THE BRONCHOMOTOR EFFECTS OF CERTAIN INTRAVENOUS BARBITURATES ON VAGAL STIMULATION IN DOGS

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THERE are statements in the literature that the bronchomotor effects of various ultrashort acting intravenous barbiturates are not alike; that is, that thiopental constricts bronchial musculature while hexobarbital (Evipal sodium) does not, that both of these compounds constrict bronchial musculature, and that hexobarbital prevents the bronchoconstrictor action of vagal stimulation (1, 2, 3). Some of these investigations were done on isolated muscle strips, some on guinea pigs, and the rest on intact cats. Inferences were made that this variety of action might be due to the *n*-methylation of one compound or the thio radical of the other.

Because of these conflicting results obtained when isolated muscle strips, guinea pigs, or cats were used, we believed it worthwhile to repeat some of this work with thiopental and hexobarbital using dogs.

METHOD

Mongrel dogs, weighing from 8.6 kg. to 30 kg., were given 0.5 mg./kg. of morphine, subcutaneously, one hour before being anesthetized with intravenous chloralose, 70 mg./kg. The dogs were then intubated with a large-bore endotracheal tube and cuff, and the tube attached to a Starling pump. (In the first 3 experiments the trachea was exposed, divided, and cannulated.) A side arm of the endotracheal tube led to an 80-cc. float recorder. With the pump maintained at a fixed volume, the recorder showed any excess of gas not entering the lungs. The pump and recorder were then manipulated until a pattern was recorded on the kymograph paper consisting of vertical lines of about 2 cm. Bronchiolar constriction was recorded as an increase in length of the vertical lines, and bronchiolar dilatation, a decrease. This method is known as the Konzett-Rössler method for recording bronchiolar constriction (4). The 2-cm. vertical line pattern represented the resting bronchomotor tone without drugs or stimulation other than the original anesthesia.

The carotid artery was then exposed, and the resting blood pressure recorded. The cervical vagus nerve was exposed and divided. In each experiment, the distal end of the cervical vagus nerve was electrically stimulated, starting from zero with increasing current until the minimal strength of current was determined that would elicit a measurable bronchiolar constrictor effect (fig. 1).

The dogs were then injected slowly with either a 2.5 per cent intravenous solution of thiopental or a 5 per cent solution of hexobarbital.

Received from the Albert Einstein Medical Center, Philadelphia 41, Pennsylvania, and accepted for publication July 1, 1957.

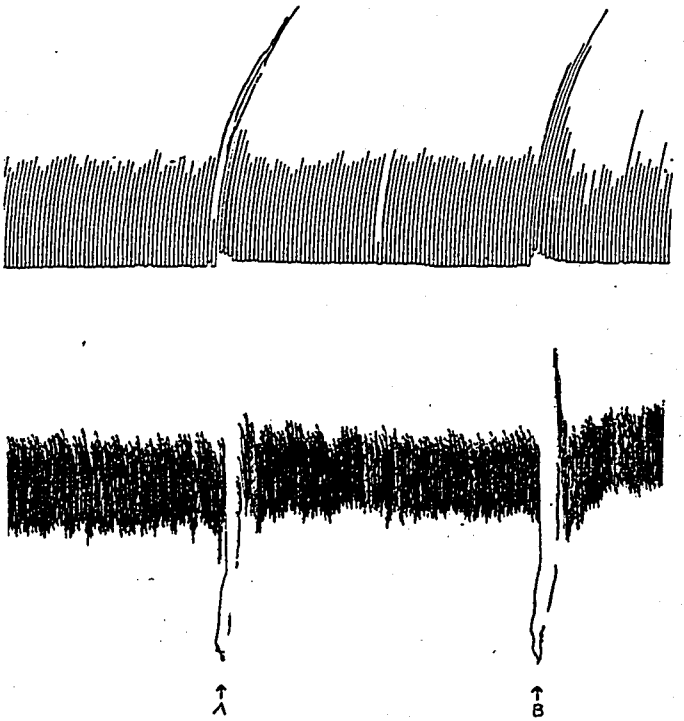

FIG. 1. Recordings indicating effect of electrical stimulation (at A and B) of distal cervical vagus nerve, showing fall in blood pressure and increase in bronchomotor tone (bronchiolar constriction). Upper tracing shows air escape through float recorder (bronchomotor tone); lower tracing shows blood pressure.

The doses ranged from 8 to 55 mg./kg. in the case of hexobarbital and from 5 to 55 mg./kg. of thiopental. The barbiturates caused an immediate but temporary effect on bronchomotor tone and resting blood pressure. After these effects were recorded and the blood pressure and bronchomotor tone had returned to their resting levels, the minimal electrical stimulus was applied and its effects noted. This stimulation was repeated at intervals of five minutes until no effects from the barbiturates were recorded. Both barbiturates were tried on individual dogs, but only after adequate waiting periods until the effects of the first barbiturate had worn off and the same basal conditions were again achieved.

Results

The results are presented in tables 1 and 2. The intravenous injection of both thiopental and hexobarbital consistently caused an immediate, but temporary, reduction in carotid blood pressure, ranging from —10 to —100 mm. of mercury. The accompanying initial changes in resting bronchomotor tone (without vagal stimulation) were variable —either no effect or temporary bronchoconstriction or bronchodilatation (tables 1 and 2).

