The Interaction of d-Tubocurarine with Antiarrhythmic Drugs

Marvin D. Harrah, M.D.,* Walter L. Way, M.D.,†
B. G. Katzung, M.D., Ph.D.‡

The antiarrhythmics lidocaine, procainamide, propranolol, and diphenhydantoin were tested in the cat anterior tibialis preparation. d-Tubocurarine neuromuscular blockade in the cat was increased approximately 10 to 25 per cent in intensity and prolonged 3 to 6 minutes when an antiarrhythmic drug was given prior to the relaxant. These findings confirm drug interactions that may be of clinical consequence. (Key words: d-Tubocurarine; Procainamide; Propranolol; Diphenhydantoin; Lidocaine; Antiarrhythmics; Neuromuscular block; Drug interaction.)

INTERACTIONS between neuromuscular blocking agents and antiarrhythmic drugs have been reported by a number of authors.1-7 Quinidine, in particular, has been implicated in recurrance in humans,1,2,6 and animal experiments in this laboratory showed that quinidine potentiates both depolarizing and nondepolarizing muscle relaxants.7

The degrees to which other antiarrhythmic drugs such as procainamide (Pronestyl), lidocaine (Xylocaine), propranolol (Inderal), and diphenhydantoin (Dilantin) affect neuromuscular function are not clear. Studies of the action of the beta-adrenergic blocking drug, propranolol, in cats have produced conflicting results. A central muscle relaxant action,8 antagonism,9 and potentiation9 of d-tubocurarine (dTc), have been reported. Intra-arterial injection of lidocaine alone has been shown to depress single-twitch and tetanic muscle tension10 in man. Lidocaine administered intravenously has been shown to prolong succinylcholine apnea in patients.3

We examined quantitatively the interactions of d-tubocurarine with procainamide, lidocaine, propranolol, and diphenhydantoin.

Methods

Cats weighing 1.5 to 5.0 kg were anesthetized with alpha-chloralose, 60-80 mg/kg, and urethane, 250 mg/kg, intraperitoneally. The tendon of the anterior tibialis muscle was attached to a Grass force-displacement transducer (FT 0.03). The sciatic nerve was sectioned in the thigh. The peroneal nerve was isolated, and shielded platinum electrodes were applied for the indirect stimulation of the muscle. At 10-sec intervals supramaximal stimuli consisting of monophasic pulses of 0.3-msec duration and 0.3-5-volt intensity were delivered by a Grass Model S4C stimulator. Muscle contractions were recorded on a Grass Model 7 Polygraph as discrete twitches so that twitch height was proportional to isometric contractile force.

The trachea, carotid artery and jugular vein were cannulated. All drugs were given intravenously via the jugular vein. Constant-volume ventilation with room air was delivered by a Harvard pump so that arterial blood gases and pH remained constant with a range of values for all experiments as follows: \( P_{\text{CO}_2} \) 20 to 42 mm Hg; \( P_{\text{O}_2} \) 75 to 110 mm Hg; pH 7.32 to 7.50. Carotid arterial pressure was measured with a strain gauge and recorded continuously. Rectal temperature was maintained between 35 and 38 C with a heating pad.

Five cats were tested with each drug combination. Each cat served as its own control, was given only one antiarrhythmic drug and used for only one experiment. The control response to dTC, 0.1 to 0.3 mg/kg, was determined by repeated doses at intervals greater than the duration of the dTC neuromuscular-blocking effect (45 minutes). No more than

* Former Research Trainee and Resident in the Department of Anesthesia.
† Associate Professor of Anesthesia and Pharmacology.
‡ Associate Professor of Pharmacology.
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six doses were given to determine the control response. Each experiment lasted less than six hours. Forty-five minutes after a consistent response to dTC had been attained, the antiarrhythmic drug being tested was slowly injected over a one-to-nine-minute interval in order to minimize changes in blood pressure. Following stabilization of blood pressure (one to six minutes after the antiarrhythmic agent), the predetermined control dose of dTC was repeated. Twitch height depression from dTC alone (control response) and that from dTC following the antiarrhythmic drug being tested were compared. An hour later the control dose of dTC was again given. After maximal twitch depression and during recovery, the antiarrhythmic drug was given to evaluate the possibility of recurruration as evidenced by twitch height depression or delayed recovery.

Doses of antiarrhythmic drugs tested were: lidocaine hydrochloride, 5 mg/kg (five cats); sodium diphenylhydantoin, 7 to 11 mg/kg (five cats); procainamide hydrochloride, 5 mg/kg (five cats) and 20 mg/kg (five cats); propranolol hydrochloride, 5 mg/kg (five cats).

Neuromuscular depression was expressed as percentage of control twitch height. Interaction of dTC with an antiarrhythmic drug was quantified by subtraction of percentage depression due to dTC alone from percentage depression produced by dTC after the antiarrhythmic drug. The duration of neuromuscular blockade was defined as the time in minutes between injection of dTC and return of twitch height to 75 per cent of control (pre-dTC) twitch height.

