VENTRICULAR TACHYCARDIA PRODUCED BY METARAMINOL DURING CYCLOPROPANE ANESTHESIA IN DOGS

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THE production of ventricular tachycardia by the intravenous administration of a standard dose of epinephrine during cyclopropane anesthesia in dogs is a well documented phenomenon. The reproducibility of this arrhythmia is such that its occurrence may be used to compare the "sensitizing" effect of various anesthetic agents on the myocardium.[1] In addition, various pressor drugs have been compared in terms of their production of ventricular tachycardia under similar circumstances.

Metaraminol (Aramine*) is a popular vasopressor agent at the present time. Since we have been unable to find evidence in the literature indicating the safety of using metaraminol during cyclopropane anesthesia, we undertook the following study.

METHOD

Unpremedicated mongrel dogs weighing about ten kilograms were anesthetized with cyclopropane by the circle absorption technique. A femoral artery was cannulated for recording the level of the arterial blood pressure, and obtaining blood samples. An infusion was started in the femoral vein using 5 per cent dextrose in 0.2 per cent saline solution. A three way stopcock was inserted for convenience of injection of drugs. The electroencephalograph for determination of depth of anesthesia, an electrocardiograph for recording changes in cardiac rhythm and a pressure transducer for recording arterial blood pressure were connected to a Gilson polygraph.† These three functions were monitored throughout the experiments.

After stabilization of anesthesia in plane 2, stage III, epinephrine, 0.01 mg./kg. of body weight, was diluted to five milliliters with 0.85 per cent saline solution and injected intravenously at a rate of one milliliter per ten seconds.[1] Respiration was assisted or controlled by manual compression of the anesthesia rebreathing bag and arterial blood samples were taken at the time of injection. The *p*H of these samples was determined to be sure ventilation had been adequate.

After a rest period, when the blood pressure and cardiac rhythm had returned to preinjection levels, 0.1 mg./kg. of body weight of metaraminol was diluted to five milliliters and injected intravenously in the same manner as the epinephrine. The arterial blood *p*H was determined at the time of injection. On a subsequent day the animals were again anesthetized with cyclopropane, and, after preparation, 0.2 mg./kg. of metaraminol was diluted to five milliliters and injected similarly.

RESULTS

The control injection of 0.01 mg./kg. of epinephrine produced ventricular tachycardia in each animal. This lasted for 20–90 (average 58.6) seconds. A rest period was allowed until the cardiac rhythm and blood pressure level had returned to normal. Metaraminol 0.1 mg./kg. of body weight was then diluted to five milliliters and injected intravenously over a fifty-second period as had been the epinephrine. Ten dogs received this dose. Multifocal ventricular tachycardia occurred in six animals, a sinus tachycardia in three and multifocal ventricular premature contractions in one (table 1).

When metaraminol, 0.2 mg./kg. of body weight was administered, multifocal ventricular tachycardia appeared in eight of the ten dogs, one had a sinus tachycardia with premature ventricular contractions, and one a bigeminal rhythm (table 2). The *p*H of the arterial blood samples taken at the time of injection of the test drug ranged from 7.38 to 7.68, averaging 7.498.

In addition to the above study, we have done several experiments in which we have simulated clinical conditions. We have anesthetized a dog with cyclopropane to plane 2, stage III and started an intravenous infusion

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TABLE 1

CARDIAC RHYTHM WHEN 0.1 MG./KG./BODY WEIGHT OF METARAMINOL IS ADMINISTERED INTRAVENOUSLY TO DOGS DURING CYCLOPROPANE ANESTHESIA

