Anesthesiology
V 42, No 1, Jan 1975

Effects of Succinylcholine and d*-Tubocurarine on Epinephrine-induced Arrhythmias during Halothane Anesthesia in Dogs*

William K. Tucker, M.D., and Edwin S. Munson, M.D.†*

The effects of subparalytic doses of succinylcholine and *d*-tubocurarine on epinephrine-induced cardiac arrhythmias during halothane anesthesia were evaluated in dogs. Succinylcholine markedly increased ($P < .05$) the arrhythmogenicity of epinephrine and *d*-tubocurarine slightly decreased ($P < .05$) its arrhythmic effect. Prior administration of atropine resulted in a partial, but significant, reversal of this action of succinylcholine. (Key words: Anesthetics, volatile: halothane; Heart: arrhythmias; Neuromuscular relaxants: succinylcholine; Neuromuscular relaxants: *d*-tubocurarine.)

MUSCLE RELAXANTS are known to affect myocardial conduction. Repeated administration of succinylcholine may produce bradycardia and supraventricular and ventricular arrhythmias in both children and adults during general anesthesia.[1,2] The effects of succinylcholine on cardiac rate and rhythm are thought to result in part from the stimulating effects of the muscle relaxant on the parasympathetic and sympathetic nervous systems.[1] The disturbances can be partially prevented by cholinergic blockade prior to succinylcholine administration. It is a widely held clinical impression that the use of *d*-tubocurarine is associated with a lower incidence of cardiac arrhythmias during anesthesia than when nonrelaxant techniques are employed. That succinylcholine-induced ventricular arrhythmias in fully digitalized patients and animals can be abolished by *d*-tubocurarine supports this belief.[3]

Since systematic inquiry into the effects of depolarizing and nondepolarizing muscle relaxants on cardiac rhythm is lacking, we have evaluated the effects of succinylcholine and *d*-tubocurarine on epinephrine-augmented pacemaker automaticity in dogs anesthetized with halothane.

Methods

Twenty experiments were performed on five male mongrel dogs with a mean weight of 15.3 kg (range 13.2 to 18.0 kg). The animals received no premedication. Following induction of halothane anesthesia, each animal's trachea was intubated with a cuffed endotracheal tube without the use of muscle relaxants. The experimental methodology is similar to that previously reported.[4] Ventilation was maintained with a volume-limited ventilator at approximately 4 per cent end-tidal CO_2 concentration, determined by a Godart Capnograph. Femoral arterial and forelimb venous cannulas were placed percutaneously. Phasic and mean arterial pressures (MAP) were recorded on a direct-writing oscillograph. Esophageal temperatures were measured with a thermistor probe and maintained at 37 ± 1 C. Cardiac rate and rhythm were recorded from lead II of the electrocardiogram.

Inspired and end-tidal halothane concentrations were monitored with a Beckman LB-2 infrared halothane analyzer calibrated by comparison with gas mixtures stored in cylinders. The composition of these mixtures was analyzed by gas chromatography.[5] Calibrations were made in the presence of CO_2 to eliminate the cross-over effect of this gas.

* Resident in Anesthesiology and NIH Research Trainee.

† Professor of Anesthesiology.

Received from the Department of Anesthesiology, Box 721, the University of Florida College of Medicine, J. Hillis Miller Health Center, Gainesville, Florida 32610. Accepted for publication May 21, 1974. Supported in part by National Institutes of Health Research Training Grant 5 TO1 GM00427-12.

The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

After induction of anesthesia, inspired halothane concentrations were reduced until end-tidal (alveolar) concentrations remained stable at 1.0 per cent (1.2 MAC). When this level had been maintained for 15 to 30 minutes, a heparinized arterial blood sample was obtained and analyzed for Pa_{O_2}, Pa_{CO_2} and *p*H using a Radiometer BMS3 blood-gas analyzer. When the calculated base deficit[6] was greater than 4 mEq/l, an appropriate amount of sodium bicarbonate was administered intravenously.

In each experiment epinephrine was administered intravenously at a rate of 2.5 μg/kg/min by a constant-volume infusion pump. Drug infusions were continued until two or more premature ventricular contractions (PVC's) occurred within 20 sec. This vasopressor dose is defined as the arrhythmogenic dose.

