QUANTITATIVE EVALUATION OF CARDIOVASCULAR-STIMULANT DRUGS IN BARBITURATE DEPRESSION OF THE HEART OF THE DOG * † ‡

KENNETH J. BONIFACE, M.D., AND JOHN M. BROWN, M.D.

Charleston, South Carolina

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INTRODUCTION

CARDIOVASCULAR depression from the administration of the barbituric acid derivatives has been observed in both clinical and laboratory usage. This depression has been attributed to asphyxia resulting from their respiratory depressant action as well as a direct effect of the barbiturates on the medullary vasomotor center, the peripheral vascular resistance and the heart. Among the procedures recommended for the management of barbiturate depression are: high concentrations of oxygen, artificial respiration, and the administration of drugs which have a stimulating action on the respiratory or cardiovascular systems.

The experiments which are reported in this paper were performed to evaluate the effectiveness of a cardiac glycoside and two sympathomimetic amines when employed to antagonize the cardiovascular depression from a typical barbiturate, pentobarbital sodium. Utilizing artificial respiration, quantitative values were obtained for the dosages of pentobarbital sodium required to produce cardiac arrest with and without the administration of cardiovascular stimulants.

METHOD

Thirty-five mongrel dogs weighing approximately 10 kg. were anesthetized with 30 mg. per kilogram of pentobarbital sodium, given intravenously. An endotracheal catheter was employed to facilitate artificial respiration with a Bird piston-type respirator. The right jugular vein was cannulated for the administration of the cardiovascular drugs and saline solution. A polyethylene catheter was inserted approximately 10 cm. into the left femoral vein and connected to a mechanical injector to provide additional pentobarbital sodium at a constant rate. The left common carotid artery was cannulated and connected by lead

* From the Departments of Pharmacology and Surgery (Anesthesiology), Medical College of South Carolina, Charleston, S. C.

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tubing to a Statham pressure transducer which recorded through a Brush strain analyser and a Brush oscillograph. In some animals, electrocardiograph tracings of limb lead II were taken at selected intervals with an E.P.L. Cardiotron.

The mechanical injector consisted of a tuberculin syringe, the plunger of which was alternately pushed and pulled by a piston. A valve directed the flow of pentobarbital solution from a reservoir, through the syringe and into the animal. The plunger made a complete cycle every two minutes to deliver a constant infusion of 1 cc. every two minutes.

After an interval of stable recordings, pentobarbital sodium was infused continuously at the rate of 5 mg. per kilogram per minute until the animal died. When respiratory arrest occurred, artificial respiration was instituted at the rate of 15 inflations per minute. When cardiac arrest appeared imminent, one of the sympathomimetic amines was injected intravenously. Repeated dosages of the drug were administered when a need was indicated by the pulse pressure recording. The ouabain was administered in a total dosage of 0.5 cat unit per kilogram during a twenty minute interval before the pentobarbital infusion was started; it was not repeated.

The initial dosages of the drugs employed were: ouabain 0.25 to 0.5 cat units per kilogram, ephedrine (phenylpropanol methylamine) 1 mg. per kilogram and aranthol® (methylamino iso-octanol) 10 mg. per kilogram.

The total quantity of fluid infused was approximately 5 cc. per kilogram for pentobarbital, and 5 cc. per kilogram for cardiovascular drugs.

RESULTS

The initial 30 mg. per kilogram of pentobarbital sodium produced anesthesia of the animals to a depth of a diminished wink reflex.

At the onset of the pentobarbital infusion the average control blood pressure was 160 mm. systolic and 130 mm. diastolic, and the average control heart rate was 155 per minute.

A typical tracing from one of the experiments using a sympathomimetic amine is shown in figure 1. The results of all experiments are summarized in table 1.

Before any drugs were administered to antagonize the cardiovascular depression produced by pentobarbital sodium, the average dosage required to produce cardiac arrest (C.A.D.) was 2.9 ±0.8 times the dosage required to produce respiratory arrest (R.A.D.). Approximately this same ratio of cardiac arrest to respiratory arrest dosage was determined for pentothal and surital® by Woods *et al.* (1).

