Dose–response relationships for neostigmine antagonism of rocuronium-induced neuromuscular block in children and adults

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Summary

Dose–response relationships for the antagonism of intermediate-acting neuromuscular blocking agents have not been evaluated previously in children. We have examined the dose–response relationships for neostigmine antagonism of 90% rocuronium-induced neuromuscular block in children and adults, during nitrous oxide–1 MAC of isoflurane anaesthesia. We studied 40 children, aged 2–10 yr, and 50 adults, aged 18–60 yr; all received a single bolus dose of rocuronium 0.6 mg kg⁻¹ and accelerometry was used to monitor neuromuscular transmission. When the first twitch of the train-of-four (TOF) response (T1) recovered to 10% of its control (T0), one of five doses of neostigmine 0, 5, 10, 20 or 50 μg kg⁻¹ was given by random allocation to each of the study groups (n = 8 children and n = 10 adults). Recovery of T1 and TOF ratio (T4/T1%) was recorded for 10 min after initial administration of neostigmine. Onset time of rocuronium-induced block was faster in children than in adults (mean 64.6 (95% confidence intervals 57.7–71.5) s vs 83.7 (70.7–96.6) s; P < 0.05). The time to 10% recovery of T1/T0 was shorter in children than in adults (25.4 (22.9–27.9) min vs 38.8 (36.1–41.4) min; P < 0.001).

Spontaneous and antagonist-assisted recovery were more rapid in children than in adults. Adequate recovery (T4/T1 of 80%) occurred in children at 4, 5 and 8 min after neostigmine 50, 20 and 10 μg kg⁻¹, respectively. Adequate recovery was not produced in adults by any dose of neostigmine within 10 min. The effective doses of neostigmine required to achieve a TOF ratio of 80% (ED80) after 10 min in children and adults were, respectively, 7.10 (5.2–9.8) μg kg⁻¹ and 56.56 (45.5–71.9) μg kg⁻¹ (P < 0.001). There was no advantage in administering doses of neostigmine greater than 20 μg kg⁻¹ to antagonize 90% rocuronium-induced neuromuscular block in children. In contrast, it appeared prudent to use neostigmine 50 μg kg⁻¹ or more for adequate antagonism of a similar degree of block in adults. (Br. J. Anaesth. 1996; 77: 710–715)

Key words

In the past, there was an undocumented belief that higher doses of neostigmine were required for adequate antagonism of long-acting neuromuscular blocking drugs in children. Later dose–response studies, however, showed that the dose of neostigmine required to antagonize tubocurarine-, pancuronium- or doxacurium-induced blocks in children was in the range of 25–50% of the adult value. Also, in a recent dose–response study of mivacurium antagonism, Bevan and colleagues reported that, compared with adults, children had a very rapid rate of spontaneous recovery to the extent that 10 min after antagonism with edrophonium or neostigmine, recovery in children was not very different from spontaneous recovery. In a subsequent study, the same group proved that it was safe to omit antagonism at the end of mivacurium-induced neuromuscular block in children but not in adults.

Several dose–response studies have evaluated antagonism of intermediate-acting neuromuscular blocking drugs with anticholinesterases in adults. Single-dose studies of neostigmine antagonism of vecuronium-induced block have demonstrated that the rate of recovery is age-dependent, being more rapid in children than in infants and adults. However, single-dose comparisons between adults and children may be misleading and dose–response studies are a more appropriate alternative. To date, antagonist dose–response studies have not been carried out for intermediate-acting neuromuscular blocking agents in children. Therefore, this study was designed to construct and compare the dose–response curves for neostigmine antagonism of an equivalent degree of neuromuscular block induced by the recently introduced intermediate-acting non-depolarizing neuromuscular blocker, rocuronium, in children and adults under similar anaesthetic conditions.

Patients and methods

We studied 40 children, aged 2–10 yr (mean 5.3 yr) and weighing 10–30 kg (mean 18.4 (SD 5.5) kg) and 50 adults aged 18–60 yr (mean 31.8 yr) and weighing 45–89 kg (mean 64.8 (9.8) kg), ASA I or II. All...
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patients were undergoing low-risk elective surgery. This study was approved by the hospital Ethics Committee and all children’s guardians and adult patients gave written informed consent. We excluded any patient suffering from cardiac, vascular, respiratory, hepatic, renal, neuromuscular disorders or small joint arthritis. Patients receiving medications known or suspected to affect normal neuromuscular transmission were also excluded.

