. Arterial pressure was determined by a catheter in the femoral artery and measured with a mercury manometer. Lead 2 of the electrocardiogram was recorded with a Sanborn direct-writing electrocardiograph. Halothane anaesthesia was started within 60 minutes after induction, when the animals were awakening from thiopental anaesthesia. Halothane vaporized with a Fluotec was administered in 1 per cent concentration in a non-rebreathing system. Drugs were given approximately 10 minutes after inhalation of halothane.

RESULTS

Isoproterenol-Halothane

Isoproterenol 10 μ g/kg was given to eight dogs anaesthetized with 1 per cent halothane. Premature ventricular contractions (PVC) lasting less than 5 seconds occurred in five dogs and sinus tachycardia (ST) in the other three animals immediately after administration of isoproterenol. One of the three animals with sinus tachycardia developed a 50-second period of bigeminal type premature ventricular contractions 3 minutes after injection of isoproterenol. The heart rate increased significantly from $142 \pm 31^*$ to 256 ± 36 ($P < 0.01$) but returned to 147 ± 24 within 10 minutes. Blood pressure decreased from 146 ± 24 mm Hg to 88 ± 23 within 1 minute after administration of isoproterenol ($P < 0.01$) but returned to 138 ± 23 mm Hg in 3 minutes, and 148 ± 22 mm Hg in 20 minutes.

Isoproterenol Following Aminophylline

Aminophylline 50 mg/kg was given intravenously within 4 minutes to 13 dogs and followed in 5 minutes by isoproterenol 10 μ g/kg. With halothane-aminophylline one dog did not have arrhythmias, four had sinus tachycardia, and eight had ventricular arrhythmias (Table I). Ventricular arrhythmias continued in three animals, and reappeared in three other animals after administration of isoproterenol but disappeared within 24 seconds. One dog developed ventricular fibrillation (VF) immediately after the administration of isoproterenol. Two animals who had had ventricular arrhythmias with halothane-aminophylline did not develop arrhythmias after isoproterenol. Sinus tachycardia induced by aminophylline continued after isoproterenol administration in three dogs. The single dog which did not show arrhythmias after aminophylline developed ventricular tachycardia (VT) for 5 seconds after isoproterenol. The heart rate increased from 133 ± 37 to 227 ± 49 after aminophylline and to 267 ± 21 after isopro-

*Standard deviation

TABLE I
ADMINISTRATION OF ISOPROTERENOL AFTER AMINOPHYLLINE*

Case	Body wt (kg)	E C G change after aminophylline (min)	E C G change after isoproterenol (sec)
3105	9.1	ST	ST
3158	11.6	ST	ST
3159	9.8	ST	ST
3104	10.0	NRS	VT (3), UPVC (2)
3157	14.1	ST	MPVC (18)
3152	8.4	VT (2), MPVC (1)	ST
3154	8.6	MPVC (1), UPVC —————→	ST
3101	13.4	MPVC + VT (2), MPVC —————→	VT
3102	6.5	MPVC (1), UPVC (2)	UPVC (3)
3151	8.4	UPVC (2.5)	VT (24)
3153	11.0	MPVC —————→	VT (2)
3155	14.1	MPVC —————→	MPVC (6)
3156	9.3	MPVC (1), UPVC (1)	MPVC (5)

*Duration of ectopic beats in parentheses. Arrow signifies that arrhythmia continued while isoproterenol was administered. See text for abbreviations.

terenol ($P < 0.01$). The blood pressure decreased from 114 ± 19 mm Hg to $66 \pm$ mm Hg after aminophylline ($P < 0.01$) but returned to 113 ± 15 mm Hg in 10 minutes.

Ephedrine-Halothane

Intravenous administration of ephedrine 0.5 mg/kg induced arrhythmias in all of seven dogs anaesthetized with halothane. Four animals developed premature ventricular contractions, and two second-grade A-V heart block and one sinus tachycardia. Arrhythmias continued for 2–10 minutes. Blood pressure increased from 152 ± 14.2 mm Hg to 207 ± 24.3 mm Hg and returned to 164 ± 22.1 mm Hg in 20 minutes.

