NEOSTIGMINE AND EDROPHONIUM ANTAGONISM OF MODERATE NEUROMUSCULAR BLOCK INDUCED BY PANCRURONIUM OR TUBOCURARINE

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SUMMARY

Edrophonium and neostigmine are anticholinesterase drugs used commonly to antagonize competitive neuromuscular block. Although it has a faster onset of action than neostigmine, edrophonium is unreliable when used to antagonize deep neuromuscular block. We have compared the antagonist characteristics of these two drugs when used to antagonize a moderate degree of pancuronium- or tubocurarine-induced neuromuscular block. Forty ASA I or II patients undergoing surgical procedures were allocated randomly to receive either pancuronium 70 μg kg⁻¹ or tubocurarine 0.5 mg kg⁻¹, and to receive either edrophonium 0.5 mg kg⁻¹ or neostigmine 0.05 mg kg⁻¹. Antagonism was attempted when the first response to train-of-four (TOF) stimulation recovered spontaneously to 25% of the control height. Neuromuscular function was monitored using the evoked integrated electromyogram of the first dorsal interosseous muscle of the hand. Adequate recovery was defined as the achievement of a TOF ratio of 0.70 or greater. Under the conditions described in this study, edrophonium 0.5 mg kg⁻¹ was less effective as an antagonist than neostigmine 0.05 mg kg⁻¹. (Br. J. Anaesth. 1993; 70: 160-162)

KEY WORDS


The role of edrophonium in the antagonism of non-depolarizing neuromuscular block is uncertain. Its potential advantages include a faster onset of action (which, unlike neostigmine, makes it feasible to titrate dose to effect) and a lower requirement for anticholinergic drugs [1, 2]. In the presence of profound neuromuscular block (single twitch height < 10% of control height) these advantages appear to be offset by the inadequacy of the degree of recovery [3].

Intraoperative neuromuscular monitoring using a peripheral nerve stimulator is now widely practised and may be used reliably to differentiate between profound and moderate degrees of neuromuscular block. The effectiveness of edrophonium as an antagonist, when used at the lesser degree of neuromuscular block, is unclear. In order to examine this question, we attempted antagonism of a moderate degree of neuromuscular block (when the first response of TOF recovered spontaneously to 25% of the control height). Adequate antagonism was defined as the achievement of a train-of-four (TOF) ratio of 0.70 or greater. Our objective, therefore, was to compare edrophonium 0.5 mg kg⁻¹ with neostigmine 0.05 mg kg⁻¹ as antagonists of a moderate degree of neuromuscular block.

PATIENTS AND METHODS

After obtaining written informed consent and Institutional Ethics Committee approval, we studied 40 ASA I or II surgical patients undergoing elective surgery. Patients with neuromuscular disease or those receiving medication known to influence neuromuscular function were excluded.

Anaesthesia was induced with thiopentone 3-5 mg kg⁻¹ and fentanyl 1-3 μg kg⁻¹ and maintained with 66% nitrous oxide in oxygen, and increments of fentanyl, thiopentone, or both, as indicated clinically. Oral tracheal intubation was facilitated using pancuronium 70 μg kg⁻¹ (n = 20) or tubocurarine 0.5 mg kg⁻¹ (n = 20) according to random allocation.

The evoked integrated electromyogram (EMG) of the first dorsal interosseous muscle of the hand in response to supramaximal ulnar nerve TOF stimulation at 2 Hz was recorded and repeated once every 20 s using a Datex 221 NMT monitor. Two stimulating surface electrodes were placed over the ulnar nerve at the wrist and a sensing electrode placed over the belly of the first dorsal interosseous muscle with the reference electrode over the base of the proximal phalanx of the index finger. The ground electrode was placed at the wrist between the stimulating and recording electrodes. The monitored hand was immobilized in a fist-like position and enclosed in a plastic bag to minimize heat loss. An EMG control response was obtained after induction of anaesthesia when the eyelid reflex was abolished.


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When the first response of TOF recovered spontaneously to 25% of the control height, neuromuscular block was antagonized using either neostigmine 0.05 mg kg\(^{-1}\) or edrophonium 0.5 mg kg\(^{-1}\) according to random allocation.

The times from antagonism to recovery of first twitch height to 75% and 90% of the control value were measured, as were the TOF ratios corresponding to each of these levels of recovery. The times at which the TOF ratio reached 0.70 were also recorded if this occurred within 30 min of antagonism. Neuromuscular monitoring was discontinued either when the TOF ratio reached 0.70 or when 30 min had elapsed after antagonism.

The frequencies of adequate recovery were compared using two-tailed Fisher's exact test. Times to recovery of first twitch height to 75% and 90% of control and the corresponding TOF ratios were analysed using Friedman's analysis of variance (ANOVA on ranks) and Student's t test. \(P < 0.05\) was taken to be significant.