All children were premedicated with midazolam 0.5 mg kg\(^{-1}\) orally, 20–30 min before surgery. Adult patients were premedicated with diazepam 10–15 mg orally, approximately 90 min before surgery. In the operating room, an i.v. infusion of warm 5% glucose in half normal saline solution was given at a rate of 4–6 ml kg\(^{-1}\) h\(^{-1}\) via a peripheral arm vein. The ECG was monitored continuously and arterial pressure was measured every 5 min. Anaesthesia was induced with propofol 3–5 mg kg\(^{-1}\) in children and with 2–3 mg kg\(^{-1}\) in adults, and alfentanil 20 \(\mu\)g kg\(^{-1}\). Tracheal intubation was performed without the use of neuromuscular blocking agents. Anaesthesia was maintained with 70% nitrous oxide in oxygen and an age-adjusted end-tidal isoflurane concentration of 1 MAC, excluding nitrous oxide (1.4–1.6% in children and 1–1.2% in adults).\(^9\) Incremental doses of alfentanil 10 \(\mu\)g kg\(^{-1}\) were given as required. Ventilation was controlled to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.6–5.3 kPa).

The temperature of the skin overlying the adductor pollicis muscle was monitored and maintained at 32–33\(^\circ\)C. Nasopharyngeal temperature in the two age groups was maintained at 36–37\(^\circ\)C by the use of a warming mattress. Concentrations of isoflurane, nitrous oxide, carbon dioxide and oxygen saturation were monitored continuously by a multiple-gas analyser (Capnomac Ultima-SVI, Datex Instrumentarium Corporation, Helsinki, Finland). The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz repeated every 15 s. An acceleration piezo-electric transducer (Biometer International, Odense, Denmark) was fastened to the volar surface of the distal phalanx of the thumb contralateral to the site of i.v. fluid infusion. For both children and adults, the arm was immobilized in a splint and free movement during evoked thumb adduction was ensured by fixation of the extended four ulnar fingers by an elastic bandage or adhesive tape. Registration of evoked thumb acceleration, in response to adductor pollicis contractions, was carried out using a TOF Guard neuromuscular monitor (Biometer International, Odense, Denmark). After stabilization of the evoked TOF responses, each patient in the two age groups received a single i.v. bolus of rocuronium 0.6 mg kg\(^{-1}\).

The onset time of rocuronium-induced neuromuscular block, the time interval between the end of injection of rocuronium and the development of maximum block, and the time required for spontaneous recovery of the first twitch in the TOF response (T1) to a value of 10\% of its control (T0), were determined for all patients. Neostigmine antagonism was induced at T1/T0 of 10\%. Patients in the two age groups were allocated randomly using closed envelopes to one of five equal dose blocks (\(n=8\) for children and \(n=10\) for adults). Patients in each age group received either no antagonist (control) or one of four doses of neostigmine (5, 10, 20 or 50 \(\mu\)g kg\(^{-1}\)). Atropine 5–20 \(\mu\)g kg\(^{-1}\) was given as appropriate. No other antagonist was given for the next 10 min and the end-tidal isoflurane concentration was not altered. First twitch height and TOF ratios (fractional height of the evoked fourth twitch in the TOF response in relation to the first twitch height T4/T1) were then recorded continuously for 10 min in the control and after the different doses of neostigmine. Additional doses of neostigmine and atropine were given if a TOF ratio of 80\% was not achieved at the end of the 10-min period. All information derived from the acceleration transducer was recorded on a memory card and subsequently a computer printout was obtained using TOF Guard Reader software (Biometer International, Odense, Denmark).

