DOSE-RESPONSE RELATIONSHIPS FOR NEOSTIGMINE ANTAGONISM OF VECURONIUM-INDUCED NEUROMUSCULAR BLOCK IN ADULTS AND THE ELDERLY

G. J. McCarthy, R. Cooper, J. C. Stanley and R. K. Mirakhur

SUMMARY
We have studied the dose-response relationship for neostigmine in 36 adult (ages 18-50 yr) and 36 elderly (ages > 70 yr) subjects during antagonism of neuromuscular block induced by vecuronium. All patients received vecuronium 0.08 mg kg\(^{-1}\) and neuromuscular block was monitored mechanomyographically using the train-of-four (TOF) mode of stimulation. Six patients of each age group were allocated randomly to receive neostigmine 5, 15, 25, 35 or 45 \(\mu\)g kg\(^{-1}\) or saline at 10\% recovery of T1 (first response in the TOF). TOF ratios were recorded continuously over the next 10 min and the values at 1-min intervals from 5 min onwards were used to construct the dose-response relationships. There was a significant difference (P < 0.05) in the time to spontaneous recovery of T1 to 10\% between the adults (24 (sd 5.5) min) and the elderly (33 (7.8) min). Dose-response curves for neostigmine were parallel in the two age groups, but those for the elderly were significantly to the right of the curves for the adults. This suggests an apparently lesser relative potency of neostigmine, or the requirement of a larger dose, in the elderly for antagonism of a moderately intense vecuronium block at the same time as in adults.

KEY WORDS

Achieving adequate antagonism of neuromuscular block depends on several factors, such as the degree of block present at antagonism, the anticholinesterase used, and its dose [1, 2]. For neostigmine, it has been suggested that its pharmacodynamic responses are similar in the young and the old [3]. However, such studies have been conducted mostly during steady state neuromuscular block maintained by a continuous infusion of the neuromuscular blocking drug, which is not the case in routine clinical practice. In this study we have assessed the dose-response relationship of neostigmine when used to antagonize neuromuscular block induced by a bolus dose of vecuronium in adult and elderly subjects.

PATIENTS AND METHODS
After obtaining informed consent and the approval of the Research Ethics Committee, we studied 36 adult (aged 18-50 yr) and 36 elderly (aged more than 70 yr) patients of ASA grades I or II undergoing elective ophthalmic surgery. Patients with obesity (weighing more than 25\% of ideal adjusted for height), renal or hepatic impairment, or receiving any medication known to interact with neuromuscular blocking drugs were excluded. Premedication comprised oral diazepam 5-10 mg administered 90 min before operation. Anaesthesia was induced with thiopentone 3-5 mg kg\(^{-1}\) and fentanyl 1-3 \(\mu\)g kg\(^{-1}\), and maintained with 70\% nitrous oxide in oxygen, halothane 1.5 MAC (end-tidal, adjusted for age: 0.45\% in adults and 0.3\% in the elderly) and increments of fentanyl 1 \(\mu\)g kg\(^{-1}\) as required. Heart rate, indirect arterial pressure, oxygen saturation and end-tidal carbon dioxide concentration were monitored routinely in all patients. The temperature over the adductor pollicis muscle was monitored to ensure a skin temperature of greater than 33\°C. Ventilation was adjusted to end-tidal carbon dioxide concentrations of 4.5-5.0\%.

The ulnar nerve was stimulated percutaneously at the wrist after the induction of anaesthesia, with supramaximal stimuli of 0.2 ms duration, in a train-of-four (TOF) mode at 2 Hz every 12 s. The resultant force of contraction of the adductor pollicis muscle was measured and recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd).

