THE FAILURE OF VARIOUS BARBITURATES TO PREVENT CYCLOPROPANE-EPINEPHRINE VENTRICULAR TACHYCARDIA IN THE DOG *

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That members of the barbituric acid series might protect against cardiac arrhythmias occurring during cyclopropane anesthesia has been suggested by several investigators (1, 2). In a previous report from this laboratory on a small series of animals it was shown that protection is not afforded by amytal, nembutal or barbital for the cardiac stimulation induced during cyclopropane anesthesia by the intravenous injection of a standard dose of epinephrine (3). In view of the favorable reports of others a further investigation of the problem seemed justified.

Methods

The methods employed were those previously reported in studies of cyclopropane-epinephrine irregularities (4). Briefly they consisted of anesthetic induction of the dog and connection by means of an endotracheal tube with an inflatable cuff and soda-lime carbon dioxide absorber to a known cyclopropane-oxygen mixture sufficient to produce anesthesia to a depth of at least partial intercostal paralysis. After time for approximate equilibrium with the cyclopropane a standard test dose of 0.01 mg. of epinephrine per kilogram, made up to a volume of 5 cc. with normal saline, was injected into the radial vein at a regular rate of 1 cc. per ten seconds. By means of electrocardiograms taken at intervals before, during, and after the injection, with constant observation of the electrocardiographic beam, and timing by stop watch, the duration of ventricular tachycardia and other alterations of cardiac automaticity were determined. Lead II was used in all recordings.

After such control experiments with cyclopropane, similar tests were made on subsequent days after the intravenous administration of pentothal (sodium ethyl (1-methylbutyl) thiobarbiturate), seconal (sodium allyl (1-methylbutyl) barbiturate), nembutal (sodium ethyl (1-methylbutyl) barbiturate), amytal sodium (sodium isoamylethyl-barbiturate), barbital sodium (sodium diethyl barbiturate), or delvinal sodium (sodium ethyl (1-methylbutenyl) barbiturate). When the particular bar-

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biturate being studied had produced its maximal depressing effect the standard epinephrine test dose, with accompanying electrocardiographic recordings, was repeated. The animal was then placed upon a cyclopropane-oxygen mixture sufficient to cause approximately the same degree of surgical anesthesia previously attained with the control cyclopropane test, and the injection of epinephrine repeated after approximate equilibration of cyclopropane had occurred. Absence of or a decrease in the duration of ventricular tachycardia after the administration of a barbiturate was accepted as evidence of protective action. Anoxemia was never permitted, the anesthetic mixture always containing at least 65 per cent oxygen; and blood gas analyses by the technic of Orcutt and Waters (5) were made frequently to confirm adequate oxygenation.

RESULTS

In table 1 the electrocardiographic results are summarized for 160 experiments. It will be noted that in general the amount of any particular barbiturate administered was approximately two-thirds to three-

TABLE 1

CARDIAC RESPONSES TO STANDARD INJECTION OF 0.01 MG. EPINEPHRINE/KG.

Procedure	Barbiturate Dosage mg./Kg.	Number of Animals	A-V Block	A-V Extrasystoles	A-V Rhythm	Ventricular Ex. S.	Slow Ven. Rhythm	Ventricular Tachy.	Ven. Fibrillation	Average Duration of Vent. Tachycardia Sec.	Animals Protected from Ven. Tachy.
Pentothal only	15–34	4	1	2	0	4	2	0	0	0	
Cyclopropane only	none	5	2	1	1	4	0	5	0	40	
Pentothal + cyclopropane	4–11	5	0	3	1	4	0	5	1	61	0
Seconal only	18–27	5	5	5	5	5	1	0	0	0	
Cyclopropane only	none	5	2	2	3	5	2	4	0	27	
Seconal + cyclopropane	18–27	5	2	3	3	4	0	5	0	67	0
Nembutal only	20–30	10	8	4	4	4	2	1	0	25	
Cyclopropane only	none	11	0	4	6	7	0	11	0	45	
Nembutal + cyclopropane	20–30	11	0	4	1	7	0	11	1	55	0
Amytal only	45–50	10	1	3	4	4	3	0	0	0	
Cyclopropane only	none	10	1	3	6	8	1	10	0	45	
Amytal + cyclopropane	45–50	10	0	1	4	8	0	8	1	48	3
Barbital only	200–225	10	4	4	6	4	3	2	0	16	
Cyclopropane only	none	10	3	3	5	7	1	10	0	47	
Barbital + cyclopropane	200–225	10	1	3	0	8	1	8	2	44	2
Delvinal only	20–30	7	5	4	3	2	1	0	0	0	
Cyclopropane only	none	7	4	5	3	6	1	7	0	33	
Delvinal + cyclopropane	20–30	7	1	2	4	6	1	7	0	24	2

fourths of the usual anesthetic dose for the dog. The only significant exception in this respect was with pentothal, the usual anesthetic dosage being 25–30 mg./Kg. Several animals were tested with a higher dosage of this barbiturate in view of the favorable impression held for it by Guedel (1).

