Is recovery of neuromuscular transmission complete after the use of neostigmine to antagonize block produced by rocuronium, vecuronium, atracurium and pancuronium?

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Summary
To test if recovery of neuromuscular transmission is complete after the use of neostigmine under standardized conditions, we have measured adductor pollicis mechanical activity in response to 0.1 Hz (twitch height), train-of-four (TOF) and 100 Hz (RF 100 Hz) ulnar nerve stimulations. We studied 56 adult anaesthetized (thiopentone, fentanyl, nitrous oxide in oxygen) patients, allocated randomly to one of four groups (n=14) to receive rocuronium (group Roc), vecuronium (group Vec), atracurium (group Atr) or pancuronium (group Pan). Recovery of neuromuscular transmission was studied for 15 min after neostigmine 40 μg kg⁻¹ was given at 25% recovery of twitch height. Fifteen minutes after antagonism, the TOF ratio was 0.91 (SEM 0.01), 0.88 (0.02) and 0.92 (0.01) (ns), and RF 100 Hz was 0.78 (0.01), 0.79 (0.02) and 0.78 (0.01) (ns) respectively, in patients in groups Roc, Vec and Atr, respectively. In patients in group Pan, TOF ratio and RF 100 Hz were only 0.76 (0.01) and 0.33 (0.04) respectively (P<0.01, one-way analyses of variance, Duncan’s multiple classification range tests). In contrast with pancuronium, antagonism of rocuronium-, vecuronium- and atracurium-induced neuromuscular blocks produced a similar high degree of recovery of neuromuscular transmission. (Br. J. Anaesth. 1996;77:496–499)

Key words

In normal patients receiving medium duration neuromuscular blocking agents (rocuronium³⁻⁷, vecuronium, atracurium) a TOF ratio of 0.7 is currently obtained after administration of neostigmine given at a twitch height of 10−25%, but even for vecuronium, data related to a TOF ratio of 0.9 are still scarce⁸⁻¹².

In addition to the 2 Hz TOF stimulation pattern, the use of high stimulation rates, especially 100 Hz tetanic stimulation, to quantify recovery of neuromuscular transmission may be desirable because of the TOF ratio limitations for detection of residual neuromuscular block in many clinical situations⁸⁻¹². In normal awake patients also, firing rates of approximately 100 Hz are often observed in different muscle types¹⁳.

The purpose of this study was to assess the level of recovery of neuromuscular transmission 15 min after administration of neostigmine 40 μg kg⁻¹ with atropine 15 μg kg⁻¹ in patients receiving rocuronium, vecuronium, atracurium and pancuronium.

Patients and methods
After obtaining approval from the hospital Ethics Committee for Human Research and written informed consent, we studied 56 young, healthy adult patients, ASA I and II, undergoing elective lower limb surgery. None had clinical or routine biochemical evidence of hepatic or renal damage. All were devoid of neuromuscular disease and drugs that are known to interfere with neuromuscular transmission.

Patients received lorazepam 0.2 mg kg⁻¹ orally, 1 h before anaesthesia, which was induced with thiopentone 3−5 mg kg⁻¹ i.v. After loss of consciousness, ventilation was controlled manually (with 50% nitrous oxide in oxygen). The trachea was intubated after i.v. administration of one of the four neuromuscular blockers. Thereafter, ventilation was controlled mechanically (open circuit, 65% nitrous oxide in oxygen) and adjusted to produce an end-tidal carbon dioxide partial pressure of 4.4 (0.3) kPa. For maintenance of anaesthesia, patients received fentanyl 5 μg

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Effective use of neostigmine in antagonizing neuromuscular block

kg\textsuperscript{-1} and dehydrobenzperidol 100 μg kg\textsuperscript{-1} i.v., followed by bolus doses of fentanyl 2 μg kg\textsuperscript{-1} if there was clinical evidence of inadequate analgesia. Heat loss from the body surface and the arms was controlled by the use of a water warming mattress (autoregulation on 37 °C rectal temperature) and surgical sheets (monitored hypothenar temperature greater than 35 °C).

