Mephentermine and Cyclopropane-Epinephrine Arrhythmias in Dogs

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INVESTIGATIONS on the cardiac action of mephentermine have shown that it can prevent or terminate the epinephrine "arrhythmia" which is actually partial block in either the dynamic or hypodynamic frog-heart preparation.[1] Both mephentermine and ephedrine apparently can protect dogs anesthetized with cyclopropane against epinephrine-induced ventricular fibrillation.[2] Mephentermine also appears to protect hypothermic dogs against spontaneous fibrillation[3] but not against fibrillation induced by manipulating the heart.[4] The report dealing with cyclopropane-epinephrine arrhythmias[2] has been interpreted as indicating that mephentermine gives absolute protection against these arrhythmias.[3] Actually, this was implied in an earlier abstract,[5] but in the complete publication only protection against epinephrine-induced ventricular fibrillation was claimed; hypertension, tachycardia, and multifocal extrasystoles produced by epinephrine during cyclopropane anesthesia were not prevented.

Since it is difficult to determine from the literature whether or not mephentermine protects against cyclopropane-epinephrine arrhythmias other than ventricular fibrillation and since promotional literature[6] maintains that mephentermine may be used to reduce the likelihood of ventricular arrhythmias owing to anesthetics such as cyclopropane or halothane, the present experiments were undertaken to clarify this point.

Methods

Unpremedicated, mongrel dogs were anesthetized with 50 per cent cyclopropane and oxygen using a canine mask, closed system, and the to-and-fro method of CO_2 absorption. After induction, tracheal intubation was performed with a cuffed tube, the cuff inflated, and anesthesia maintained by respiratory signs as close to plane 2 as possible by adjusting the concentration of cyclopropane in the system. The exact concentration needed varied from animal to animal and was usually between 25–40 per cent. Needle electrodes were used to pick up the standard limb ECG leads of which lead 2 was the usual one recorded. Arterial pressure was measured directly by means of a polyethylene catheter in a femoral artery attached to a model P23AA Statham strain gage. To aid determination of depth of anesthesia, respiration was monitored with a Fleisch pneumotachograph attached to a model PM5d Statham differential strain gage. All recording was done on a Grass model 5 polygraph. Injections were given into a foreleg vein via implanted needle or polyethylene catheter kept open by a slow drip of 0.9 per cent NaCl. After each preparation had stabilized, one or more control injections of epinephrine, 10 μg./kg. in 5 ml. of 0.9 per cent NaCl, were given over 50-second periods. The resulting cardiac arrhythmias were recorded, and after recovery mephentermine, 3 mg./kg., was given intravenously to each of six dogs. One additional dog received 0.5 mg./kg. and another was given 2.9 mg./kg. in two divided doses. At varying intervals ranging from four to 42 minutes after mephentermine administration, the challenge dose of epinephrine was repeated one or more times and the resulting arrhythmias recorded for later study.

Six other dogs were anesthetized with sodium pentobarbital, 30 mg./kg. intraperitoneally, set up for recording blood pressure and ECG, and for comparative purposes were given either the 10-μg./kg. dose of epinephrine in 50 seconds or the 100-μg./kg. dose

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by rapid injection, as done by Lynch and associates.[2]

Results

The results from the animals anesthetized with cyclopropane are summarized in table 1. Seven of 8 dogs responded to the control dose of epinephrine with a typical cyclopropane-epinephrine arrhythmia consisting of multifocal ventricular premature beats or in one case a bigeminal rhythm. Elapsed time after induction made no difference, arrhythmias were produced just as consistently after prolonged anesthesia as during the first 30 minutes. The single dog that did not show a significant arrhythmia showed only an A-V nodal rhythm when challenged with 40 μg./kg. of epinephrine. Protection against the typical arrhythmia was afforded by inhalation of 10 per cent CO_2 by one dog and 20 per cent by another as shown by Allen and coworkers.[7] In both cases the arrhythmia was produced after the CO_2 was blown off.

The rapid injection of mephentermine did not result in the production of arrhythmias except in one dog in which ventricular premature beats were noted for two minutes. When each dog had stabilized at the higher blood pressure level produced by the mephentermine, the challenge dose of epinephrine was repeated one or more times. As shown in table 1, typical cyclopropane-epinephrine arrhythmias occurred in 7 of the 8 dogs which were similar in type to the control arrhythmias. The fact that five of the seven arrhythmias that occurred after mephentermine began

TABLE 1. Characteristics of Cardiac Arrhythmias Produced by Epinephrine in Dogs Anesthetized with Cyclopropane Before and After Administration of Mephentermine