Each animal served as its own control. The

<table>
<thead>
<tr>
<th>Twitch Depression of Two Consecutive Doses of dTC Alone</th>
<th>Twitch Depression</th>
<th>Increase Due to</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Dose</td>
<td>Second Dose</td>
<td>Lidocaine + dTC</td>
</tr>
<tr>
<td>(Per Cent)</td>
<td>(Per Cent)</td>
<td>(Per Cent)</td>
</tr>
<tr>
<td>Cat 1</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Cat 2</td>
<td>64</td>
<td>69</td>
</tr>
<tr>
<td>Cat 3</td>
<td>58</td>
<td>69</td>
</tr>
<tr>
<td>Cat 4</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Cat 5</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>Average</td>
<td>42</td>
<td>43</td>
</tr>
</tbody>
</table>

$t$ test for paired data was used to analyze the results. *\(^{11}\)

Results

The stability of the control dTC response was confirmed in the series of five cats treated with lidocaine. As shown in table 1, there were only small differences between the twitch depressions induced by two consecutive test doses of dTC. The average increase in depression between the two control doses of dTC in the five animals was 2.8 ± 2.4 (SE) per cent. In contrast, the dose of dTC given after lidocaine, 5 mg/kg, resulted in significantly greater twitch depression in every animal. The dose of procainamide (see below) further substantiates the stability of the preparation.

The magnitudes and durations of interaction of dTC with all of the antiarrhythmic agents tested are summarized in tables 2 and 3.

Lidocaine, 5 mg/kg, given to five cats over a one-minute interval did not depress twitch height directly but did increase the twitch depression due to dTC significantly ($P < 0.025$). The duration of neuromuscular blockade was also significantly increased ($P < 0.025$).

Diphenylhydantoin, 7 mg/kg in one cat, 11 mg/kg in one cat, and 8 mg/kg in three cats, had no direct effect on twitch height, but significantly increased the magnitude and duration of dTC block ($P < 0.05$).

Propranolol, 5 mg/kg, had no consistent direct effect on twitch height. In some animals twitch height increased slightly and in others it decreased slightly or did not change. The magnitude and duration of dTC neuromuscular blockade were significantly increased after propranolol ($P < 0.01$).
TABLE 2. The Effects of Antiarrhythmic Drugs on the Intensity of Action of d-Tubocurarine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Twitch Depression, dTC Alone (Per Cent)</th>
<th>Mean Twitch Depression, dTC and Antiarrhythmic Drug (Per Cent)</th>
<th>Additional Twitch Depression (Per Cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine, 5 mg kg, 5 cats</td>
<td>50</td>
<td>75</td>
<td>25 ± 8</td>
</tr>
<tr>
<td>Diphenylhydantoin, 7-11 mg kg, 5 cats</td>
<td>60</td>
<td>71</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>Propranolol, 5 mg kg, 5 cats</td>
<td>58</td>
<td>72</td>
<td>14 ± 6</td>
</tr>
<tr>
<td>Procainamide, 5 mg kg, 5 cats</td>
<td>49</td>
<td>56</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Procainamide, 20 mg kg, 5 cats</td>
<td>60</td>
<td>81</td>
<td>21 ± 4</td>
</tr>
</tbody>
</table>

* Not significant.

Procainamide, 5 mg kg, had no direct effect on twitch height and did not significantly alter the intensity or duration of a standard dTC neuromuscular blockade. Procainamide, 20 mg/kg, also had no direct effect on twitch height, but significantly increased the intensity and duration of the standard dTC blockade ($P < 0.005$).

Recanarization with each of the antiarrhythmic drugs was observed as transient twitch depression or delay in recovery. The magnitude of this response was quite small and was not quantitated. Typical responses are shown in figure 1.

Each antiarrhythmic drug changed arterial blood pressure. Since the rate of administration was limited to that which produced minimal cardiovascular changes, the mean decrease of blood pressure for all experiments was 13 per cent. Of 25 experiments, the blood pressures decreased transiently in 18, increased in three, and did not change in four.

Discussion

All of the antiarrhythmic drugs tested increased the intensity and duration of a dTC neuromuscular block when given prior to a standard dose of dTC. However, with procainamide at the 5 mg/kg dose level, the interactions was not significant. For all drugs, the magnitudes of responses were not large, and the mean duration of blockade was not prolonged more than ten minutes beyond the control value. A small degree of transient twitch depression or delay in recovery occurred with each antiarrhythmic drug given during early recovery from dTC depression (fig. 1).

Our results with propranolol are in partial agreement with those of Usubiaga, who found marked recanarization of the cat soleus preparation when propranolol was given during recovery from dTC blockade. We found no evidence that propranolol antagonized the action of dTC, as claimed by Wislicki and Rosenblum. In a subsequent paper these authors reported potentiation of dTC with injection of propranolol via the femoral artery.