Ephedrine Following Aminophylline

Seven dogs were given aminophylline 50 mg/kg followed in 5 minutes by ephedrine 0.05 mg/kg. Four animals with halothane-aminophylline had premature ventricular contractions (Table II) but the others only an increase in heart rate from 96 ± 18 to 193 ± 30 ($P < 0.01$). All of the dogs with premature ventricular contractions after aminophylline developed multifocal premature ventricular contractions (MPVC), three of which progressed to ventricular

TABLE II
ADMINISTRATION OF EPHEDRINE AFTER AMINOPHYLLINE*

Case	Body wt (kg)	E C G change after aminophylline (min)	E C G change after ephedrine (sec)
3356	14.1	ST	ST
3351	13.6	NSR	VT (789)
3352	15.9	ST	MPVC (80), VF
3353	15.4	MPVC —————→	VF
3354	9.0	UPVC (2)	VF
3355	10.9	UPVC —————→	MPVC (36), VF
3357	11.6	UPVC (1)	MPVC (1080)

*Duration of ectopic beats in parentheses. Arrow signifies that arrhythmia continued while ephedrine was administered.

tachycardia and then ventricular fibrillation after ephedrine. Of the three dogs which developed nodal sinus rhythm or sinus tachycardia after aminophylline, two showed ventricular tachycardia or ventricular fibrillation, and the remaining sinus tachycardia.

DISCUSSION

It has been reported that isoproterenol produced ventricular arrhythmias during cyclopropane anaesthesia^{19,20}. Dresel *et al*, with intravenous isoproterenol 5–300 $\mu\text{g/kg}$ during cyclopropane anaesthesia, found only nodal tachycardia,²¹ however, when the drug was injected into the anterior descending coronary artery idioventricular beats were produced.²² Isoproterenol during halothane anaesthesia in our series produced an increase in heart rate, a fall in arterial pressure, and ventricular arrhythmias lasting for several seconds. The hypotension was brief (1–15 minutes) and blood pressure returned to pre-existing levels within 3 minutes. Heart rate had returned to normal values within 10 minutes. Clinically the intrapulmonary instillation of isoproterenol by aerosol would probably be without hazard, since we have found that the circulatory effects of the drug were minimal and of short duration even when it was given intravenously and in large dosage to a species recognized as being more prone to development of arrhythmias. Can this apply, however, to a patient who has been pretreated with aminophylline? The appearance of a brief period of premature ventricular contractions with halothane–isoproterenol and the capacity of aminophylline–halothane to induce arrhythmias suggest that the drugs (isoproterenol–aminophylline) may produce synergistic effects when given together during halothane anaesthesia. The results in our experiments were, however, inconsistent. Arrhythmias ceased immediately after isoproterenol administration in some dogs, but became worse in others, including ventricular fibrillation in one animal. The above findings suggest that, in clinical use, aminophylline–isoproterenol given intravenously may be deleterious but that this may not be true if it is given by aerosol. On the other hand, the presence of hypoxia and hypercarbia occurring as the result of severe bronchospasm could be expected to predispose to arrhythmias^{23, 24} and perhaps make the drug combinations more hazardous.

Halothane, aminophylline, and isoproterenol produce falls in blood pressure, the combination of which in our studies caused pressure decreases of almost 70 mm Hg. The significance of a protective effect of hypotension on development of arrhythmias with sympathomimetic amine–cyclopropane has been reported by others²⁵ but the role of hypotension in the present studies is unexplained. The possibility of demand hypoxia of the myocardium from the cardiac stimulation of sympathomimetic amine and aminophylline in the presence of hypotension cannot be dismissed.

It appears that the effects of ephedrine and aminophylline are synergistic in the production of cardiac arrhythmias since ventricular fibrillation (4–7 dogs) only occurred when the combination was given during halothane administration.

Combinations of xanthine (caffeine, aminophylline) and sympathomimetic amines are also used clinically for asthma, cardiac resuscitation, myocardial failure, anaphylactic shock with bronchospasm, and for barbiturate intoxication.

Sudden death is not uncommon during therapy of these conditions and the available evidence suggests that the cause may be related to synergism of the xanthines and sympathomimetic amines leading to ventricular fibrillation

CONCLUSION

Isoproterenol and ephedrine administered intravenously to dogs anaesthetized with halothane led to ventricular arrhythmias. The arrhythmias were more severe when aminophylline was given prior to ephedrine but the results were inconsistent with isoproterenol. Ventricular fibrillation was found only when aminophylline was given prior to ephedrine or isoproterenol.

RÉSUMÉ

L'isoprotérénol et l'éphédrine, administrés par une voie endoveineuse à des chiens anesthésiés à l'halothane, produisent de l'arythmie ventriculaire. Si, au préalable, on administre de l'aminophylline, l'arythmie était plus prononcée avec l'éphédrine et inconstante avec l'isoprotérénol. Nous avons observé une fibrillation ventriculaire seulement lorsque l'aminophylline était donnée avant l'éphédrine ou l'isoprotérénol.