Dog No.	Epinephrine* (μg./kg.)	Onset of Arrhythmias (seconds)	Duration of Arrhythmias (seconds)	Mephentermine (mg./kg.)	After Mephentermine before Epinephrine (minutes)	Epinephrine (μg./kg.)	Onset of Arrhythmias (seconds)	Duration of Arrhythmias (seconds)	Description of Arrhythmias
1	10	40	80						Ventricular premature beats
				3	15	10	30	120	Ventricular premature beats
					30	10	25	>105	Ventricular premature beats
2	10	20	65						Ventricular premature beats then A-V nodal rhythm
	10	30	90						Ventricular premature beats then A-V nodal rhythm
				3	15	10	15	140	Predominately ventricular premature beats
					30	10	30	80	Ventricular premature beats then A-V nodal rhythm
					42	10	15	110	Predominately A-V nodal beats
3	10	20	110						Bigeminal rhythm
				3	4	10	45	90	Bigeminal rhythm
4	10	50	5						Two ventricular premature beats
	40	90	150						A-V nodal rhythm
				3	20	10	40	70	Ventricular premature beats
					25	40			No arrhythmia
5	10	45	60						Ventricular premature beats
				3	8	10	15	120	Ventricular premature beats
					23	10	20	>100	Ventricular premature beats
6	10	15	120						Ventricular premature beats
				3	16	10	25	120	Ventricular premature beats
7	10	30	120						Ventricular premature beats
				0.5	8	10	20		Ventricular fibrillation
8	10	25	75						Ventricular premature beats
				2.9	5	15			No arrhythmia
					8	15			No arrhythmia

* Ephinephrine given in 50 seconds—controls.

sooner and lasted longer than controls supports the view that elevated blood pressure lowers the threshold for the development of arrhythmias.[8] The one dog that received the low dose of 0.5 mg. kg. of mephentermine developed ventricular fibrillation when challenged with epinephrine eight minutes after mephentermine administration. One dog was apparently protected by 2.9 mg. kg. of mephentermine, but since it had breathed 20 per cent CO_2 for 70 minutes before mephentermine administration, it was not strictly comparable to other animals in the series.

As a control, six dogs anesthetized with sodium pentobarbital were given the challenge dose of epinephrine (10 μg./kg. in 50 seconds). In three cases arrhythmias failed to appear. Two dogs developed sinus arrhythmia, and in one dog this was followed by a few ventricular premature beats. One dog developed A-V nodal beats ten seconds after completion of the injection which persisted for 40 seconds. Doses of 100 μg. kg. in 5 ml. given as rapidly as possible to five dogs produced multifocal premature beats in all cases and ventricular tachycardia in four cases. Ventricular fibrillation did not occur as reported by Lynch and associates[2] in dogs anesthetized with cyclopropane.

Discussion

When the arrhythmias produced by the challenge dose of epinephrine in dogs anesthetized with cyclopropane are compared with those seen in dogs anesthetized with sodium pentobarbital differences of incidence, type, and duration are apparent. Increased incidence, severity, and duration of arrhythmias in the presence of cyclopropane confirm the well-known ability of this agent to "sensitize the myocardium to epinephrine." Thus 10 μg./kg. of epinephrine, administered in 50 seconds, did not produce arrhythmias in three of six dogs anesthetized with pentobarbital, while seven of eight dogs anesthetized with cyclopropane developed disturbances of rhythm. When arrhythmias were seen in the pentobarbital-anesthetized group they were usually supraventricular in contrast to the predominantly ventricular arrhythmias produced during cyclopropane anesthesia. Ventricular arrhythmias occurring in the pentobarbital-treated group were brief in comparison to their duration in animals during cyclopropane anesthesia.

Mephentermine administration did not result in arrhythmias, except in one dog (3) that exhibited ventricular premature beats for about two minutes following drug administration. However, when the challenge dose of epinephrine was given at intervals from four to 42 minutes after mephentermine, the arrhythmias that occurred were indistinguishable from the controls, except that one fatal ventricular fibrillation occurred. In only one dog (8) was there evidence of protection by mephentermine, and this case was complicated by prolonged exposure to CO_2. Otherwise, the incidence, type, and duration of the arrhythmias were very similar to those produced by epinephrine before administration of mephentermine.

Thus, although mephentermine may have antifibrillatory actions as claimed by Lynch and co-workers,[2] it does not appear to protect dogs against cyclopropane-epinephrine arrhythmias which under ordinary circumstances may terminate in ventricular fibrillation. While it is not the purpose of this paper to review the complex and controversial subject of cyclopropane and cyclopropane-epinephrine-induced cardiac arrhythmias, it should be pointed out that it is unwise to extrapolate from dogs to human beings in this field. For example, an elevated P_{CO_2} protects against cyclopropane-epinephrine arrhythmias in dogs as shown by Allen and co-workers[7] in 1941 and confirmed in this study but apparently has no such protective effect in man.[9] Indeed, it regularly produces ventricular arrhythmias in human beings that can be reversed by lowering the inspired P_{CO_2}.[10] Until mephentermine is tested against cyclopropane-induced arrhythmias in man, it should not be regarded as "valuable in reducing the likelihood of ventricular arrhythmias due to such anesthetic agents as cyclopropane or halothane."[6]

Summary

Mephentermine was found incapable of reversing cyclopropane-epinephrine arrhythmias *per se* in dogs in contrast to its reported ability

to decrease the incidence of ventricular fibrillation in dogs anesthetized with cyclopropane and given epinephrine.

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