These results, along with those cited for quinidine, indicate that these antiarrhythmic drugs can interact with nondepolarizing neuromuscular blocking agents. Comparison of the present results with those previously reported for quinidine suggests that at equal dos-

TABLE 3. The Effects of Antiarrhythmic Drugs on the Duration of Action of d-Tubocurarine

<table>
<thead>
<tr>
<th>Antiarrhythmic Drug</th>
<th>Mean Duration Neurmuscular Blockade, dTC Alone (min)</th>
<th>Mean Duration, dTC and Antiarrhythmic Neurmuscular Blockade (min)</th>
<th>Additional Duration of Blockade (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine, 5 mg kg, 5 cats</td>
<td>16.3</td>
<td>22.4</td>
<td>6.1 ± 1.9</td>
</tr>
<tr>
<td>Diphenylhydantoin, 7-11 mg kg, 5 cats</td>
<td>19.5</td>
<td>22.4</td>
<td>2.9 ± 1.1</td>
</tr>
<tr>
<td>Propranolol, 5mg/kg, 5 cats</td>
<td>12.1</td>
<td>18.6</td>
<td>6.5 ± 1.5</td>
</tr>
<tr>
<td>Procainamide, 5 mg/kg, 5 cats</td>
<td>12</td>
<td>15</td>
<td>3 ± 1.5</td>
</tr>
<tr>
<td>Procainamide, 20 mg/kg, 5 cats</td>
<td>12.7</td>
<td>22.5</td>
<td>9.8 ± 0.4</td>
</tr>
</tbody>
</table>

* Not significant.
ages (5 mg kg) quinidine is a more effective potentiator of dTC. Whether this is also true for depolarizing neuromuscular blocking agents is not known.

Among factors that influence neuromuscular blockade, cumulative effects of multiple doses of dTC must be considered. However, Miller et al. showed that repeated doses of dTC at 45-minute intervals over a six-hour period produced no significant change in twitch height depression with each dose. In the present study, stability of the dTC response was also shown for two successive doses of dTC (table 1) and confirmed for three doses by the lack of significant "interaction" with a 5 mg kg dose of procainamide (table 2).

Variations in blood pressure and regional blood flow with resultant changes in dTC concentration at the receptor site may account for part of the drug interaction observed. As regional blood flow was not measured, we can only speculate about this factor.

Procainamide, lidocaine, and propranolol have local anesthetic properties and may potentiate dTC by blocking conduction of nerve impulses. Local anesthetics prevent the increase in sodium conductance which normally occurs with membrane depolarization. In this manner these antiaarrhythmic drugs may potentiate neuromuscular blockade by impairing transmission at the motor nerve terminals. Local anesthetics may also displace muscle relaxants bound to plasma proteins, thus providing increased concentrations at the myoneural junction.

Recent work in this laboratory attempting to clarify the mechanism of quinidine potentiation of relaxants indicated a presynaptical site of action when quinidine was given intravenously via the jugular vein. In contrast, a neuromuscular effect resembling depolarization was observed when the quinidine was injected into the femoral artery, probably owing to the lower local concentration when given by this route. The drugs investigated in the present study probably act in a fashion similar to that of quinidine, since they have also been shown to potentiate depolarizing neuromuscular blocking agents. The increased fatiguing during tetanic stimulation shown for diphenylhydantoin by Norris et al. and the suppression of posttetanic repetitive (PTR)

![Fig. 1. Effects of antiaarrhythmic drugs on recovery from partial d-tubocurarine (dTC) neuromuscular blockade. Note that in most cases the magnitudes and durations of depression induced by the antiaarrhythmics ("recruration") were small. Anterior tibialis-peroneal nerve preparation, stimulation at 10-sec intervals.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931587/)
rhythmics suggests that they stabilize cardiac muscle membranes. With the exception of procainamide, all of the agents studied in this experiment as well as quinidine, appear to depress PRA activity in the motor nerve terminal.5, 12, 13, 23 This correlation invites the speculation that the membrane of the motor nerve terminal bears a greater similarity to cardiac cell membranes than to the membrane of the motor nerve axon.

The clinical significance of these observations is that the doses of lidocaine, diphenhydantoin, and procainamide studied here are occasionally used in clinical situations in man. Although a reported adverse effect of propranolol is muscle weakness,24 the dose used clinically, 0.15 mg/kg, is approximately 20 times smaller than that used in this study, and it is doubtful that the weakness reported was related to an effect on the neuromuscular junction. Patients receiving recommended doses of these antiarrhythmic drugs alone should not experience muscle weakness in the absence of dTC. However, patients receiving large doses of antiarrhythmics, such as intravenous lidocaine, as part of a general anesthetic technique or as a continuous drip for persistent arrhythmias may demonstrate increased sensitivity to dTC. Epileptic patients treated with diphenhydantoin might also be expected to have increased sensitivity to dTC.

Our findings thus extend the evidence that a potentially important drug interaction may occur between muscle relaxants and antiarrhythmic agents.

References