**RESULTS**

The patient characteristics were similar in the four groups studied (table I). A Friedman ANOVA

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Sex (M:F)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium-neostigmine</td>
<td>46.9 (22-79)</td>
<td>9:1</td>
<td>71.7 (11.6)</td>
</tr>
<tr>
<td>Pancuronium-edrophonium</td>
<td>46.3 (26-68)</td>
<td>8:2</td>
<td>67.7 (18.8)</td>
</tr>
<tr>
<td>Tubocurarine-neostigmine</td>
<td>35.4 (29-61)</td>
<td>7:3</td>
<td>68.3 (22.6)</td>
</tr>
<tr>
<td>Tubocurarine-edrophonium</td>
<td>44.2 (21-65)</td>
<td>9:1</td>
<td>70.3 (11.7)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Our results indicate that, even when the depth of neuromuscular block is moderate and spontaneous recovery is well established, edrophonium 0.5 mg kg\(^{-1}\) is an unreliable antagonist of either pancuronium- or tubocurarine-induced neuromuscular block. Of 20 patients in whom antagonism was attempted using edrophonium, only seven demonstrated adequate recovery within 30 min. Eighteen of 20 patients in whom an equipotent dose of neostigmine was used demonstrated adequate recovery within 15 min. The insignificant \(P\) value (0.14), obtained using the ANOVA on ranks for antagonist effect on the time to reach a TOF ratio of 0.70 after antagonism is misleading. This occurred because patients who received edrophonium achieved TOF ratio = 0.70 either very rapidly or not at all (within the 30-min post-antagonism study period). Therefore, patients in the edrophonium group were ranked either very low or very high in terms of time to reach TOF ratio = 0.70, with a resultant cancelling effect.

Early investigations of edrophonium as an antagonist of non-depolarizing neuromuscular block indicated that it was unpredictable and that, because
of its short duration of action, it was associated with recurvarization [4]. When used to antagonize tubocurarine-induced neuromuscular block, edrophonium 10–20 mg initially produced a prompt increase in twitch height followed by a return of the recovery slope to pre-antagonism [5].

A subsequent investigation indicated that edrophonium, used in a larger bolus of 0.7 mg kg\(^{-1}\), was an effective ant curarirre agent [6]. Independent work by Kopman [7] supported this finding, but emphasized the importance of the degree of neuromuscular block at which antagonism was attempted. It was concluded that, provided four detectable responses to TOF stimulation were present, edrophonium produced adequate and sustained recovery.

Reports followed to suggest the adequacy of edrophonium as an antagonist in a dose of 0.5 mg kg\(^{-1}\) or greater. Edrophonium 50–100 mg/70 kg was found to be effective in antagonizing pancuronium-induced neuromuscular block at 10% recovery of muscle twitch [8]. At equiantagonistic doses, the duration of action of edrophonium was equal to that of neostigmine (0.5 mg kg\(^{-1}\) and 0.043 mg kg\(^{-1}\), respectively) [1]. It was pointed out, however, that, as the dose–response curve of edrophonium was not parallel to those for neostigmine and pyridostimine, the relative potencies of the drugs would change with the degree of neuromuscular block at the time of administration. When neostigmine or edrophonium was used to antagonize atracurium-induced neuromuscular block of similar degree, adequate recovery (TOF ratio > 0.70) was demonstrable in all patients who received neostigmine 0.05 mg kg\(^{-1}\), but in only 13 of 20 in whom edrophonium 0.5 mg kg\(^{-1}\) was used [9].

By 1986, it was apparent that edrophonium might be used successfully under certain circumstances only. Rupp and colleagues [10] compared edrophonium with neostigmine as antagonists of profound (single twitch ≤ 10%) and mild or moderate (single twitch > 10%) neuromuscular block. These authors concluded that the dose equivalent to neostigmine 0.04 mg kg\(^{-1}\), was edrophonium 1.0 mg kg\(^{-1}\) for profound block and 0.5 mg kg\(^{-1}\) for mild or moderate block. The shortcomings of this work, however, have been noted previously, in particular the small doses of neuromuscular blockers used and the fact that adequacy of antagonism was determined as the point at which the single twitch recovered to 90% of control [11]. The present study contradicts the findings of Rupp’s groups that mild to moderate neuromuscular block was equally and effectively antagonized with both edrophonium 0.5 mg kg\(^{-1}\) and neostigmine 0.04 mg kg\(^{-1}\). Although the dose of neostigmine in our study (50 µg kg\(^{-1}\)) was greater than that used by Rupp’s group, we consider it unlikely that this difference accounts for the discrepancy in these results. We consider it more likely that the return of single twitch height to 90% of control does not truly reflect adequate recovery.

Comparing edrophonium 0.5 mg kg\(^{-1}\) and neostigmine 0.04 mg kg\(^{-1}\) as antagonists of pancuronium-induced moderate neuromuscular block, Sanfilippo and colleagues [12] demonstrated that adequate antagonism using the former was inconsistent. However, these authors administered a smaller initial dose of pancuronium (0.05 mg kg\(^{-1}\)) after recovery from suxamethonium 1 mg kg\(^{-1}\). Under these circumstances, a prolonged non-depolarizing block with pancuronium has been demonstrated [13]. We used a greater initial dose of pancuronium (70 µg kg\(^{-1}\)) to facilitate intubation in order to avoid this complicating factor.

Even when it is attempted to antagonize a moderate degree of neuromuscular block induced by pancuronium or tubocurarine, edrophonium 0.5 mg kg\(^{-1}\) is an inadequate antagonist. Thus we conclude that, in most situations, its relatively minor advantages are outweighed by this important factor.

REFERENCES