When ouabain was administered to the experimental animals to antagonize the cardiovascular depression, the C.A.D./R.O.D. ratio was elevated to 4.0 ±0.9.

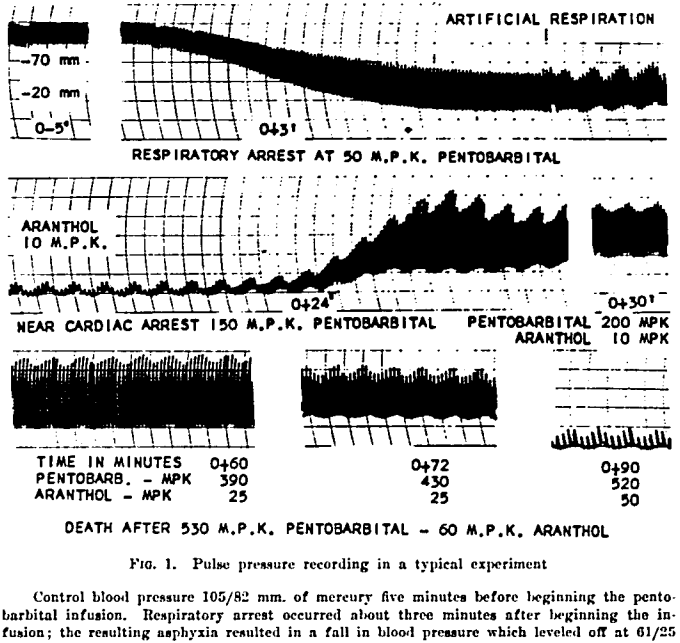

FIG. 1. Pulse pressure recording in a typical experiment

Control blood pressure 105/82 mm. of mercury five minutes before beginning the pentobarbital infusion. Respiratory arrest occurred about three minutes after beginning the infusion; the resulting asphyxia resulted in a fall in blood pressure which leveled off at 61/25 mm. of mercury following artificial respiration. The blood pressure had dropped to 28/14 mm. of mercury just preceding the estimated time for cardiac arrest. The administration of a sympathomimetic amine resulted in elevation of the blood pressure to 100/36 mm. of mercury. At seventy-two minutes the blood pressure was 72/25 mm. of mercury. Just preceding cardiac arrest the blood pressure had fallen to 18/00 mm. of mercury and a partial heart block developed.

TABLE 1

DOSAGES OF SODIUM PENTOBARBITAL

Function Observed	Number of Observations	Mean Dosage, Mg./Kg.	Standard Deviation, Mg./Kg.
Respiratory arrest	29	50	±7
Cardiac arrest without stimulant drugs	29	143	±45
Cardiac arrest after:			
Ouabain	6	224	±42
Ephedrine	6	457	±39
Aranthol	6	468	±103

The administration of ephedrine elevated the C.A.D./R.A.D. ratio to 9.5 ±1.4, and the administration of aranthol elevated the C.A.D./R.A.D. ratio to 9.7 ±2.3.

COMMENT

Analeptic drugs with widely separated sites of action have been employed in the treatment of barbiturate overdosage. Some of these drugs act principally upon the central nervous system to counteract respiratory depression, increase the synaptic reflex irritability or produce a central vasomotor stimulation (metrazol, coramine, picrotoxin). Others act chiefly on the cardiovascular system (ouabain, neosynephrine, aranthol). A few drugs possess both central nervous system and cardiovascular actions (ephedrine, amphetamine, caffeine).

Ouabain, the common standard for the cardiac glycosides, acts directly upon the heart to increase its contractile force (2). Ephedrine acts upon the heart to increase its contractile force (3), acts peripherally on the arterioles to increase the peripheral vascular resistance, and acts centrally to produce cerebral excitation. Aranthol is virtually without action on the central nervous system in the usual dosage range. With this drug several repeated doses can be depended upon to increase the contractile force of the heart and the arterial pressure. These stimulant effects become progressively less pronounced but, in contrast to ephedrine, there are no stages of marked hypotension and cardiac depression (3, 4).

