Antiarrhythmic Effects of Skeletal Muscle Relaxants

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The antiarrhythmic effects of *d*-tubocurarine, gallamine and succinylcholine were evaluated in mongrel dogs mechanically ventilated with nitrous oxide–oxygen. Arrhythmias were induced by intravenous administration of epinephrine. The severity and incidence of ventricular arrhythmias were significantly reduced by the muscle relaxants in comparison with thiopental. Repeated injections of epinephrine were less effective in producing ventricular arrhythmias while they continued to produce the same degree of pressor response. The results suggest that neuromuscular blocking drugs may protect against some types of ventricular arrhythmias. (Key words: *d*-Tubocurarine; Gallamine; Succinylcholine; Thiopental; Epinephrine; Antiarrhythmics; Atropine; Tachyphylaxis; Ventricular arrhythmias.)

INTERACTIONS between neuromuscular blocking agents and antiarrhythmic drugs at the myoneural junction have been reported in several recent studies.[1-7] Neuromuscular blocking agents may be potentiated by lidocaine,[3, 5, 7] propranolol,[4, 7] diphenylhydantoin,[6, 7] quinidine,[1, 2] and procainamide,[1, 7] all of which protect against atrial and/or ventricular arrhythmias. These findings suggest some common site of drug–receptor interaction for muscle relaxants and antiarrhythmic drugs. The present study evaluates and compares possible antiarrhythmic effects of *d*-tubocurarine, gallamine and succinylcholine with thiopental against epinephrine-induced arrhythmias in dogs.

Methods

Subjects of the study were 15 mongrel dogs weighing 15–25 kg. The tracheas were intubated following intravenous administration of succinylcholine (0.3 mg/kg) and the dogs were mechanically ventilated with 70 per cent N_2O–30 per cent O_2 by an Ohio model 500/DO ventilator. The respiratory rate was 16/min, with tidal volumes of 15–20 ml/kg. Inspiratory flow rate of the gases was adjusted to maintain Pa_{CO_2} between 30 and 35 torr. Under these conditions Pa_{O_2} values were 107–148 torr and *p*H values were 7.32–7.47 in all experiments. Each of ten dogs received commercial preparations of *d*-tubocurarine (Abbott Laboratories), gallamine (Davis and Geck), succinylcholine (Burroughs Wellcome and Co.), and thiopental (Abbott Laboratories), but only one drug was given during each study. At least seven days were allowed between studies and order of drug administration was randomized. The drugs were given intravenously in amounts just sufficient to maintain quiescence. The approximate mean doses were: *d*-tubocurarine, 0.3 mg/kg/hr; gallamine, 1.5 mg/kg/hr; succinylcholine, 1.5 mg/kg/hr; thiopental, 15 mg/kg/hr.

A catheter was placed in the femoral artery for continuous pressure measurement and blood sampling. Central venous pressure was recorded with a catheter placed in the right atrium via the right saphenous vein. Pressures were recorded on a Hewlett Packard 7700 polygraph with Statham 9-23BB transducers and Hewlett Packard 350-1100C preamplifiers. Electrocardiogram was recorded from standard limb lead II with a Hewlett Packard 350-2700C high-gain preamplifier. Esophageal temperatures were maintained between 35.5 and 38.5 C in all experiments.

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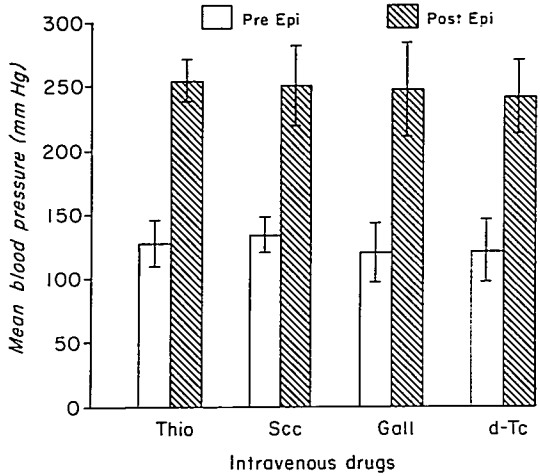

FIG. 1. Mean blood pressures before and after intravenous injection of epinephrine. Each bar ± standard deviation represents at least 50 determinations. Thio = thiopental; SCC = succinylcholine; Gall = gallamine; d-Tc = *d*-tubocurarine.

When heart rate and blood pressure had been stable for 15–20 minutes, epinephrine (10 μg/kg) in 5 ml of saline solution was injected intravenously in a 50-second period.[8] The same dose of epinephrine was repeated every 30 minutes, for a total of six injections. Ventricular arrhythmias, consisting of premature ventricular contractions, bigeminy or trigeminy, and/or ventricular tachycardia, were identified and counted following each epinephrine challenge. The per cent change in heart rate in response to epinephrine was determined during one minute beginning 30 seconds after each injection of epinephrine.

