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,1,4 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 N2O-30 per cent O2 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 PaCO2 between 30 and 35 torr. Under these conditions PaO2 values were 107-148 torr and pH 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.
When heart rate and blood pressure had been stable for 15–20 minutes, epinephrine (10 \( \mu g/kg \)) in 5 ml of saline solution was injected intravenously in a 50-second period. 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 \( N_2 O-O_2 \) 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 different 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 \( \pm \) 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 \( 172 \pm 37 \) (SD), which was significantly higher than that obtained after each injection of epinephrine, \( 128 \pm 32 \) \( (P < 0.01) \).

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

<table>
<thead>
<tr>
<th></th>
<th>Premature Ventricular Contractions</th>
<th>Bicephaly or Triceminy</th>
<th>Ventricular Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental</td>
<td>74 (10)</td>
<td>192 (6)</td>
<td>210 (3)</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>63 (5)</td>
<td>145 (3)</td>
<td>60 (1)</td>
</tr>
<tr>
<td>Gallamine</td>
<td>24 (6)</td>
<td>55 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>d-Tubocurarine</td>
<td>55 (3)</td>
<td>14 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Each unclosed number represents the frequency of arrhythmie 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 N₂O–O₂, 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 nonanesthetized preparations (see above).

Discussion

Cardiac cells which show spontaneous depolarization during diastole are capable of self-excitation and have been called automatic cells.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 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.¹⁶ Moreover, Han and Moe¹² 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 aberrant 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 systolic 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)

<table>
<thead>
<tr>
<th>Injection</th>
<th>Thiopental</th>
<th>Succinylcholine</th>
<th>Gallamine</th>
<th>d-Tubocurarine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,156</td>
<td>270</td>
<td>157</td>
<td>95</td>
<td>1,678</td>
</tr>
<tr>
<td>2</td>
<td>650</td>
<td>113</td>
<td>31</td>
<td>45</td>
<td>839</td>
</tr>
<tr>
<td>3</td>
<td>275</td>
<td>149</td>
<td>18</td>
<td>59</td>
<td>437</td>
</tr>
<tr>
<td>4</td>
<td>291</td>
<td>58</td>
<td>9</td>
<td>29</td>
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<tr>
<td>5</td>
<td>244</td>
<td>86</td>
<td>22</td>
<td>38</td>
<td>390</td>
</tr>
<tr>
<td>6</td>
<td>479</td>
<td>103</td>
<td>14</td>
<td>12</td>
<td>608</td>
</tr>
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</table>
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 cyclopro-

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Control</th>
<th>After First Epinephrine</th>
<th>After Atropine</th>
<th>After Second Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132</td>
<td>108</td>
<td>192</td>
<td>289</td>
</tr>
<tr>
<td>2</td>
<td>210</td>
<td>192</td>
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<td>282</td>
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<td>3</td>
<td>172</td>
<td>130</td>
<td>202</td>
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<td>4</td>
<td>183</td>
<td>163</td>
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</tr>
<tr>
<td>5</td>
<td>170</td>
<td>150</td>
<td>187</td>
<td>230</td>
</tr>
</tbody>
</table>

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

An interesting alternative exists for the antiarrhythmic effects of these neuromuscular blocking agents. Several antiarrhythmic drugs, including lidocaine,23 propranolol,24 25 diphenylhydantoin,26 quindine,27 and procainamide,28 have been shown to potentiate skeletal muscle relaxants in laboratory animals. In a study of surgical patients under halothane-N₂O-O₂ anesthesia, lidocaine injected into the brachial or radial artery also produced an immediate reduction of the tetanic muscle tension of the adductor pollicis muscle.29 With the exception of procainamide, all of these antiarrhythmic agents24-26 appear to depress posttetanic repetitive neural activity in the motor nerve terminal, a property shared by d-tubocurarine24 and succinylcholine.30 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.31 The neurodepressant dose range is identical to the antiarrhythmic range for beta-adrenergic blocking agents,24 25 diphenylhydantoin,6 and lidocaine.32 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

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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 pH was the best measurement of fetal well-being during labor. The pH 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. (Kereny, T. D., and others: Acid-Base Balance and Oxygen Saturation of Fetal Scalp Blood during Normal and Abnormal Labor, Obstet. Gynec. 35: 398 (Sept.) 1970.)