For pentothal it will be noted from table 1 that there was no significant difference in the number of instances of A-V block, A-V extrasystoles, A-V rhythm, or ventricular extrasystoles, whether pentothal only, cyclopropane only, or the two agents combined were present at the time the epinephrine stimulus to the cardiac automatic tissues was supplied. None of the animals showed ventricular tachycardia under pentothal alone; but all five animals tested under cyclopropane or cyclopropane and pentothal showed ventricular tachycardia, and one animal in the latter group was lost due to ventricular fibrillation. It can also be seen that the duration of ventricular tachycardia in the control test with cyclopropane alone averaged but forty seconds, but when pentothal was also present the group average was sixty-one seconds. The duration of ventricular tachycardia for each animal is shown in table 2. It can be seen that every animal tested with pentothal had an equivalent or more pronounced run of ventricular tachycardia under the influence of pentothal and cyclopropane than in the cyclopropane control test. In no instance was there any evidence of a protective action of pentothal.

Tests under the influence of seconal revealed disturbances of automaticity chiefly referable to the auriculo-ventricular node, since each of the 5 animals in the group gave A-V block, A-V extrasystoles and A-V rhythm. They also showed ventricular extrasystoles, and one had a slow ventricular rhythm. While 4 of the animals showed ventricular tachycardia under cyclopropane anesthesia alone, all 5 had this disturbance when under the effects of cyclopropane combined with seconal. In the latter group the average duration of tachycardia was sixty-seven seconds against the control of but twenty-seven seconds. While but one of the animals tested in the group was among those tested with pentothal, the results are equally conclusive in the failure of protection by seconal.

The results of tests with nembutal also are given in tables 1 and 2. It is evident that nembutal alone in the dose used interferes less with normal cardiac automaticity, as is evidenced by fewer irregularities resulting from the epinephrine stimulation in its presence. Yet nembutal and cyclopropane, when tested with epinephrine, show the same disturbances of automaticity as cyclopropane alone, with the exception of a reduction from six to one in the number of cases of A-V nodal rhythm. One animal fibrillated in the presence of the barbiturate and cyclopropane, but this one example may not be of great significance. The duration of ventricular tachycardia, with the exception of a reduction from forty-eight to forty seconds in dog 24, and fifty to forty

TABLE 2

DURATION OF VENTRICULAR TACHYCARDIA PRODUCED BY THE INTRAVENOUS INJECTION OF THE STANDARD DOSE OF EPINEPHRINE IN CYCLOPROPANE ANESTHESIA ALONE AND COMBINED WITH VARIOUS BARBITURATES

Dog No.	Cyclopropane Alone	Cyclopropane +Pentothal	Cyclopropane +Seconal	Cyclopropane +Delvinal	Dog No.	Cyclopropane Alone	Cyclopropane +Nembutal	Cyclopropane +Amytal	Cyclopropane +Barbital
	Seconds	Seconds	Seconds	Seconds		Seconds	Seconds	Seconds	Seconds
1	30	Ven. Fib.			10	18	45		
2	53	61			11	20	49		
3	30	28			13	48	70		
		100			14	55	70		
4	31	66			15	13		10	0*
5	57	53	53	27	16	49	48	44	
6	35			53	17	44	82	8	0
								18*	0*
7	50			40	18	46	60	105	40
								45	
8	20			15					
	22			0*	19	34	50	0	
								0*	
9	35			10					
	32			0*	20	76		68	Ven. Fib.
10	18		46	19	21	36			45
11	20		97	0	22	70			40
				35					
12	0		77		23	15		Ven. Fib.	
15	13		60		24	48	40		
					25	50	40	0*	
Av'g. duration of V.T. with the barbiturate		61	67	24	26	80	Ven. Fib.		
					27	30		55	30
					28	50			Ven. Fib.
Control duration of V.T. for this group		40	27†	33†	29	10			50
					30	90		75	60
					Av'g. duration of V.T. with the barbiturate		55	48	44
					Control duration of V.T. for this group		45	45	47

* = Protection in the presence of the barbiturate.

† = The groups of animals tested with Delvinal and Seconal were under light (10–25%) cyclopropane.

Ven. Fib. = Ventricular fibrillation.

seconds in dog 25, was greater in all other cases. For the group of 11 animals the control average was forty-five seconds against an average of fifty-five seconds when nembutal was also present. Again there was no evidence of any protective action by this barbiturate, at least during the time it produced its most marked depression.

Not until amytal was tested were any protective results obtained. It is evident from the tabulated data that but 8 of the 10 animals showed tachycardia in the presence of cyclopropane and amytal, al-

though all 10 had this irregularity in the control tests. Furthermore, from table 2 it can be seen that dog 17 was definitely protected with respect to the duration of tachycardia, since in one experiment it had a run of but eight seconds and on another day but eighteen seconds, compared to its control test of forty-four seconds. Several of the animals had tests repeated with the same barbiturate as a check on the methods and results. The average duration of ventricular tachycardia for the control cyclopropane tests was forty-five seconds and for the amytal and cyclopropane forty-eight seconds for the 8 animals in which tachycardia occurred. Although these particular averages have no significance it is felt from the individual records that there was definite protection in 3 of the 10 animals tested.