A separate group of five dogs were anesthetized with thiopental and N_2O–O_2 in the manner described above and received atropine (0.1 mg/kg) intravenously five minutes before the second injection of epinephrine. Ventricular arrhythmias and rate changes were determined following each injection of epinephrine.

Results

The blood-pressure responses to repeated epinephrine challenges were not significantly difficult among the four groups studied. Mean arterial blood pressures before and after epinephrine challenges are shown in figure 1. Each bar represents the mean of at least 50 determinations ± one standard deviation. There were no statistical differences ($P > 0.05$) between the blood pressures in any group before and after epinephrine challenges. No statistical differences ($P > 0.05$) in heart-rate changes following repeated injection of epinephrine were demonstrable. The mean heart rate per minute before each injection of epinephrine in these experiments was 172 ± 37 (SD), which was significantly higher than that obtained after each injection of epinephrine, 128 ± 32 ($P < 0.01$).

The severity and incidence of ventricular arrhythmias following intravenous injections of epinephrine in ten dogs are summarized in table 1. Premature ventricular contractions occurred in 10 of 10 experiments in the thiopental group; 5 of 10 in the succinylcholine and *d*-tubocurarine groups; and 6 of 10 in the gallamine group. The number of arrhythmic beats was also greatest in the thiopental group. Bigeminy or trigeminy occurred in 9 of 10 thiopental experiments, but severity and incidence were less when succinylcholine, gallamine or *d*-tubocurarine was used. Ventricu-

TABLE 1. Severity and Incidence of Ventricular Arrhythmias Following Intravenous Administration of Epinephrine (10 μg/kg)*

	Premature Ventricular Contractions	Bigeminy or Trigeminy	Ventricular Tachycardia
Thiopental	74 (10)	192 (9)	210 (3)
Succinylcholine	63 (5)	145 (3)	60 (1)
Gallamine	24 (6)	55 (2)	0 (0)
d-Tubocurarine	55 (5)	14 (1)	0 (0)

* Each unenclosed number represents the frequency of arrhythmic beats per experiment, while the enclosed number represents the number of experiments in a total of ten in which the arrhythmias occurred.

lar tachycardia was an infrequent finding, occurring in three thiopental experiments, one succinylcholine experiment, and no nondepolarizing muscle relaxant experiments.

The numbers of arrhythmias in all groups were far greater after the initial epinephrine injections than after subsequent injections. The numbers of arrhythmias tended to decrease following successive injection of epinephrine (table 2).

In the five dogs anesthetized with thiopental and N_2O–O_2, atropine sulfate (0.1 mg/kg) completely abolished all epinephrine-induced ventricular arrhythmias. Epinephrine increased the heart rate following atropine in these experiments (table 3), while it decreased the heart rate in nonatropinized preparations (see above).

Discussion

Cardiac cells which show spontaneous depolarization during diastole are capable of self-excitation and have been called automatic cells.[9, 10] Automaticity, then, is a function of the rate of diastolic (phase 4) depolarization to achieve threshold of excitation.[9, 10] Although there are many atrial and ventricular automatic cells, only one pacemaker is in control during each cardiac cycle. Normally, the automatic cells of the sinoatrial node have the fastest rate of diastolic depolarization; hence, it is the pacemaker. Therefore, conditions which suppress atrial autonomic cells or atrial–ventricular conduction may allow ventricular automatic cells to become the pacemaker. However, ventricular arrhythmias will be induced by simultaneous enhancement of the automaticity of several ventricular foci.

Epinephrine mediates its arrhythmogenic effects by increasing automaticity[9, 10] of cardiac cells and by decreasing ventricular fibrillatory threshold (*i.e.*, increasing excitability).[10–12] Since automatic cells differ in sensitivity, the action of catecholamines may cause a shift in the pacemaker site.[10] Moreover, Han and Moe[13] have shown that sympathetic stimulation has quantitatively different effects on adjacent areas of ventricular myocardium, producing irregular, shortened refractory periods of automatic cells. Nonuniformity of recovery of these cells following sympathetic stimulation would favor abberant conduction of impulses during the relative refractory period and increasing the change of re-entry.