Dose–response curves were constructed using log dose vs probit transformation of antagonist-assisted recovery of TOF ratios. Antagonist-assisted recovery was defined as total recovery minus spontaneous recovery that would have taken place in the absence of neostigmine. This was calculated by subtracting from the total recovery of the TOF ratio mean spontaneous recovery observed in patients who did not receive neostigmine. The result was expressed as a percentage of the maximum possible antagonist-assisted recovery, which is equal to 100\% minus percentage mean spontaneous recovery.\(^6,7\) Linear regression analyses of the dose–response curves were used to calculate the effective doses of neostigmine required to achieve 50\% and 80\% recovery of the TOF ratio (ED\(_{50}\) and ED\(_{80}\), respectively), every minute for 10 min after initial administration of neostigmine. Regression lines were compared using analysis of covariance. First we tested the lines to determine if they deviated from parallelism; if they did not, the F test was applied to determine if the elevations were different. If so, Newman–Keuls multiple comparison test was applied to determine which line differed in elevation.\(^10\) Unpaired t test was used to compare the two age groups with respect to: overall onset times, times to 10\% recovery of T1/T0, T1 and TOF ratio at 5 and 10 min in the control and after different doses of neostigmine. For each age group, Dunnett’s test was used to compare the degree of recovery of T1 and TOF ratio recorded at 5 and 10 min after different doses of neostigmine to the corresponding values recorded in the control group.\(^10\) Unless otherwise specified, all results are expressed as mean (95\% confidence intervals) and were considered statistically significant when \(P<0.05\). Most of the statistical analyses were performed using SPSS 6.0 statistical package for Windows.

Results

All patients in the two age groups developed 100\% neuromuscular block in response to the bolus doses
of rocuronium. The overall onset time of rocuronium-induced neuromuscular block in children was faster than that in adults (64.6 (57.7–71.5) s vs 83.7 (70.7–96.6) s; P < 0.05). The time required for 10% spontaneous recovery of T1/T0 after rocuronium was shorter in children than in adults (25.4 (22.9–27.9) min vs 38.8 (36.1–41.4) min; P < 0.001).

At the end of surgery, first twitch height always recovered to baseline in the two age groups. Spontaneous and antagonist-assisted recovery were more rapid in children than in adults. The courses of T1 and total recovery of the TOF ratio over the 10-min period in the control and after different doses of neostigmine in children and adults are shown in figures 1 and 2, respectively. Doses of neostigmine in the range 10–50 μg kg⁻¹ resulted in more than 90% recovery of T1 and adequate total recovery of the TOF ratio (80% or more) by the end of the 10-min period in children (table 1). A level of 80% TOF ratio was achieved in children at 4, 5 and 8 min after initial administration of neostigmine 50, 100 and 200 μg kg⁻¹, respectively, while adults achieved a level of 80% TOF ratio at 5 and 10 min after administration of neostigmine 200 μg kg⁻¹ (table 1).

**Table 1** Total recovery of the first twitch in the train-of-four (T1) in relation to control (T0) and train-of-four (TOF) ratio, spontaneously and after different doses of neostigmine in children and adults. Values are mean (95% confidence intervals). *Significantly different from the same dose of neostigmine in adults; †significantly different from control in the same age group

<table>
<thead>
<tr>
<th></th>
<th>Children (n=8 each)</th>
<th>Adults (n=10 each)</th>
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<tbody>
<tr>
<td></td>
<td>T1/T0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 min</td>
<td>10 min</td>
</tr>
<tr>
<td>Control 0 μg kg⁻¹</td>
<td>31.7 (24.1–39.2)*</td>
<td>55.1 (41.5–68.7)*</td>
</tr>
<tr>
<td>Neostigmine 5 μg kg⁻¹</td>
<td>61.6 (46.9–76.2)**</td>
<td>87.3 (76.1–98.6)**</td>
</tr>
<tr>
<td>Neostigmine 10 μg kg⁻¹</td>
<td>68.8 (63.8–73.9)**</td>
<td>93.7 (88.7–98.7)**</td>
</tr>
<tr>
<td>Neostigmine 20 μg kg⁻¹</td>
<td>79.0 (70.1–87.8)**</td>
<td>93.7 (89.7–97.7)**</td>
</tr>
<tr>
<td>Neostigmine 50 μg kg⁻¹</td>
<td>85.1 (79.5–90.7)**</td>
<td>96.1 (92.0–99.0)**</td>
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<tr>
<td></td>
<td>TOF ratio (T4/T1%)</td>
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</tr>
<tr>
<td></td>
<td>5 min</td>
<td>10 min</td>
</tr>
<tr>
<td>Control</td>
<td>24.3 (19.9–28.6)*</td>
<td>48.0 (39.0–57.9)*</td>
</tr>
<tr>
<td>Neostigmine 5 μg kg⁻¹</td>
<td>39.1 (17.1–61.1)*</td>
<td>73.0 (54.8–91.9)*</td>
</tr>
<tr>
<td>Neostigmine 10 μg kg⁻¹</td>
<td>61.7 (50.5–72.9)*</td>
<td>88.5 (81.7–95.2)*</td>
</tr>
<tr>
<td>Neostigmine 20 μg kg⁻¹</td>
<td>84.6 (73.6–95.6)*</td>
<td>97.7 (94.9–99.0)*</td>
</tr>
<tr>
<td>Neostigmine 50 μg kg⁻¹</td>
<td>92.5 (85.8–99.0)*</td>
<td>98.7 (96.1–99.9)*</td>
</tr>
</tbody>
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**Table 2** Effective doses of neostigmine required for 50% (ED₅₀) and 80% (ED₈₀) antagonist-assisted recovery of the train-of-four ratio in children and adults. Values are mean (95% confidence intervals)