Each of five animals was studied once in each of four groups. Group I (control) received the epinephrine infusion but no muscle relaxant. Group II received an intravenous dose of 0.25 mg/kg succinylcholine 4 minutes prior to epinephrine infusion. Supramaximal stimulus of the ulnar nerve showed that this dose of succinylcholine resulted in approximately 50 per cent reduction in twitch height of the digital flexor muscles for an 8–10-minute period using a Wellcome nerve stimulator. Muscle tension was recorded on a direct-writing oscillograph using the force transducer described by Walts.[7] In Group III, atropine, 0.10 mg/kg, was given 10 minutes prior to succinylcholine administration as in Group II. Arterial blood samples were drawn in all succinylcholine experiments for determination of serum potassium levels before administration of the muscle relaxant and at the onset of epinephrine-induced arrhythmias. Group IV received 0.1 mg/kg *d*-tubocurarine 6 minutes prior to epinephrine infusion. This dose of drug also represented a subparalytic dose of relaxant, producing 10 to 30 per cent depression in muscle twitch tension following ulnar nerve stimulation.

Only one epinephrine infusion was given in any experiment. Commercially available preparations of succinylcholine (Anectine, Burroughs Wellcome and Co.) and *d*-tubocurarine (Tubocurarine Chloride, E.R. Squibb and Sons, Inc.) were employed Studies were separated by intervals ranging from 4 to 7 days and all animals survived the procedures described. Quantitative data were analyzed using the analysis of variance. Student's *t* test was used to compare results between two groups when a significant ($P < .05$) F ratio was obtained.

Results

Results are shown in table 1. The arrhythmogenic dose of epinephrine in Group I (controls) was 4.15 μg/kg. Succinylcholine pretreatment in Group II significantly ($P < .05$) decreased the arrhythmogenic dose of epinephrine in every animal, showing a mean value of 1.60 μg/kg. In addition, the MAP at which arrhythmias occurred was significantly lower than in the control group ($P < .05$). Pretreatment with atropine before administration of succinylcholine in Group III significantly increased ($P < .05$) the arrhythmogenic dose of epinephrine compared with the Group II (succinylcholine) animals (2.26 *vs.* 1.60 μg/kg, respectively). In addition, the change in MAP was significantly ($P < .01$) less than Group I values. In Group IV, *d*-tubocurarine significantly increased ($P < .05$) the arrhythmogenic dose of epinephrine to above control values, showing a mean dose of 4.90 μg/kg. In addition, the MAP at which arrhythmias occurred was significantly higher ($P < .05$) than in the control group.

No significant change in heart rate occurred in any of the groups studied. In all experiments Pa_{CO_2} values were maintained between 35 and 45 torr and base deficit values were within 4 mEq/l of normal. Pa_{O_2} values were maintained above 400 torr. Control serum potassium level (mean ± SD) was 4.2 ± 1.1 mEq/l; the corresponding value was 4.1 ± 2.1 mEq/l ($P > .05$) after administration of succinylcholine.

Discussion

Our findings show that succinylcholine increases the arrhythmogenicity of epinephrine during light levels of halothane anes-

TABLE 1. Effects of Succinylcholine and *d*-Tubocurarine on Epinephrine Arrhythmogenicity in Five Dogs Anesthetized with Halothane*

	Dose (μg/kg)†	Mean Arterial Pressure (MAP) (torr)	Δ MAP (Per Cent)	Heart Rate (HR) (Beats/Min)	Δ HR (Per Cent)
Group I, control	4.15 ±.58	140 ±11	30 ±20	112 ±18	− 7.6 ±13
Group II, succinylcholine	1.60‡ ±.63	126 ±13	9‡ ± 9	122 ±31	18.6 ±11
Group III, atropine–succinylcholine	2.26‡§ ±.62	129 ±37	14 ±10	149 ±13	14.2 ± 9
Group IV, *d*-tubocurarine	4.90‡ ±.43	172 ±15	93‡ ±50	98 ± 8	− 5.6 ±10

* Values represent means ± SD.
† Epinephrine infusion rate 2.5 μg/kg/min.
‡ Compared with Group I, $P < 0.05$.
§ Compared with Group II, $P < 0.05$.

thesia in dogs. The ability of atropine partially to reverse this action suggests that a weak beta-agonist effect may be present. However, this must be qualified, since atropine (average dose 1.5 mg) may have incompletely blocked the parasympathetic nervous system. The observation that *d*-tubocurarine decreases arrhythmogenicity might suggest a weak beta-adrenergic blockade. However, further work with alpha- and beta-adrenergic blocking drugs will be needed before the definitive mechanism is known. In addition, further studies are needed to investigate the time course and antiarrhythmic action of the larger doses of *d*-tubocurarine frequently administered prior to intubation doses of succinylcholine, and to determine whether they produce any modification of the arrhythmic action of the latter drug described in this report.

