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Single versus Divided Doses of Atracurium: Does 0.05 + 0.10 Equal 0.15?

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Other authors have reported that pretreatment with a small subparalyzing dose of atracurium may expedite the onset of neuromuscular block resulting from a second, larger dose of atracurium.1,2 This strategy also may diminish the total muscle relaxant dose required to achieve conditions suitable for endotracheal intubation.2,3 In apparent contrast to these studies,2,5 0.25 mg/kg of atracurium given by single bolus injection produces more intense neuromuscular blockade than does the same dose given incrementally.4 All these studies,1–4 however, employed total muscle relaxant doses in excess of the E_{D95} for atracurium5 and therefore were not ideally suited to detect subtle alterations in drug effect. However, a total dose of atracurium that corresponds to the steep portion of its dose–response curve will render perceptible the drug effects obscured by large (“off-scale”) doses. This study was designed specifically to determine, using the E_{D95} of atracurium, if the combined effect of pretreatment with a small (subclinical) dose of atracurium followed by a second (therapeutic) dose produces a degree of neuromuscular blockade that differs from that resulting from a single bolus injection.

MATERIALS AND METHODS

The study protocol was approved by the institution’s Human Investigation Committee, and written informed consent was obtained from all patients. The subjects were 20 adult patients, ASA physical status 1 or 2. No premedication was given. After placement of a blood pressure cuff and electrocardiographic electrodes, anesthesia was induced with thiopental 4–6 mg/kg iv and maintained with fentanyl 3–5 μg/kg iv and N_{2}O, 67% in O_{2}.

Neuromuscular blockade was monitored with a force-
displacement transducer (Grass FT-10®), which measured adductor pollicis twitch tension in response to supra-
maximal ulnar nerve stimulation at 0.15 Hz, delivered for a duration of 0.15 ms via 25-gauge needles placed subcutaneously. A strip chart continuously recorded the force transducer measurements from 10 min before to 50 min after atracurium administration.

Patients were allocated randomly by blinded lottery to receive either a single dose of atracurium, 0.15 mg/kg, or divided doses of atracurium, 0.05 mg/kg, followed 5 min later by 0.10 mg/kg. The time to initial twitch depression, the magnitude of neuromuscular block, and time to maximal neuromuscular block were measured, as were times to 25, 50, and 95% recovery of initial twitch height. Student’s t test was used to test statistical significance between groups, with P < 0.05 considered significant.

RESULTS

Maximal neuromuscular block (twitch height depression) and the times to initial and maximal twitch depression are shown in table 1. The small pretreatment dose of atracurium provoked no discernible change in twitch height over 5 min. Atracurium 0.10 mg/kg after the pretreatment dose resulted in a more rapid onset of initial twitch height depression than did the same total dose delivered as a single injection. However, maximal neuromuscular block and the time required to achieve maximal neuromuscular block were unaltered by pretreatment. The profiles of twitch height recovery following atracurium 0.15 mg/kg in single and divided doses, shown in table 1, were similar for both treatment protocols. Thus, pretreatment with a subparalyzing dose of atracurium de-
TABLE 1. Neuromuscular Block and Recovery Following Atracurium in Single and Divided Doses

<table>
<thead>
<tr>
<th>Atracurium Dose (mg/kg)</th>
<th>Maximal Neuronal Block (%)</th>
<th>Time to Initial Twitch Height Depression (min)</th>
<th>Time to Maximal Neuronal Block (min)</th>
<th>Time (min) to 25% Recovery from Neuronal Block Following Last Atracurium Dose</th>
<th>Time (min) to 50% Recovery from Neuronal Block Following Last Atracurium Dose</th>
<th>Time (min) to 95% Recovery from Neuronal Block Following Last Atracurium Dose</th>
</tr>
</thead>
<tbody>
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<tr>
<td>0.15</td>
<td>73 ± 7</td>
<td>1.6 ± 0.2</td>
<td>7.3 ± 0.5</td>
<td>18 ± 2</td>
<td>24 ± 2</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>0.05* + 0.10</td>
<td>74 ± 7</td>
<td>1.1 ± 0.2†‡</td>
<td>7.6 ± 0.9‡</td>
<td>22 ± 4</td>
<td>26 ± 4</td>
<td>34 ± 2</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* Neuromuscular block did not occur in any patient following 0.05 mg/kg dose.
† P < 0.05.
‡ Time after 0.10 mg/kg dose.

Increased by 30 s the time to a measurable effect of the second dose, but it did not alter the maximal neuromuscular blockade, the time required to achieve maximal neuromuscular blockade, or the duration of neuromuscular blockade.

Discussion

For a total atracurium dose of 0.15 mg/kg, pretreatment with a small, clinically undetectable dose did not alter measurably the intensity of neuromuscular block nor the time required to achieve maximal neuromuscular block following a larger, clinically effective dose. However, the onset of initial twitch depression was more rapid with the divided dose regimen. The recovery of twitch height was similar in both groups.