<table>
<thead>
<tr>
<th>Time after initial injection of neostigmine</th>
<th>Children</th>
<th>Adults</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>ED₅₀ μg kg⁻¹</td>
<td>9.86 (7.6–12.8)</td>
<td>34.38 (24.0–42.5)</td>
</tr>
<tr>
<td></td>
<td>ED₈₀ μg kg⁻¹</td>
<td>17.51 (13.4–22.9)</td>
<td>101.23 (81.5–126.5)</td>
</tr>
<tr>
<td>10 min</td>
<td>ED₅₀ μg kg⁻¹</td>
<td>4.17 (3.0–5.7)</td>
<td>21.30 (17.2–26.8)</td>
</tr>
<tr>
<td></td>
<td>ED₈₀ μg kg⁻¹</td>
<td>7.10 (5.2–9.8)</td>
<td>56.56 (45.5–71.9)</td>
</tr>
</tbody>
</table>
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20 and 10 \(\mu\text{g kg}^{-1}\), respectively (fig. 2). In contrast, only the highest dose of neostigmine (50 \(\mu\text{g kg}^{-1}\)) resulted in substantial recovery of T1 to reach a value of 95.8 (94.0–98.3) % after 10 min in adults. However, adequate total recovery of 80% TOF ratio was not achieved with any of the four doses of neostigmine in adults within the same time interval (table 1, fig. 2). It is interesting to note that with respect to TOF recovery, neostigmine 5 \(\mu\text{g kg}^{-1}\) in children was as effective as 50 \(\mu\text{g kg}^{-1}\) in adults after 10 min (table 1, fig. 2).

The dose–response curves for antagonist-assisted TOF ratio recovery at 5 and 10 min were parallel in the two age groups (fig. 3). For each group, the lines constructed at 10 min were shifted significantly to the left from those constructed at 5 min \((P<0.001\text{ in children and }P<0.05\text{ in adults})\). The dose–response curves for children were shifted significantly to the left compared with those for adults \((P<0.001)\). The effective doses of neostigmine required to achieve 50 % (ED50) and 80% (ED80) antagonist-assisted recovery of the TOF ratios at 10 and 5 min were significantly lower in children compared with adults (table 2). The values for ED50, ED80 in children and ED50 in adults are expressed as a function of time in figure 4. The ED50 values for adults were consistently higher than the ED50 and ED80 values in children.

**Discussion**

Antagonism of non-depolarizing neuromuscular block may depend on several factors including: type and dose of anticholinesterase,\(^6\) degree of block at the time of antagonism,\(^12\) anaesthetic technique used,\(^16\) rate of spontaneous recovery and type of neuromuscular blocking drug.\(^6\) In this study, most of these factors were standardized for the two age groups. The anaesthetic and neuromuscular monitoring techniques were similar and equal doses of neostigmine were used to antagonize 90% neuromuscular block after single standard intubating doses of rocuronium. Despite these apparent similarities, children had a more rapid onset and a shorter duration of rocuronium-induced neuromuscular block. A more rapid rate of recovery was also produced with substantially lower doses of neostigmine in children compared with adults. These age-related differences in response to rocuronium-induced neuromuscular block and its antagonism with neostigmine may have a kinetic or dynamic basis, or both.