These results should be interpreted in light of the work of Dowdy and colleagues,[8] who showed that the various antibacterial preservatives added to commercial preparations of *d*-tubocurarine had a significant depressant effect on the contractile amplitude of stimulated rabbit atrial strips. However, we believed it was important to utilize clinically available preparations of muscle relaxants. It should be noted that each 3 mg of Tubocurarine Chloride contained 9 mg benzyl alcohol and 1 mg sodium bisulfite, and that the maximum dose of *d*-tubocurarine we utilized in any animal was 1.8 mg.

The effect of altered blood pressure also may have an important role in the production of cardiac arrhythmias. Moe *et al.*[9] and Dresel and associates[10] reported that the production of a sudden increase in aortic pressure resulted in a significant increase in the incidence of epinephrine-induced arrhythmias. On the contrary, a subsequent sudden decrease in pressure terminated arrhythmias. However, Murphy *et al.*[11] found that epinephrine-induced arrhythmias during cyclopropane anesthesia could be produced in normotensive dogs. Katz[12] showed that isoproterenol produced cardiac arrhythmias in cats with decreased arterial blood pressure, and that aortic occlusion to increase arterial pressure facilitated arrhythmogenicity. The lack of significant change of MAP in any of our animals suggests that the changes we observed were related to myocardial rather than hemodynamic changes.

These observations may have important

clinical implications. The use of succinylcholine during halothane anesthesia when exogenously administered catecholamines are present may predispose the patient to a greater risk of cardiac arrhythmias. Whether succinylcholine would increase myocardial irritability during anesthesia with other inhalation agents usually considered safe in the presence of sympathomimetic amines is unknown. Finally, the current recommendations of the safe amount of epinephrine injected during general anesthesia may have to be modified according to the muscle relaxant employed.

The authors gratefully acknowledge the technical assistance of William Embro and Marjorie H. Malagodi, Ph.D., and the helpful comments of Doctors Dean Morrow and Thorkild W. Andersen, who reviewed the manuscript.

References

1. Craythorne NWB, Turndorf R, Dripps RD: Changes in pulse rate and rhythm associated with the use of succinylcholine in anesthetized children. ANESTHESIOLOGY 21:465–470, 1960
2. Williams CN, Deutsch S, Linde HW, et al: Effects of intravenously administered succinylcholine on cardiac rate, rhythm, and arterial blood pressure in anesthetized man. ANESTHESIOLOGY 22:947–954, 1961
3. Dowdy EG, Fabian LW: Ventricular arrhythmias induced by succinylcholine in digitalized patients. Anesth Analg (Cleve) 42:501–513, 1963
4. Tucker WK, Rackstein AD, Munson ES: Comparison of arrhythmic doses of epinephrine, metaraminol, ephedrine and phenylephrine during isoflurane and halothane anesthesia in dogs. Br J Anaesth 46:392–396, 1974
5. Tham MK, Hardy CA, Shah DO: Gas-chromatographic method using surfactants for analysis of volatile anesthetics in blood. ANESTHESIOLOGY 37:647–649, 1972
6. Siggaard-Andersen O: Blood acid–base alignment nomogram. Scand J Clin Lab Invest 15:211–217, 1963
7. Walts LF: The "boomerang"—a method of recording adductor pollicis tension. Can Anaesth Soc J 20:706–708, 1973
8. Dowdy EG, Holland WC, Yamanaka I, et al: Cardioactive properties of *d*-tubocurarine with and without preservatives. ANESTHESIOLOGY 34:256–261, 1971
9. Moe GK, Malton SD, Rennick BR, et al: The role of arterial pressure in the induction of idioventricular rhythms under cyclopropane anesthesia. J Pharmacol Exp Ther 94:319–327, 1948
10. Dresel PE, MacCannel KL, Nickerson M: Cardiac arrhythmias induced by minimal doses of epinephrine in cyclopropane-anesthetized dogs. Circ Res 8:948–955, 1960
11. Murphy Q, Crumpton CW, Meek WJ: Effect of blood pressure rise on production of cyclopropane–epinephrine induced cardiac irregularities. ANESTHESIOLOGY 10:416–420, 1949
12. Katz RL: Effects of alpha and beta adrenergic blocking agents on cyclopropane–catecholamine cardiac arrhythmias. ANESTHESIOLOGY 26:289–298, 1965