To measure isometric contraction of the adductor pollicis, a force displacement transducer (UC3 cell Statham TM), fitted with tension attenuator (ULE-20, Statham TM) and incorporated in a hand grip, was preloaded to 100 g and secured with adhesive tape onto the patient’s left hand. Mechanical activity of the adductor pollicis was induced by square wave pulses of 0.2 ms duration at supramaximal intensity, delivered at 0.1 Hz from an Organon Teknika Digit-Stim III TM stimulator, via two paediatric surface electrodes placed near the ulnar nerve at the wrist. The resulting analogue signals were amplified and recorded. Skin thenar temperature was measured with a surface electrothermometer (YSI 409B TM).

The 56 patients were allocated randomly to one of four groups of 14 patients each to receive rocuronium (group Roc), vecuronium (group Vec), atracurium (group Atr) or pancuronium (group Pan). After a 5-min recording of control twitch height, 100 Hz, 5-s duration was assessed and control RF 100 Hz was measured during thiopentone–nitrous oxide in oxygen anaesthesia, but in the absence of neuromuscular blocker. When twitch height had regained its control value, rocuronium 600 μg kg\textsuperscript{-1}, vecuronium 100 μg kg\textsuperscript{-1}, atracurium 500 μg kg\textsuperscript{-1} or pancuronium 80 μg kg\textsuperscript{-1} was given i.v. Thereafter, to achieve a neuromuscular block of about 1 h, when twitch height had spontaneously regained 25% of control, patients received two additional doses of rocuronium 120 μg kg\textsuperscript{-1} (group Roc), vecuronium 20 μg kg\textsuperscript{-1} (group Vec), atracurium 100 μg kg\textsuperscript{-1} (group Atr), while in group Pan, patients received only an initial dose of pancuronium 80 μg kg\textsuperscript{-1}.

The 56 randomized patients received atropine 15 μg kg\textsuperscript{-1} mixed with neostigmine 40 μg kg\textsuperscript{-1} at the end of the surgical procedure, exactly when twitch height had spontaneously regained 25% of control. Thereafter, twitch height (every 10 s) and TOF ratio (2 Hz, every 3 min) were measured for 15 min in the four groups. Immediately after the TOF ratio at 15 min, 100 Hz tetanic stimulation, 5-s duration, was assessed. Residual force after 100 Hz tetanic stimulation (RF 100 Hz) was calculated as the ratio between tension at the end of the 5-s stimulation period and maximum response registered. Statistical analysis of the data was performed using one-way analysis of variance\textsuperscript{14}. In case of significant differences observed by ANOVA, Duncan’s multiple classification range tests were performed to indicate the best recovery scores.

**Results**

There were no significant differences between patients in the four groups in terms of their characteristics (table 1). Mean age of all patients was 37 (range 18–58) yr, mean weight 73 (SEM 2) (53–108) kg and mean height 174 (1) (154–194) cm (n = 56) (table 1). Mean clinical duration of neuromuscular block (time elapsed from maximum block achieved after the initial dose of neuromuscular blocker to administration of neostigmine) was 69 (SEM 3) min for all patients (n = 56), and 68 (5) (range 43–86) min, 67 (6) (42–96) min, 70 (6) (44–100) min and 68 (6) (45–130) min in patients in groups Roc, Vec, Atr and Pan, respectively (table 1). Control RF 100 Hz during thiopentone–nitrous oxide in oxygen anaesthesia under normothermal conditions (cutaneous hypothenar temperature greater than 35 °C), but in the absence of neuromuscular blockers, was 0.9 (0.003) (0.85–0.95) (n = 56).