Dog No.	Cardiac Rhythm	Duration of Ventricular Tachycardia, Seconds		pH at Time Injection of Metaraminol
		Epinephrine	Metaraminol	
1	Sinus tachycardia with premature ventricular contractions; one "burst" of multifocal ventricular tachycardia	60	5	7.30
3A	Multifocal ventricular tachycardia	70	75	7.55
4A	Sinus tachycardia	75	0	7.57
5	Multifocal ventricular tachycardia	90	504	7.45
6	Sinus tachycardia	85	0	7.38
7	Multifocal ventricular tachycardia	65	240	7.45
8	Sinus tachycardia	55	0	7.54
10	Multifocal ventricular tachycardia	20	108	7.49
12	Bigeminal rhythm; "bursts" of multifocal ventricular tachycardia	72	252	7.38
15	Multifocal ventricular premature contractions	42	0	7.68
	Average	63.4	118.4	7.49

of metaraminol, 10 mg. in 250 ml. of normal saline solution. The drip was sufficiently rapid to elevate the blood pressure from 150/130 to 200/150. Multifocal ventricular tachycardia occurred in forty seconds and continued for sixty seconds. This was followed by a ventricular tachycardia (single focus) with a rate of 300 per minute, and intermittent bursts of multifocal ventricular tachycardia for seven minutes even though the metaraminol infusion had been discontinued when the ventricular tachycardia began. The animal had received about 0.125 mg./kg. at that time. The ventricular rhythm changed to a bigeminal rhythm. Sinus rhythm at a rate comparable to that before the administration of metaraminol did not return for fifty minutes. Another animal was sedated with sufficient thiobarbiturate for endotracheal intubation and performance of a cutdown, and then allowed to regain cough and eyelid reflexes (66 minutes). During this period of thiobarbiturate sedation, a test run of metaraminol infusion was given and in sixty seconds a bigeminal rhythm occurred. The infusion was stopped immediately and the bigeminal rhythm lasted three minutes with essentially no elevation in blood pressure

TABLE 2

CARDIAC RHYTHM WHEN 0.2 MG./KG./BODY WEIGHT OF METARAMINOL IS ADMINISTERED INTRAVENOUSLY TO DOGS DURING CYCLOPROPANE ANESTHESIA

Dog No.	Cardiac Rhythm	Duration of Ventricular Tachycardia, Seconds		pH at Time of Injection of Metaraminol
		Epinephrine	Metaraminol	
1	Multifocal ventricular tachycardia	60	120	7.61
2	Multifocal ventricular tachycardia	60	75	7.52
3A	Multifocal ventricular tachycardia	70	660	7.62
6	Multifocal ventricular tachycardia	85	420	7.45
9	Sinus rhythm; occasional premature ventricular contractions	84	0	7.38
10	Multifocal ventricular tachycardia	20	600	7.38
11	Multifocal ventricular tachycardia	60	516	7.46
14	Multifocal ventricular tachycardia	20	225	7.59
16	Bigeminal rhythm	40	0	7.67
17	Multifocal ventricular tachycardia	48	12	7.38
	Average	53.9	263.8	7.506

during the test. When the dog had recovered cough and eyelid reflexes, metaraminol infusion was restarted. Cyclopropane was given as soon as the pressor effect had become established (2 minutes of infusion). Ninety seconds after the cyclopropane was started, a bigeminal rhythm was evident and after five and a half minutes of infusion and three minutes and 30 seconds of cyclopropane anesthesia, multifocal ventricular tachycardia occurred. Both the cyclopropane and the metaraminol infusion were discontinued with the appearance of ventricular tachycardia. This bout of tachycardia lasted 120 seconds, and four hundred seconds of sinus tachycardia followed. Cyclopropane was again administered and when the rate, rhythm and blood pressure levels had returned to normal, metaraminol 0.02 mg./kg. was given intravenously. No elevation in blood pressure occurred, but within thirty seconds ventricular tachycardia recurred, lasting 156 seconds.

Discussion

Early investigators of the effect of sympathomimetic amines on cardiac automaticity during cyclopropane anesthesia found that drugs having a catechol amine nucleus were the *most* effective in producing ventricular tachycardia.[2, 3] Pressor amines without the catechol nucleus may produce ventricular tachycardia if large enough doses are used.[2] In order to obtain comparable effects, the sympathomimetic drugs have been tested in doses equal in vasopressor action to epinephrine 0.01 mg./kg. of body weight. We have adhered to such doses in our experiments with metaraminol.