After stabilization of control responses for 10 min, all patients received vecuronium 0.08 mg kg\(^{-1}\) as a single bolus. When T1 (first response in the TOF) had recovered spontaneously to 10\% of control, six patients in each age group were allocated randomly to receive neostigmine 5, 15, 25, 35 or 45 \(\mu\)g kg\(^{-1}\) or normal saline. All solutions were diluted to the same volume (5 ml) and were administered with an appropriate dose of glycopyrronium. The TOF ratios were recorded continuously over the subsequent 10 min, at which point the study was terminated. Additional anticholinesterase was administered if required, ventilation was continued, or both, until a TOF of greater than 70\% had been obtained.

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The results were subjected to arc—sine transformation and dose—response curves constructed at each 1 min from 5 min onwards, after regression analysis. Analysis of variance, analysis of covariance, and t tests were used to assess the statistical significance of the results.

RESULTS

The physical characteristics of the patients are shown in table I. The average age of the young patients was 32 yr and that of the elderly, 78 yr. The time taken for spontaneous recovery to T1 of 10% of control was significantly longer in the elderly compared with the adults (33 (7.8) min vs 24 (5.5) min) (P < 0.05).

TABLE I. Age, weight and recovery of vecuronium block (mean (range or SD))

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32 (18–50)</td>
<td>78 (70–89)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 (11)</td>
<td>62 (9)</td>
</tr>
<tr>
<td>Time to recovery</td>
<td>24 (5.5)</td>
<td>33 (7.8)</td>
</tr>
<tr>
<td>of T1 to 10% (min)</td>
<td></td>
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</tbody>
</table>

TABLE II. Mean (sd) TOF ratios at 1-min intervals after administration of saline and different doses of neostigmine in adult patients. —= No TOF ratio present

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose of neostigmine (µg kg⁻¹)</td>
</tr>
<tr>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>3 (10)</td>
</tr>
<tr>
<td>3</td>
<td>5 (8)</td>
</tr>
<tr>
<td>4</td>
<td>10 (8)</td>
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<tr>
<td>5</td>
<td>15 (4)</td>
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<tr>
<td>6</td>
<td>25 (4)</td>
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<tr>
<td>7</td>
<td>30 (10)</td>
</tr>
<tr>
<td>8</td>
<td>35 (10)</td>
</tr>
<tr>
<td>9</td>
<td>40 (8)</td>
</tr>
<tr>
<td>10</td>
<td>45 (8)</td>
</tr>
</tbody>
</table>

TABLE III. Mean (sd) TOF ratios at 1-min intervals after administration of saline and different doses of neostigmine in the elderly patients. —= No TOF ratio present

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 (10)</td>
</tr>
<tr>
<td>2</td>
<td>10 (9)</td>
</tr>
<tr>
<td>3</td>
<td>16 (6)</td>
</tr>
<tr>
<td>4</td>
<td>20 (7)</td>
</tr>
<tr>
<td>5</td>
<td>24 (7)</td>
</tr>
<tr>
<td>6</td>
<td>28 (6)</td>
</tr>
<tr>
<td>7</td>
<td>34 (6)</td>
</tr>
<tr>
<td>8</td>
<td>38 (10)</td>
</tr>
<tr>
<td>9</td>
<td>43 (10)</td>
</tr>
<tr>
<td>10</td>
<td>47 (12)</td>
</tr>
</tbody>
</table>

Increasing doses of neostigmine were associated with faster recovery in both adult and elderly groups, as shown by greater TOF ratios (tables II, III). TOF ratios up to 5 min were small in patients receiving the placebo, indicating little spontaneous recovery. The TOF ratios were generally greater and the recovery apparently faster with every dose of neostigmine in adults compared with the elderly. Doses of neostigmine 25 µg kg⁻¹ or less did not achieve satisfactory antagonism by 10 min from this intensity of block, particularly in the elderly (tables II, III).