At the time of antagonism, when twitch height had regained 25% of its control value, mean TOF ratio was 0.07 (0.003) for all patients (range 0.02–0.14) and there were no significant differences between the four groups (fig. 1). Evolution of the TOF ratios were similar in patients who received rocuronium 840 μg kg\textsuperscript{-1}, vecuronium 140 μg kg\textsuperscript{-1} and atracurium 700 μg kg\textsuperscript{-1}, except that the TOF ratio was significantly higher (0.68 (0.03); P < 0.05) 3 min after neostigmine 40 μg kg\textsuperscript{-1} in patients who received vecuronium compared with those who received rocuronium (0.57 (0.03)) and atracurium (0.56 (0.03)). Fifteen minutes after administration of neostigmine, TOF ratios were 0.91 (0.01) (range 0.81–0.95), 0.88 (0.02) (0.71–0.99) and 0.92 (0.01) (0.87–0.95) in groups Roc, Vec and Atr, respectively (fig. 1). In con-

**Table 1** Patients characteristics (mean (SEM) [range]). Clinical duration of block = time elapsed from maximum block achieved after the initial dose of neuromuscular blocker to administration of neostigmine

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Clinical duration of block (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roc</td>
<td>38</td>
<td>75 (3)</td>
<td>176 (2)</td>
<td>68 (5) [43–86]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[20–56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vec</td>
<td>39</td>
<td>70 (3)</td>
<td>170 (2)</td>
<td>67 (6) [42–96]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[18–58]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atr</td>
<td>35</td>
<td>76 (4)</td>
<td>174 (2)</td>
<td>70 (6) [44–100]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[18–57]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan</td>
<td>37</td>
<td>73 (3)</td>
<td>174 (3)</td>
<td>68 (5) [45–130]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[27–47]</td>
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</tbody>
</table>

Figure 1 Evolution of the train-of-four (TOF) ratio (mean) recorded at 3-min intervals after administration of neostigmine 40 μg kg\textsuperscript{-1} when twitch height had returned to 25% of its initial value in groups Roc (■), Vec (○), Atr (●) and Pan (□). *P < 0.05, one-way analysis of variance and Duncan multiple classification range tests (group Vec vs groups Roc and Atr). **P < 0.01, one-way analysis of variance and Duncan multiple classification range tests (group Pan vs groups Vec, Roc, Atr).
trast, during the 15-min period after administration of atropine–neostigmine, TOF ratios were always lower ($P<0.01$) in patients who received pancuronium 80 $\mu$g kg$^{-1}$ (fig. 1). At 15 min, the TOF ratio was 0.76 (0.01) (0.67–0.86) (fig. 1). Fifteen minutes after administration of neostigmine, mean values for RF 100 Hz were similar in groups Roc, Vec and Atr: 0.78 (0.01) (0.71–0.85), 0.79 (0.02) (0.60–0.95) and 0.78 (0.01) (0.65–0.85), respectively. These values were much higher ($P<0.01$) than the RF 100 Hz of 0.33 (0.04) (0.09–0.65) measured in group Pan (fig. 2).

**Discussion**

Our results have confirmed previous data indicating that rocuronium, in common with vecuronium and atracurium, can be antagonized easily to an endpoint of a TOF ratio of 0.7 when neostigmine 40 $\mu$g kg$^{-1}$ is given at 25% recovery of control twitch height$^{8–12}$. But the “gold standard” of these authors (a TOF ratio of 0.7) does not imply complete recovery of neuromuscular transmission. Moreover, Eriksson and colleagues showed recently that the ventilatory response to hypoxaemia was decreased if the TOF ratio was reduced to 0.7 by vecuronium in awake volunteers, and that it returned to normal when the TOF ratio was 0.9$^{9,11}$. These results suggest that a TOF ratio of 0.9 may be considered as a new end-point for defining adequate recovery of neuromuscular transmission. In patients who received rocuronium, our data indicated that such a high (0.9) TOF ratio may be observed 15 min after administration of neostigmine 40 $\mu$g kg$^{-1}$ when twitch height has regained 25% of its initial value, in common with patients who received vecuronium and atracurium. In contrast, under the same conditions, a TOF ratio of only approximately 0.75 was observed in patients who received pancuronium.