The reproducibility of ventricular tachycardia when epinephrine is administered intravenously to dogs anesthetized with cyclopropane makes this an excellent control. Ventricular tachycardia occurred in all of our dogs following injection of epinephrine, except one, which had ventricular fibrillation and was not available for further experiments. As can be seen from table 1, the six dogs exhibiting ventricular tachycardia after administration of 0.1 mg./kg. of metaraminol had tachycardias which, in all but two animals, persisted for longer periods of time than that produced by epinephrine. The average duration of tachycardia after epinephrine was 58.6 seconds, ranging from 20–90 seconds. After 0.1 mg./kg. of metaraminol, tachycardias occurred which persisted for 5–504 seconds, averaging 118.4 seconds. When 0.2 mg./kg. of metaraminol was administered (table 2), the average duration of tachycardia was 263.8 seconds. There were two animals in which tachycardia lasted for 10 minutes or more. Another dog had ventricular tachycardia lasting over 900 seconds; however, this animal was not included in the study because the *p*H of his arterial blood at the time of injection was too low, presumably due to inadequate ventilation.

Studies by Price and his co-workers[4, 5, 6] indicate that cyclopropane anesthesia causes an elevation of the blood levels of epinephrine, and particularly norepinephrine, in man. They postulate that the excess catechol amines are produced by sympathetic nerve endings in the myocardium rather than from the adrenal medulla, since bilateral stellate ganglion block decreases or eliminates ventricular arrhythmias during cyclopropane anesthesia. Hypercarbia also elevates the catechol amine level, and they suggest that cyclopropane may reduce "the P_{CO_2} level at which arrhythmias occur." We, therefore, eliminated all experiments in our series in which the *p*H of the arterial blood was below 7.38.

The pressor effect seemed unrelated to the occurrence of ventricular tachycardia. This has been a moot question in the past.[7, 8, 9, 10] In our series of experiments, ventricular tachycardia occurred several times after the administration of 0.1 mg./kg. of metaraminol *before* the blood pressure had shown any change. Nickerson[10] found that isoproterenol produced ventricular tachycardia during cyclopropane anesthesia when the drug caused a fall in the blood pressure level. Also, Cummings[11] found isoproterenol to cause ventricular tachycardia or ventricular fibrillation as the blood pressure level fell. We have confirmed this in our laboratory.

Although none of the dogs to which metaraminol was administered had ventricular fibrillation, there is no reason to expect that it should not occur at any time in the presence of such severe ventricular arrhythmias. Past experience has shown that ventricular fibrillation occurs in 2–3 per cent of animals receiving epinephrine during cyclopropane anesthesia.

O'Brien, Murphy and Meek [12] have shown that ventricular tachycardia following epinephrine injection during cyclopropane anesthesia is accompanied by a sharp elevation in arterial plasma potassium. The administration of dihydroergotamine or dibenzyline not only prevents the tachycardia, but also reduces the rise in potassium. O'Brien, Eid, Murphy and Meek [13] later demonstrated that elimination of the liver from the circulation prevents the potassium rise and the tachycardia produced by epinephrine during cyclopropane anesthesia, as well. O'Brien [12] also pointed out that ventricular tachycardia produced during cyclopropane anesthesia is not always accompanied by a marked increase in arterial potassium since methyl-amino-methylheptanol (Aranthol), an aliphatic sympathomimetic amine is capable of producing this arrhythmia with only a slight potassium rise. Metaraminol appears to behave in a similar manner. Preliminary work in progress in our laboratory indicates that there is only a slight change in arterial blood potassium when ventricular tachycardia occurs after injection of metaraminol.

Summary

The effect on cardiac rhythm of the intravenous administration of metaraminol during cyclopropane anesthesia in dogs has been investigated. Injection of a standard dose of epinephrine, sufficient to produce ventricular tachycardia, was used as a control. Metaraminol in a dose of 0.1 mg./kg. of body weight produced multifocal ventricular tachycardia in six of the ten dogs anesthetized with cyclopropane. When the dose was increased to 0.2 mg./kg. of body weight, a dose closely approximating an equal vasopressor dose of epinephrine, eight of the ten dogs developed this arrhythmia. The controlled study and the experiments simulating clinical conditions would indicate that the use of metaraminol is contraindicated during cyclopropane anesthesia. Further, cyclopropane should not be administered to a patient receiving, or recently having received metaraminol.

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