In this study, the mean dosage of pentobarbital sodium which will produce respiratory arrest is used synonymously with the $L.D._{100}$ of Trevan (5), and Holck and Kanan (6), since the dogs would ordinarily die from respiratory paralysis. Quantitatively, this value of 50 mg. per kilogram for the respiratory paralysis compares favorably with the 45 mg. per kilogram value for the $L.D._{100}$ of Werner, Pratt and Tatum (7). The mean dose of 143 mg. per kilogram of pentobarbital which will produce cardiac arrest represents the dosage which will produce cardiovascular death in the presence of adequate oxygenation with artificial respiration.

The ratio of the mean dosage which will produce cardiac arrest to the dosage which will produce respiratory arrest confirms the clinical impression that artificial respiration and adequate oxygenation are of paramount importance in the treatment of barbiturate depression. Satisfactory oxygenation should be accomplished before any other measures are undertaken. This procedure alone often will result in survival of a patient who otherwise would die because of hypoxia secondary to a respiratory fatal dose of a barbiturate.

Following the administration of ouabain, approximately 50 per cent more pentobarbital was required to produce cardiac arrest in the animals. The sympathomimetic amines were more effective in maintaining cardiovascular competency. With ephedrine and aranthol, approxi-

mately 200 per cent more pentobarbital was required to produce cardiac arrest in the animals. Even in the presence of a dosage of pentobarbital larger than that normally necessary to produce cardiac arrest, satisfactory cardiovascular function could be quickly and easily established with a therapeutic dose of the sympathomimetic amines.

Ephedrine and aranthol were about equal in their over-all ability to antagonize the cardiovascular depression produced by massive doses of pentobarbital sodium. Ephedrine appeared to have a slightly more prolonged action than aranthol but produced tachyphylaxis more readily. Cardiovascular depression after administration of ephedrine was observed on one occasion when the circulatory status was good, but was observed with aranthol only in the terminal stages of each experiment. These observations agree with other experiments which measure the comparative action of ephedrine and aranthol (2).

In two experiments in which sympathomimetic amines were utilized, epinephrine (12γ per kilogram) was employed to resuscitate an arrested heart. In these experiments the subsequent course and the final outcome were indistinguishable from the other experiments.

The results of animal experimentation cannot always be applied directly to clinical medicine, but certain conclusions of this work may be of value in supporting impressions obtained from clinical experience:

1. In patients who are given respiratory depressing doses of barbiturates, artificial respiration and adequate oxygenation will permit survival because the cardiac arrest dose is considerably greater than the respiratory depressing dose.

2. Cardiovascular depression due to the barbituates can be effectively antagonized by the administration of certain cardiovascular stimulants.

3. By comparison, ouabain is less effective in antagonizing barbiturate depression than are ephedrine and aranthol. Ephedrine and aranthol exhibited only minor differences in their effectiveness in antagonizing the cardiovascular depression of a barbiturate. Aranthol, however, is considered preferable because it is not likely to produce cardiovascular depression.

SUMMARY AND CONCLUSIONS

Sodium pentobarbital was administered to 35 dogs in order to obtain quantitative values for (1) the respiratory arrest dose; (2) the cardiac arrest dose employing artificial respiration, and (3) the relative extent to which three cardiovascular-stimulant drugs can be used to increase the cardiac arrest dose levels of the barbiturates.

When pentobarbital was continuously infused at a fixed rate and dosage based on body weight, the cardiac arrest dose could be increased by about 50 per cent with previously administered ouabain. Under similar conditions the cardiac arrest dose could be increased by about

200 per cent with ephedrine and aranthol. Although these latter two drugs were approximately equal in their over-all results, there were occasions in which ephedrine produced a type of cardiovascular depression not observed with aranthol.

ADDENDUM

In a subsequent series of experiments, it was demonstrated that with the use of artificial respiration cardiovascular stimulants were capable of bringing about full recovery from doses of pentobarbital approximately three times the usual respiratory arrest dose. This basic treatment was supplemented with endotracheal suction intramuscularly, changes of position and administration of saline intravenously, antibiotics intramuscularly and antiseptics in the conjunctival sacs. Following 150 mg. per kilogram of pentobarbital sodium administered intravenously, recovery time was approximately eighteen hours for spontaneous respiration and ninety-six hours for normal walking movements. Subsequent mentality and behavior appeared to be entirely normal.

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