Nagashima et al.2 found that 0.25 mg/kg of atracurium 6 min after a 0.075 mg/kg dose resulted in maximal block and conditions suitable for endotracheal intubation (80% twitch height depression) more rapidly than either 0.4 mg/kg or 0.5 mg/kg of atracurium given as a single dose. An earlier study by Gergis et al.1 showed that for a total atracurium dose of 0.5 mg/kg, but not 0.4 mg/kg, a divided-dose regimen provided more rapid maximal twitch suppression than did a bolus injection of the same dose. These and other studies6-8 evaluated the ease of endotracheal intubation following various schedules of atracurium administered in doses that exceeded the ED95 for this drug.5 Such large doses may obscure possible interactions between the divided doses because they result in effects that are at the extreme of the dose-response curve.

These studies reflect the recent interest in developing an alternative to succinylcholine for achieving muscle relaxation to aid in rapid endotracheal intubation.9 As previously described for pancuronium,10 larger doses of atracurium produce a more rapid onset of maximal neuromuscular block4,5,7,8 and conditions conducive to endotracheal intubation.7,8 However, a single injection of 1 mg/kg succinylcholine results in a more rapid onset of neuromuscular block than does a single bolus injection of atracurium 0.6 mg/kg (a dose three times its ED95).5,6

Gergis et al.1 first used, and Foldes5 later formulated, the “priming principle” in an attempt to accelerate the response to nondepolarizing relaxants. This strategy employs a small “priming” dose of competitive muscle relaxant to provide a degree of receptor blockade that is subclinical by virtue of the “margin of safety” of neuromuscular transmission,11 yet in effect sensitizes the neuromuscular junction to subsequent doses of relaxant.

Recent reports15,16 and an editorial on this topic17 support the use of the “priming principle” in the clinical practice of anesthesiology. This phenomenon may apply to all nondepolarizing relaxants; it is reported to facilitate neuromuscular blockade and tracheal intubation when used with atracurium,1,3 vecuronium,1,12,15 alcuronium,13 or pancuronium.14,16

Foldes predicted,5 and it was later shown,2,12,15 that such pretreatment also would diminish the total dose required for a given degree of neuromuscular block, implying that the effect of pretreatment is more than simply additive. However, these studies employed total relaxant doses in excess of the ED95 and thereby produced a degree of blockade that diminished the ability to discriminate subtle, possibly nonarithmetic, drug effects.

We chose a smaller total dose of atracurium, 0.15 mg/kg, so that the resultant neuromuscular block was on the steep slope of the neuromuscular dose-response curve, thereby designing our experiment specifically to detect subtle alterations of neuromuscular block engendered by pretreatment. The maximal neuromuscular block (73 and 74%) achieved with atracurium 0.15 mg/kg in the two groups in our study is in agreement with previously reported values for the ED95 of atracurium,9 and this dose provides a sensitive measure of the effects of a cumulative dose regimen. Our results show a more rapid onset of initial twitch depression following the second dose in a divided dose regimen without significant differences in the intensity, time to maximal neuromuscular block, or duration of neuromuscular block produced by single or combined doses of atracurium.

Direct application or extrapolation of these results to clinical situations employing larger relaxant doses may not be justified, since the dose-response curves for atracurium at high and low total doses may not be parallel. However, our data are consistent with an additive mechanism for the “priming” phenomenon and do not support
the notion of synergy or true sensitization of the neuromuscular junction by a small pretreatment dose of atracurium.

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Anesthesiology
64:113–115, 1986

Hypoxia Following Tricuspid Valve Resection

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Hypoxia after cardiopulmonary bypass (CPB) may result from a variety of causes, such as pulmonary edema from cardiac or noncardiac causes, excessive secretions, endotracheal tube malpositioned in a main stem bronchus, and equipment malfunction. We recently observed an unusual case of hypoxia associated with tricuspid valve resection.

REPORT OF A CASE

The patient is a 41-year-old man admitted for IV antibiotic treatment of subacute bacterial endocarditis (SBE) involving the tricuspid valve. Because this was refractory to optimal antibiotic therapy, a tricuspid valvectomy was scheduled. History was significant for intravenous drug abuse of cocaine and heroin over many years and no prior cardiac history or symptoms. Traumatic amputation of the left arm occurred several years before admission. Physical examination revealed a cachectic patient, lying flat in no acute distress. His weight was 55 kg, arterial blood pressure (BP) 110/80 mmHg, central venous pressure (CVP) 14 mmHg, heart rate 120 beats/min and regular, and temperature 38.8°C. There was no significant "V" wave on the CVP tracing. There was jugular venous distention of 3–4 cm at 30 degrees and on auscultation of the heart there was an apical systolic ejection murmur and soft S1. The lungs were clear. The remainder of the physical examination was within normal limits. On echocardiogram there was tricuspid insufficiency and extensive vegetations on the valve. A chest roentgenogram showed increased interstitial markings. Preoperatively pH was 7.46, PaO2 74 mmHg, PaCO2 29 mmHg, HCO3 17 mEq/L, and oxygen saturation 99% (room air) (table 1). Serum electrolytes and coagulation profile were within normal limits. The patient was pre-