Both thiopental and hexobarbital were capable of blocking the bronchoconstriction (and bradycardia) elicited by electrical stimulation of the distal end of the vagus. The blockade was seen with doses ranging

TABLE 1

Effects of Sodium Hexobarbital (Evipal Sodium) on Blood Pressure and Bronchomotor Tone in Dogs

	Experiment Number	Weight (kg.)	Dose (mg./kg.)	Immediate Effects		Influence on Vagal Bronchoconstriction (produced by electrical stimulation)
				Carotid Blood Pressure (mm. of Hg)	Bronchomotor Musculature	
Small dose 8 to 20 mg./kg.	12	30.0	8	0	No effect	Blocked for 20 minutes
	10	23.0	12	0	No effect	Blocked for 15 minutes
	14	14.1	14	−10	No effect	None
			14	−10	No effect	None
	11	27.5	18	−10	No effect	Blocked for 15 minutes
			18	−10	No effect	Blocked for 20 minutes
	9	20.0	20	0	No effect	None
			20	0	No effect	None
			20	0	No effect	None
Medium dose 25 to 35 mg./kg.	5	11.0	27	−80	Dilatation	Blocked for 20 minutes
			27	−80	Construction	Blocked for 20 minutes
	4	16.8	30	−40	No effect	—
	3	10.0	30	−10	No effect	Blocked for 10 minutes
			30	−10	No effect	—
	2	9.1	33	−30	Dilatation	None
			33	−40	Dilatation	None
	1	14.5	34	−60	No effect	None
Large dose 40 to 55 mg./kg.	15	13.2	40	−60	Dilatation	None
	17	11.8	42	−100	Constriction	—
			42	−100	Constriction	None
	19	9.1	44	−60	Dilatation	Blocked for 10 minutes
			44	−90	Constriction	—
	20	8.6	47	−100	Constriction	Blocked for 15 minutes
	6	9.1	55	−100	Constriction	—

TABLE 2

EFFECTS OF SODIUM THIOPENTAL (PENTOTHAL SODIUM) ON BLOOD PRESSURE AND BRONCHOMOTOR TONE IN DOGS

	Experiment Number	Weight (kg.)	Dose (mg./kg.)	Immediate Effects		Influence on Vagal Bronchoconstriction (produced by electrical stimulation)
				Carotid Blood Pressure (mm. of Hg)	Bronchomotor Musculature	
Small dose 5 to 20 mg./kg.	10	23.0	5	−30	No effect	—
	12	30.0	8	−30	Constriction	Blocked for 10 minutes
	15	13.2	10	−60	Constriction	None
			10	−60	No effect	None
	19	9.1	11	−40	Constriction	—
	9	20.0	20	−10	No effect	None
Large dose 25 to 55 mg./kg.	5	11.0	27	−80	Dilatation	Blocked for 10 minutes
			27	−40	Constriction	Blocked for 20 minutes
	3	10.0	30	−10	No effect	Blocked for 10 minutes
	4	16.8	30	−40	No effect	—
	2	15.0	33	−30	Dilatation	None
				−40	Dilatation	None
	1	14.5	34	−60	No effect	None
	16	11.8	42	−70	No effect	Blocked for 10 minutes
	6	9.1	55	−100	Constriction	—

from 8 to 50 mg./kg. of both thiopental and hexobarbital and lasted from five to twenty minutes. The most conspicuous feature of the blockade was that it was observed in only about half of the 20 dogs. The appearance of the blockade was not related to the size of the dose of barbiturate. The susceptibility of the dogs varied from animal to animal, but when a dog was susceptible to blockade from one barbiturate, it was also susceptible to blockade from the other drug. The second barbiturate was only given to the animal when all blocking effects of the first barbiturate had worn off. This was evidenced by a fall in mean blood pressure and an increase in resting bronchomotor tone on peripheral vagal stimulation. The time for this to occur varied in the animals (table 1 and 2). Although the drug was still present in the blood, apparently the concentration was not sufficient to affect the bronchiolar musculature when distal vagal stimulation was applied.

DISCUSSION

The immediate and initial effects of the injected barbiturates on resting bronchomotor tone may be due to one or more of several factors. The bronchodilatations may be due to a vagolytic action of the drug

which is apparent in a dog with pre-existing increased vagal tone. This would be true only for the animals that showed susceptibility to the barbiturates blocking the effects of vagal stimulation, but not for the animals that are not susceptible. The bronchodilatation may also be the result of increased sympathetic tone brought about by the initial fall in carotid blood pressure. A reflex increase in sympathetic tone is reflected not only in the bronchi but also in the cardiovascular system, which is partly responsible for the recovery of the blood pressure. Naturally, this factor was not present when the effects of vagal stimulation of the bronchi were noted as the pressure was again normal.

If bronchoconstriction occurred, it may be due to local action of the barbiturates on bronchial smooth muscle, similar to the results obtained by Adriani and Rovenstine (2) in excised lung tissue. When no initial effects on resting bronchomotor tone are apparent, then none of the previously mentioned actions occurred, or they all occurred simultaneously to a degree that the different effects tended to cancel each other. The fall in the mean blood pressure from the ultrashort acting barbiturates was recently shown to be due to direct myocardial depression, rather than central depression and may be reversed by calcium.

Our results show the difficulties inherent in the investigation of the bronchial muscles. The results of Emmelin (3) in cats and of Mayrhofer (1) in guinea pigs, concerning the ability of hexobarbital to block bronchoconstriction induced by electrical stimulation of the vagus nerve (using methods similar to those used in our present experiment), are confirmed in dogs. Thiopental has been shown in our experiment to be capable of inducing a similar blockade. The clinical impression that bronchospasm is more likely to occur with thiopental than with hexobarbital (2) cannot be explained by any difference in their actions on vagal innervation of the bronchial muscle in dogs.

Summary

In dogs, both thiopental and hexobarbital are capable of blocking the bronchial constriction caused by vagal stimulation. These drugs also can cause initially bronchial constriction, bronchial dilatation, or have no effect. There is variation of effects within the species, and its probable occurrence in human beings is suggested.

This work was aided by a grant from Winthrop Laboratories, New York, New York.

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