Barbital sodium similarly afforded protection from the cyclopropane-epinephrine ventricular tachycardia in 2 of the 10 animals tested. One of these was dog 17, discussed in the preceding paragraph. Tests on two occasions showed no tachycardia. The group averages for the tachycardia are virtually the same, namely, forty-four versus forty-seven seconds for the control compared to the test when barbital was also present.

None of the 7 animals in the delvinal group showed ventricular tachycardia when tested with the barbiturate alone, while all 7 showed runs of it on the cyclopropane control and on at least one occasion with the combination of agents. For dogs 8 and 9 there was reduction in duration of the tachycardia in one of the combined tests, and absence of it on another trial. Thus these two cases could be considered as possible protection, or at least diminution in severity of the epinephrine stimulation. While dog 11 failed to show any tachycardia on one test, at another time it had an even longer run of this irregularity than on its control and hence it was not considered to be protected.

Discussion

The work of Robbins et al (2) evidently proves that the appearance of cardiac irregularities induced by anoxemia during cyclopropane anesthesia can be definitely delayed by the presence of a barbiturate. That protection by the barbiturates does not occur when sympathetic stimulation is the cause of the cardiac irregularities is evident from the results of the present study.

That depth of anesthesia and duration of ventricular tachycardia are directly related was shown by Meek, Hathaway and Orth in their original study (4). They found that in light cyclopropane anesthesia the average duration of tachycardia was but nineteen seconds; while in deep anesthesia their group of 17 animals had an average tachycardia of forty-four and five-tenths seconds. In this study the control

tests in all groups except those later tested with delvinal and seconal were run on 30 to 33 per cent cyclopropane in order to produce anesthesia to the depth of partial intercostal paralysis. Such an amount of the anesthetic gas could not be presented to the animal when it was partially depressed by the barbiturate; hence the combined barbiturate and cyclopropane tests were made in the presence of but 20 to 25 per cent cyclopropane. Thus any tendency of a barbiturate to afford protection should be even more favored by the lowered cyclopropane administered to the animal. The average durations of tachycardia of the four groups in deep anesthesia in the control tests were forty, forty-five, forty-five, and forty-seven seconds, even though 21 different animals were used in various groupings in the tests. Seconal and delvinal were the last drugs used and with them both control tests and cyclopropane and barbiturate were run at 20 to 25 per cent of the gas.

Members of the barbiturate series from the ultra-short to the very long acting were tested. Rather than affording protection to the epinephrine induced cardiac irregularities in cyclopropane anesthesia, several of the barbiturates had a pronounced tendency to potentiate such irregularities. This is evident in the individual responses as well as in the group averages for pentothal, seconal, and nembutal. A similar chemical group in each of these three drugs may be a factor. While barbital completely prevented tachycardia in 2 of 10 animals, amytal afforded protection in 3 of 10; delvinal reduced or eliminated it in two of seven. The fact remains that in no instance with any of the six barbiturates tested was protection general or predictable. For the entire study there was more likely to be increased duration of tachycardia in the presence of a barbiturate and cyclopropane than with cyclopropane alone.

SUMMARY

1. Pentothal, seconal, nembutal, amytal sodium, barbital sodium and delvinal sodium administered intravenously in sub-anesthetic doses have been tested for their ability to reduce or eliminate cyclopropane-epinephrine ventricular tachycardia.

2. Two of 10 animals with barbital, 2 of 7 with delvinal, and 3 of 10 with amytal showed reduction or prevention of such tachycardia.

3. In no instance with any of the six barbiturates tested was protection generally secured or predictable. The tendency was for the tachycardia to be of greater duration in the presence of a barbiturate and cyclopropane than in the controls.

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For the information of anesthesiologists who are contemplating application for certification by the American Board of Anesthesiology, Inc., or who are training physicians for the specialty, the following questions have been employed for Part I (written) examination in the past in *Anatomy:*

1. Draw a cross section near the elbow, showing and labeling the nerves that innervate the hand and the landmarks helpful in locating these nerves.
2. Describe the larynx. (Illustrate with drawings if you wish.)
3. What spinal nerve roots form the brachial plexus? What landmarks would be used and where would needles be placed for blocking the plexus with a local anesthetic?
4. Draw and label a typical spinal nerve, showing roots, ganglion, branches and connections to the sympathetic or autonomic ganglia ted cord.
5. Locate the most accessible veins in the upper and lower extremities available for intravenous therapy. (Illustrate with drawings if you wish.)
6. What is Horner's Syndrome, and how is it produced?
7. Following a successful caudal and transsacral block, what structures are anesthetized?
8. What nerves supply the anterior abdominal wall? Draw a diagram showing their respective distribution.
9. What landmarks are used, and where are needles placed in relation to them, in performing cervical plexus block by the lateral route?
10. From what nerve roots do the ileoinguinal and genitofemoral nerves arise, and what is their sensory distribution?
11. State the spinal root segments involved in the sensory cutaneous innervation at: *a.* the nipple; *b.* the ensiform cartilage; *c.* the umbilicus; *d.* the pubis.
12. Describe the epidural ("peridural") space. What is its significance in regional anesthesia?