In our study the automaticity of the sinoatrial node presumably was depressed by vagotonic impulses reflexly elicited by an increase in mean systemic arterial pressure in response to injection of epinephrine. This depression of sinoatrial nodal cells shifts the automatic activity in secondary pacemaker areas along the conduction pathway. The effect of vagal

TABLE 2. Total Number of Ventricular Arrhythmias Following Repeated Intravenous Injection of Epinephrine (10 μg/kg)
(Each Number Represents Ten Experiments)

Injection	Thiopental	Succinylcholine	Gallamine	*d*-Tubocurarine	Total
1	1,156	270	157	95	1,678
2	650	113	31	45	839
3	273	149	18	59	499
4	291	88	9	29	427
5	244	86	22	38	390
6	479	103	14	12	608

stimulation on epinephrine-induced arrhythmias in dogs has been well documented.[11, 14] When vagal tone was blocked by atropine, epinephrine increased the heart rate (table 3) and no ventricular arrhythmias were observed.

Our data show that repeated administration of epinephrine tends to produce tachyphylaxis to its arrhythmogenic response while producing the same degree of pressure response. These results further confirm the finding that elevated arterial blood pressure is important but not absolutely essential for the production of cardiac arrhythmias.[15] The tachyphylactic arrhythmogenic response would also be compatible with the finding that *continuous* infusion of epinephrine produces an initial decrease followed by a marked increase in atrial and ventricular fibrillatory thresholds.[10-12]

It is inferred from the above discussion that factors which maintain or accelerate the rate of the sinoatrial node would have an antagonistic effect on epinephrine-induced ventricular arrhythmias. Although our results do not show significant changes in heart rate with these drugs following injections of epinephrine, the atropine-like effect of gallamine and the ganglionic blocking action of *d*-tubocurarine cannot be excluded as possible antiarrhythmic factors. The cardiac effect of succinylcholine is more complex, because stimulation of sympathetic as well as parasympathetic nervous systems has been suggested.[16-18] One might expect it to have a lesser protective effect against epinephrine-induced arrhythmias. Indeed, the effect was intermediate, since ventricular arrhythmias in the succinylcholine experiments were significantly less than those in the thiopental experiments, but greater than those in the gallamine and *d*-tubocurarine experiments.

Thiopental lowered the incidence of hypothermia-induced ventricular fibrillation and the mean temperature at which ventricular fibrillation occurred when compared with pentobarbital anesthesia in dogs.[19] Induction with thiopental alone resulted in a lower incidence of ventricular arrhythmias compared with thiopental–cyclopropane induction in man.[20, 21] In contrast to the above findings, thiopental increased cardiac arrhythmias in dogs and other laboratory animals [22] and potentiated cyclopropane–epinephrine-induced cardiac arrhythmias in dogs.[23] These opposing results may reflect differences in species and experimental conditions.

TABLE 3. Heart Rate (beats/min): Effects of Epinephrine before and after Atropine (0.1 mg/kg)

Experiment	Control	After First Epinephrine	After Atropine	After Second Epinephrine
1	132	108	192	289
2	210	192	210	282
3	172	130	202	280
4	183	165	192	257
5	170	150	187	230

An interesting alternative exists for the antiarrhythmic effects of these neuromuscular blocking agents. Several antiarrhythmic drugs, including lidocaine,[3, 7] propranolol,[4, 7] diphenylhydantoin,[6, 7] quinidine,[1, 2] and procainamide,[1, 7] have been shown to potentiate skeletal muscle relaxants in laboratory animals. In a study of surgical patients under halothane-N_2O–O_2 anesthesia, lidocaine injected into the brachial or radial artery also produced an immediate reduction of the tetanic muscle tension of the adductor pollicis muscle.[5] With the exception of procainamide, all of these antiarrhythmic agents[2-4, 6] appear to depress posttetanic repetitive neural activity in the motor nerve terminal, a property shared by *d*-tubocurarine [24] and succinylcholine.[25] These findings suggest a common site of drug receptor interaction for these drugs. It has been suggested by Standaert *et al.* that the ability of a drug to antagonize digitalis-induced ventricular arrhythmias is closely correlated with its capacity to depress nerve function.[26] The neurodepressant dose range is identical to the antiarrhythmic range for beta-adrenergic blocking agents,[4, 7, 25] diphenylhydantoin,[6] and lidocaine.[3] A plausible explanation would be that the neuromuscular blocking agents have a depressant effect on cardiac nerve terminals, thereby increasing the threshold of excitation and/or decreasing automaticity of cardiac cells.