Fisher and colleagues\(^2\) demonstrated that the steady state volume of distribution for neostigmine in infants and children is not different from that in adults. However, infants and children have shorter elimination half-lives for neostigmine and more rapid clearance rates than adults. Therefore, the age-related differences in the rate of recovery and antagonist requirements do not seem to have a neostigmine-related kinetic basis.\(^19\) Local differences at the neuromuscular junction such as acetylcholine reserves, acetylcholinesterase enzyme activity or the quantity of receptors at the neuromuscular junction have been suggested as possible contributing factors for the lower dose requirements of anticholinesterases in paediatric patients.\(^20\) In contrast,
it is well known that there are age-related pharmacodynamic and pharmacokinetic differences in the response to non-depolarizing neuromuscular blockers. The more rapid circulation time and increased cardiac output in children are expected to expedite drug delivery to the neuromuscular junction and its removal. Clinically, this results in acceleration of onset of neuromuscular block, more rapid rate of spontaneous recovery and reduction in duration of block in children. This was confirmed with the use of rocuronium in this and other studies. In common with other neuromuscular blocking drugs, children have a shorter elimination half-life for rocuronium. Smith, Donati and Bevan suggested that the use of intermediate-acting neuromuscular blocking agents is associated with rapid reductions in their concentrations at the bio-phase. This implies that, with time, fewer receptors are occupied by the neuromuscular blocking drug with a consequent improvement in both total and antagonist-assisted recovery. This was probably the case in this study, as the effective doses of neostigmine were reduced progressively with time (fig. 4). Therefore, it appears more likely that the more rapid rate of spontaneous recovery from the effects of rocuronium-induced neuromuscular block was the predominant mechanism to explain the reduced neostigmine dose requirements and the more complete recovery observed in children.

Our results are in agreement with previously reported trends for antagonism of long-acting neuromuscular blockers, tubocurarine, pancuronium and doxacurium, in the two age groups. However, the effective doses of neostigmine required for adequate TOF recovery were reduced considerably when rocuronium rather than longer-acting neuromuscular blockers were used. Differences of long- and intermediate-acting neuromuscular blockers have been recognized previously in adults and were attributed to different rates of spontaneous recovery.

Rocuronium has a relatively longer duration of action than mivacurium in both adults and children. Therefore, at a comparable degree of neuromuscular block, anticholinesterases are expected to be more effective in antagonizing the effects of the latter. However, Bevan and colleagues reported recently that 10 min after administration of neostigmine 0, 5, 10, 20 and 50 μg kg⁻¹ to antagonize approximately 90% mivacurium-induced block in children during nitrous oxide–propofol–fentanyl anaesthesia, the TOF ratio had recovered to mean 83.7 (SD 5.2) %, 79.3 (6.9) %, 92.8 (8.1) %, 92.2 (6.3) % and 97.0 (2.7) %, respectively. Our corresponding mean values for neostigmine antagonism of rocuronium in children were: 48.0 (95% confidence intervals 39.0–57.9) %, 73.0 (54.8–91.9) %, 88.5 (81.7–95.2) %, 97.7 (94.9–99.0) % and 98.7 (96.1–99.9) %, respectively. It is clear that when no antagonist was given, spontaneous recovery was more pronounced during recovery from mivacurium- than rocuronium-induced neuromuscular block. Therefore, the presence of comparable degrees of antagonist-assisted recovery may reflect a more effective neostigmine antagonism of rocuronium than mivacurium-induced neuromuscular block in children. This finding may appear surprising, however, factors other than anticholinesterase activity at the acetylcholine receptor level may be considered in the return of neuromuscular activity after administration of neostigmine. Szenohradszky and colleagues reported recently that neostigmine was less effective in antagonizing the neuromuscular effects of mivacurium than vecuronium when administered during a continuous infusion of each blocker. In the same study, administration of neostigmine was associated with increased plasma concentrations of mivacurium. The authors suggested that the neostigmine-induced increase in mivacurium plasma concentrations may be responsible for the less effective antagonism compared with vecuronium. Neostigmine is a potent inhibitor of the butrylcholinesterase enzyme which is important for spontaneous recovery from mivacurium-induced neuromuscular block.

In this study, inhalation of isoflurane was continued during the reversal process to ensure adequate depth of anaesthesia and prevent accidental patient movement in response to surgery, peripheral nerve stimulation, or both. This may be partly responsible for the increased dose requirements of neostigmine in adults. Other investigators have also reported that neostigmine doses in the range 40–50 μg kg⁻¹ were required for adequate antagonism of 90% neuromuscular block induced by other intermediate-acting neuromuscular blockers during enflurane anaesthesia in adults. Maintenance of anaesthesia with enflurane or isoflurane has been reported to impede the reversal process. In clinical practice, however, inhalation anaesthetics are usually discontinued at the time of antagonism. This has been shown to reduce but not eliminate impairment of the reversal process.

**References**

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