RF 100 Hz mean values ranged from 0.8 to 0.9, associated with a TOF ratio of 0.9, and were also observed previously to antagonize vecuronium-induced block, 15 min after administration of neostigmine 40 $\mu$g kg$^{-1}$ at 25–50% twitch height$^{9,11,12}$. Mean values in patients who received rocuronium were as high (about 0.8) as in patients who received vecuronium and atracurium. In contrast with patients who received neuromuscular blockers of intermediate duration of action, the mean value for RF 100 Hz in patients in group Pan was only approximately 0.3, confirming the previously reported very high sensitivity of RF 100 Hz$^{9–12}$. The use of RF 100 Hz is important also because a small, but statistically significant and clinically important 0.15 TOF ratio difference is amplified by a factor of 3–4 for the compound investigated in this study. Moreover, our data were obtained in the absence of halogenated agents, which are known to potentiate neuromuscular blockers and impair antagonism of non-depolarizing neuromuscular blockers by anticholinesterases$^{15–19}$ by various mechanisms$^{20,22}$.

In the past, the response to 100 Hz tetanic stimulation was also observed by Kopman, Epstein and Flashburg in halothane anaesthetized patients$^{22}$. Pancuronium-induced block was antagonized when the TOF ratio was in excess of 0.1 with 5-mg increments of edrophonium until the TOF ratio exceeded 0.7. At a mean TOF ratio of 0.79, the mean value of the response to 100 Hz, 2 s tetanic stimulation, was very weak (0.28), indicating incomplete recovery of neuromuscular transmission when poor reversal conditions co-exist (long-acting neuromuscular blockers and sustained concentrations of halogenated agents).

When recovery of neuromuscular transmission was assessed by measuring the TOF ratio, neostigmine 36–50 $\mu$g kg$^{-1}$, given at 10% twitch height, produced a mean TOF ratio of approximately 0.7–0.8 after a 20–30-min period in fentanyl–nitrous oxide in oxygen anaesthetized patients and a TOF ratio of approximately 0.6 in enflurane–or halothane–nitrous oxide in oxygen anaesthetized patients$^{22,23}$. In contrast, in a previous study in humans, vecuronium and pancuronium were considered to be antagonized effectively and equally by neostigmine because the duration of the effect of neostigmine on twitch height recovery was not different$^{23}$. However, when assessing recovery of neuromuscular transmission, monitoring twitch height appears to be an insensitive test. Twitch height has little or no discriminating ability for the influence of pre-reversal twitch heights or edrophonium and neostigmine dose, or both, mainly because apparent antagonism by these measures is so complete$^{20,21}$. Whalley, Lewis and Bedocs showed also that equipotent doses of atracurium, compared with pancuronium, were not associated with a shorter time to complete recovery from neuromuscular block induced by pancuronium$^{21}$. In this study, all patients received an initial dose of pancuronium 0.1 mg kg$^{-1}$; no patient received only atracurium and complete recovery was defined by a TOF ratio of 0.7.

In patients receiving short-acting neuromuscular blockers such as mivacurium, neostigmine, given under the same clinical conditions, also accelerated recovery of the TOF ratio to 0.9. However, unlike the patients in this study who received medium-acting neuromuscular blockers, all patients obtained a TOF ratio of 0.9 within 15 min of administration of neostigmine, compared with 50% of patients during spontaneous recovery of mivacurium-induced block$^{26}$. The use of short-acting neuromuscular blockers such as mivacurium should probably make

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*Figure 2*  Values for residual force (RF) after 100 Hz tetanic stimulation (RF 100 Hz) recorded 15 min after administration of neostigmine 40 $\mu$g kg$^{-1}$ when twitch height had regained 25% of its initial value (mean, sem). **$P<0.01$, one-way analysis of variance, Duncan multiple classification range tests (group Pan vs groups Roc, Vec and Atr).
adequate or even complete antagonism an easier problem to solve in many patients.

References