Although dose—response curves were constructed from 5 min onwards, only the representative curves for the TOF responses at 10 min are shown in figure 1. These were parallel, but the curve for the elderly was significantly to the right of that for the adults. The time of 5 min onwards was chosen because antagonism before this time was generally inadequate. The estimated doses required for a TOF ratio of 70% (ED₇₀%TOF) from 5 min onward are given in table IV. The dose of neostigmine required for this end-point was significantly greater in the elderly at each time point. Obviously the dose of

![Fig. 1. Dose—response curves at 10 min for TOF ratios after administration of neostigmine in adults and the elderly. Individual points represent mean TOF ratios attained with each dose and the bars represent sd.](image-url)
NEOSTIGMINE IN THE ELDERLY

Table IV. Estimated dose of neostigmine for attaining a TOF ratio of 70% (ED$_{70}$) within 5–10 min, in adults and the elderly (95% confidence limits in parentheses). *P < 0.05 compared with adults.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Estimated dose (µg kg$^{-1}$)</th>
<th>Adults</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>41 (31–56)</td>
<td>58 (44–75)*</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>36 (27–49)</td>
<td>48 (38–60)*</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>30 (23–38)</td>
<td>42 (34–52)*</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>26 (20–34)</td>
<td>37 (31–45)*</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>22 (14–25)</td>
<td>34 (28–40)*</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>19 (14–25)</td>
<td>31 (26–37)*</td>
<td></td>
</tr>
</tbody>
</table>

Neostigmine required decreased with increasing time, being 41 µg kg$^{-1}$ and 58 µg kg$^{-1}$ at 5 min in the adults and elderly, respectively, decreasing to 19 µg kg$^{-1}$ and 31 µg kg$^{-1}$, respectively, at 10 min for attaining a TOF ratio of 70%.

DISCUSSION

The present study, which was designed to assess age-related changes in the dosage of neostigmine, has shown that a greater dose of neostigmine was required in the elderly than in the young to produce adequate antagonism of vecuronium-induced neuromuscular block.

The antagonism of neuromuscular block depends on the degree of block present before antagonism, the neuromuscular blocker used, the type and dose of anticholinesterase administered and the time allowed for antagonism to occur. It is not clear if it is also related to age. In this study we examined the period between 5 and 10 min for antagonism to occur, as this is a clinically relevant time. Clearly, if enough time were allowed, there would be no need to administer an anticholinesterase, because of spontaneous recovery. For neostigmine, it has been reported that doses as small as 1.25 mg are capable of producing TOF ratios of 70% from a T1 of 10% in adults within 10 min [4]. The estimated ED$_{70}$% of 19 µg kg$^{-1}$ (approximately 1.25 mg) derived from our dose–response data at 10 min in an average adult weighing 65 kg is in keeping with this report. The corresponding dose requirement in the elderly was, however, significantly greater—31 µg kg$^{-1}$. This gave a relative potency of neostigmine of 1:1.6 at 10 min in the young and the elderly, respectively, under the conditions of our study.

Previous workers reported no significant age related difference in dose requirements of neostigmine for the elderly [3]. Neostigmine exhibited a prolonged duration of maximum response in the elderly compared with the young, although plasma concentrations of the drug for a given effect were not significantly different [3, 5]. These studies, however, ignored the effect of spontaneous recovery as they used continuous background infusion of the neuromuscular blocker. Although theoretically appropriate, this is clearly not the situation in routine clinical practice when antagonism is attempted against a background of decreasing paralysis, particularly with the use of intermediate acting drugs in single doses.

The rate of concurrent spontaneous recovery is likely to be an important factor during neostigmine-induced antagonism of single doses of drugs with an intermediate duration of action such as vecuronium. The difference in the dose of neostigmine observed in the present study between the two age groups may be caused by the different rates of spontaneous recovery from vecuronium. This is supported by the observation of a significantly longer time to recovery of T1 to 10% in the elderly in the present study and the previously reported longer duration of action and slower rate of recovery of vecuronium, based on its reduced rate of clearance, in the elderly [6–8]. Further evidence for this is provided by the observation of greater TOF ratios, when present in adult subjects who received no neostigmine, compared with the elderly (fig. 1). However, in view of the parallel dose–response curves, there appears to be no difference in the mode or site of action of neostigmine in the two age groups.

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REFERENCES