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References

1. Cuthbert M: The effect of quinidine and procainamide on the neuromuscular blocking action of suxamethonium. Brit J Anaesth 38:775, 1966
2. Miller RD, Way WL, Katzung BG: The neuromuscular effects of quinidine. Proc Soc Exp Biol Med 129:215, 1968
3. Usubiaga JE, Standaert F: The effects of local anesthetics on motor nerve terminals. J Pharmacol Exp Ther 159:353, 1968
4. Usubiaga JE: Neuromuscular effects of beta-adrenergic blockers and their interaction with skeletal muscle relaxants. ANESTHESIOLOGY 29:484, 1968
5. Usubiaga JE, Moya F: Neuromuscular effects of six local anaesthetics on anaesthetized subjects. Canad Anaesth Soc J 15:56, 1968
6. Raines A, Standaert RG: Pre- and postjunctional effects of diphenylhydantoin at the cat soleus neuromuscular junction. J Pharmacol Exp Ther 153:361, 1966
7. Harrah MD, Way WL, Katzung BG: The interaction of *d*-tubocurarine with antiarrhythmic drugs. ANESTHESIOLOGY 33:406, 1970
8. Meek WJ, Hathaway HR, Orth OS: The effects of ether, chloroform and cyclopropane on cardiac automaticity. J Pharmacol Exp Ther 61:240, 1937
9. Hoffman BF, Cranefield PF: The physiological basis of cardiac arrhythmias. Amer J Med 37:670, 1964
10. Hoffman BF, Singer DH: Appraisal of the effects of catecholamines on cardiac electrical activity. Ann NY Acad Sci 139.914, 1967
11. Szekeres L: Discussion of a paper by West TC: "Fibrillatory and antifibrillatory drugs" in Pharmacology of Cardiac Function. New York, The Macmillan Co. Proc Second International Pharmacological Meeting (Aug. 20–23, 1963), 5:143, 1964
12. Papp JG, Szekeres L: The arrhythmogenic action of sympathomimetic amines. Europ J Pharmacol 3:4, 1968
13. Han J, Moe GK: Nonuniform recovery of excitability in ventricular muscle. Circ Res 14:44, 1964
14. Dresel PE: Sites of vagal action in adrenaline-induced cardiac arrhythmias. Canad J Biochem Physiol 40:1655, 1962
15. Katz RL: The effects of alpha and beta adrenergic blocking agents on cyclopropane–catecholamine cardiac arrhythmias. ANESTHESIOLOGY 26:289, 1965
16. Galindo AH, Davis TB: Succinylcholine and cardiac excitability. ANESTHESIOLOGY 23: 32, 1962
17. Lupprian KG, Churchill-Davidson HC: Effect of suxamethonium on cardiac rhythm. Brit Med J 2:1774, 1960
18. Williams CH, Deutsch S, Linde HW, *et al.*: Effect of intravenously administered succinylcholine on cardiac rate, rhythm, and arterial blood pressure in anesthetized man. ANESTHESIOLOGY 22:947, 1961
19. Riley PA, Barila TG, Hughes CW: Ventricular fibrillation in hypothermic dogs as influenced by thiopental, pentobarbital and succinylcholine. ANESTHESIOLOGY 17:277 1956
20. Seuffert CW, Urbach KF: Influence of thiopental induction on incidence and types of cardiac arrhythmias during cyclopropane anesthesia. Anesth Analg 46:267, 1967
21. Strong MJ, Lukban CP, Keats AS: Cyclopropane–carbon dioxide arrhythmic threshold in patients with cardiovascular disease. ANESTHESIOLOGY 29:295, 1968
22. Gruber CM: The effects of anesthetic doses of sodium thio-pentobarbital, sodium thioethamyl and pentothal sodium upon the respiratory system, the heart and blood pressure in experimental animals. J Pharmacol Exp Ther 60:143, 1937
23. MacCannell KL, Dresel PE: Potentiation of cyclopropane–adrenaline cardiac arrhythmias. Canad J Physiol Pharmacol 42:627, 1964
24. Standaert FG: The action of *d*-tubocurarine on the motor nerve terminal. J Pharmacol Exp Ther 143:181, 1964
25. Galindo A: Mode of action of depolarizing neuromuscular blockers. J Physiol 211:42P, 1970
26. Standaert FG, Levitt B, Roberts J, *et al.*: Antagonism of ventricular arrhythmias induced by digitalis—a neural phenomena. Europ J Pharmacol 6:209, 1969

Obstetrics and Pediatrics

FETAL ACIDOSIS Values in fetal scalp, maternal antecubital vein, and umbilical artery and vein blood were measured in 33 patients and fetuses during labor to determine acid–base status and oxygen saturation. Fetal scalp blood *p*H was the best measurement of fetal well-being during labor. The *p*H of blood from the umbilical vein was a good indicator at the time of delivery. Fetal oxygen tensions fluctuated rapidly and widely but did not result in fetal acidosis unless the hypoxia was severe and prolonged. (*Kerenyi, T. D., and others: Acid–Base Balance and Oxygen Saturation of Fetal Scalp Blood during Normal and Abnormal Labors, Obstet. Gynec. 35: 398 (Sept.) 1970.*)