REFERENCES

- 1 SHNIDER, S. M. & PAPPER, E. M. Anesthesia for the Asthmatic Patient *Anesthesiology* 22 886 (1961)
- 2 ABAJIAN, J., BRAZELL, E. H., DENTE, G. A., & MILLS, E. L. Experience with Halothane in More than 55 Cases *JAMA* 171 535 (1959)
- 3 AUSERMAN, H. M., & ADAN, A. Fluothane A New Nonexplosive Volatile Anesthetic Agent—Preliminary Report of 2000 Administrations, *Southern Med J* 52 46 (1959)
- 4 STEPHEN, C. R., LAWRENCE, J. H., FABIAN, L. W., BOURGEOIS-GAVARDIN, M., DENT, S., & GROSSKREUTZ, D. C. Clinical Experience with Fluothane *Anesthesiology* 19 197 (1958)
- 5 CHANG, J., MACCARTNEY, H. H., & GRAVES, H. B. Clinical Experience with Fluothane A New Non-Explosive Anesthetic Agent *Canad Anaesth Soc J* 4 187 (1957)
- 6 DELANCE, J. J. Cardiac Arrest with Halothane and Adrenaline *Anaesthesia* 18 537 (1963)
- 7 VAREJES, L. The Use of Solutions Containing Adrenaline during Halothane Anaesthesia *Anaesthesia* 18 507 (1963)
- 8 STEPHEN, C. R., MARGOLIS, G., FABIAN, L. W., & BOURGEOIS-GAVARDIN, M. Laboratory Observations with Fluothane *Anesthesiology* 19 770 (1958)
- 9 TAKAORI, M., & LOEHNING, R. W. Ventricular Arrhythmias with Aminophylline-Halothane in Dogs (Unpublished data)
- 10 MERRILL, G. A. Aminophylline Deaths *JAMA* 123 1115 (1943)
- 11 BRESNICK, E., WOODWARD, W. K., & SAGEMAN, C. B. Fatal Reactions to Intravenous administration of Aminophylline *JAMA* 136 397 (1948)
- 12 NOLKE, A. C. Severe Toxic Effects from Aminophylline and Theophylline Suppositories in Children *JAMA* 161 693 (1956)
- 13 GARDNER, R. A., HANSEN, A. E., EWING, P. L., & EMERSON, G. A. Unexpected Fatality in Child from Accidental Consumption of Anti-asthmatic Preparation Containing Ephedrine, Theophylline and Phenobarbital *Tex J Med* 46 516 (1950)
- 14 SMITH, O. & LOQUE, B. Arrhythmias and Cardiac Arrest Induced by Metaraminol (Aramine) Bitartrate *JAMA* 174 1635 (1960)
- 15 MEZZASALMA, G. Spunti Patogenetici Sulle Aritmie Sperimentali da Caffaina-adrenalina *Boll Soc Ital Biol Sper* 32 1637 (1956)

- 16 UEDA, I, LOEHNING, R W, & UHEYAMA, H Relationship between Sympathomimetic Amines and Methylxanthines Inducing Cardiac Arrhythmias *Anesthesiology* 22 926 (1961)
- 17 GOODMAN, L S & GILMAN, A The Pharmacological Basis of Therapeutics, pp 533, 508, 342 New York Macmillan Co (1955)
- 18 SEVERINGHAUS, J W & CULLEN, S C Depression of Myocardium and Body Oxygen Consumption with Fluothane *Anesthesiology* 19 165 (1958)
- 19 CUMMINGS, J R & HAYS, H W Cardiovascular Studies of Adrenergic and Ganglionic Stimulating Drugs Administered during Cyclopropane *Anesthesiology* 17 314 (1956)
- 20 NICKERSON, M & NOMAGUCHI, G. Mechanism of Dibenamine Protection against Cyclopropane-Epinephrine Cardiac Arrhythmias *J Pharmacol & Exper Therap* 95 1 (1949)
- 21 DRESEL, P E & SUTTER, M C Factors Modifying Cyclopropane-Epinephrine Cardiac Arrhythmias *Cir Res* 9 1284 (1961)
- 22 DRESEL, P E, HART, M C, & STROMBLAD, B C R Cardiac Arrhythmias Induced by Injection of Isoproterenol into the Coronary Arteries *J Pharmacol Exper Therap* 140 67 (1963)
- 23 HARRIS, A S & MATLOCK, W P Effects of Anoxia on Excitatory Conduction and Refractoriness of Mammalian Cardiac Muscle *Am J Physiol* 150 493 (1947)
- 24 HOFFMAN, B E, SIEBENS, A A, CRANFIELD, P E, & BROOKS, C M Effect of Epinephrine and Norepinephrine on Ventricular Vulnerability *Circ Res* 3 140 (1955)
- 25 MOE, G K, MALTON, S D, RENNICK, B R, & FREYBURGER, W. A Role of Arterial Pressure in Induction of Idioventricular Rhythms under Cyclopropane Anesthesia *J Pharmacol & Exper Therap* 93 319 (1948)