Dose Responses for Neostigmine and Edrophonium as Antagonists of Mivacurium in Adults and Children

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Background: Reversal of neuromuscular blockade induced with pancuronium, d-tubocurarine, or doxacurium is achieved using smaller doses of neostigmine in adults than in children. Also, pancuronium- and doxacurium-induced blockade is reversed with smaller doses of edrophonium in children than in adults. The purpose of this study was to compare the spontaneous and neostigmine- and edrophonium-assisted recovery of mivacurium-induced neuromuscular block in adults and children.

Methods: Fifty-four adults, aged 40 ± 10.9 yr, and 54 children, aged 4.9 ± 0.7 yr, physical status ASA 1–2, were studied during propofol/fentanyl/nitrous oxide anesthesia. A Datex relaxograph was used to monitor the electromyographic response of the adductor pollicis to train-of-four stimulation of the ulnar nerve every 10 s. After induction of anesthesia, 0.2 mg·kg⁻¹ intravenous mivacurium was administered followed by an infusion to maintain 90–95% T1 block. At the end of surgery, one of four doses of neostigmine (5, 10, 20, and 50 μg·kg⁻¹) or edrophonium (100, 200, 400, and 1,000 μg·kg⁻¹) or placebo was given, by random allocation, when T1 had recovered to 10%. Values of T1 and train-of-four were measured for 10 min. Results: Spontaneous recovery proceeded more rapidly in children than in adults. At 10 min, T1 had recovered to 97 ± 2% (SD) in children compared with 69 ± 11% in adults and train-of-four to 84 ± 5% versus 50 ± 13% (P < 0.0001). In children, 10 min after reversal, recovery of T1 and train-of-four was not different from control after edrophonium and was enhanced only by the larger doses of neostigmine. In adults, recovery was accelerated by both edrophonium and neostigmine. Five minutes after reversal, recovery was improved by either drug in adults and in children.

Conclusions: Spontaneous recovery from mivacurium-induced neuromuscular block is more rapid in children than in adults. Ten minutes after attempted reversal, recovery is accelerated by edrophonium and usually by neostigmine in adults but not in children. Thus, when reversal is required, edrophonium may be preferred to neostigmine. (Key words: Anesthesia: adult; pediatric. Antagonists, neuromuscular relaxants; edrophonium; neostigmine. Neuromuscular relaxants. mivacurium.)

MIVACURIUM is a short-acting benzylisoquinolinium neuromuscular blocking drug.1–5 It is metabolized by plasma cholinesterase,5 which results in rapid spontaneous recovery from mivacurium-induced paralysis. The recovery index after mivacurium, time from 25% to 75% recovery of T1, is 5–7 min in adults.2,4 compared with 14–18 min for atracurium and vecuronium6 and more than 30 min for long-acting neuromuscular blocking drugs, such as pancuronium.7 Spontaneous recovery from mivacurium block is more rapid in children than in adults. After 0.2 mg·kg⁻¹ mivacurium, return of T1 to 95% of control occurred in 20 min in children,8 compared with 30 min in adults.1 The rapid recovery of mivacurium is largely independent of dose1 and mode of administration, bolus or infusion,9,10 suggesting that antagonism might be required less frequently than after other nondepolarizing agents. Avoiding reversal agents would reduce the incidence of anticholinesterase-induced side effects, such as postoperative nausea and vomiting.11,12

Attempts at reversal of mivacurium neuromuscular block with neostigmine resulted in only minor acceleration of the rate of recovery in adults.1 Dose-response curves have been constructed. Block in adults do not achieve the same degree of recovery after mivacurium and vecuronium and that after pancuronium13 and edrophonium.14,15 Other attempted reversal of mivacurium block was 44.5 μg·kg⁻¹ for neostigmine and 50 μg·kg⁻¹ for edrophonium and neostigmine in children after pancuronium14 and recovered that doses of neostigmine required to produce similar recovery in adults and in children.16,17 When administered as a continuous infusion of neostigmine,18 but not increased in children and adults.19,21 However, this is not possible due to adult concomitant medications.

Two hypotheses were tested. First, recovery from neostigmine and after attempted reversal or neostigmine, is more rapid in adults. Second, recovery after edrophonium or neostigmine, was more rapid in children than adults. Support for this hypothesis was provided by the current study. Recovery after neostigmine and edrophonium was compared, and reversal was more rapid in children than adults.

Methods

After institutional approval, 54 healthy patients, ASA physical status 1, scheduled for elective surgery and 54 children (aged 4–10 yr, 34 boys, 20 girls) were included in this prospective, randomized, double-blind study. General anesthesia was induced and maintained with propofol 2 mg·kg⁻¹ and fentanyl 5 μg·kg⁻¹. After surgical preparation, mivacurium 0.2 mg·kg⁻¹ was administered followed by an infusion to maintain 95–97% of T1. Anesthesia was maintained with 66% nitrous oxide, 33% oxygen, and 0.5% to 1% isoflurane. The study was approved by the University of British Columbia’s Ethics Committee and all patients, or their guardians, gave informed consent. Anesthesia was induced and maintained with propofol 2 mg·kg⁻¹ and fentanyl 5 μg·kg⁻¹. After surgical preparation, mivacurium 0.2 mg·kg⁻¹ was administered followed by an infusion to maintain 95–97% of T1. Anesthesia was maintained with 66% nitrous oxide, 33% oxygen, and 0.5% to 1% isoflurane. The study was approved by the University of British Columbia’s Ethics Committee and all patients, or their guardians, gave informed consent.
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curves have been constructed for the reversal of mivacurium-block in adults and demonstrated that, to achieve the same degree of recovery, smaller doses were required after mivacurium than after atracurium and vecuronium and that the potency ratio of neostigmine:edrophonium was reduced. The ED90 5 min after attempted reversal of 90% mivacurium-induced block was 44.5 μg·kg⁻¹ for edrophonium and 8.2 μg·kg⁻¹ for neostigmine. Dose-response curves for edrophonium and neostigmine have not been obtained for mivacurium in children. However, previous studies after pancuronium and doxacurium have demonstrated that doses of neostigmine or edrophonium required to produce similar degrees of recovery were lower in children and infants than previously reported in adults.16,17 When administered during a continuous infusion of d-tubocurarine, the ED90 of neostigmine, but not of edrophonium, was decreased in children and infants compared with adults.20,21 However, these previous studies used historical data for adult comparisons.

Two hypotheses were tested in the current study. First, recovery from neuromuscular block, both spontaneous and after attempted reversal with edrophonium or neostigmine, was more rapid in children than in adults. Second, recovery from mivacurium was so rapid that edrophonium or neostigmine, even at high therapeutic doses, would not be necessary to achieve adequate neuromuscular function as defined by train-of-four (TOF) >70%. 10 min after reversal was administered, when TOF was 10% of control.

Neuromuscular block was maintained at 90–95% TOF depression with a mivacurium infusion during balanced anesthesia with propofol, fentanyl, and nitrous oxide. At the end of surgery, neuromuscular block was allowed to recover spontaneously or reversed with one of four doses of edrophonium or neostigmine, and the ensuing recovery was compared with the control spontaneous recovery group. The studies in adults and children were performed concurrently by the same group of investigators using identical equipment and anesthetic techniques.

Methods

After institutional approval and written, informed patient or parental consent, 54 adults (aged 20–60 yr) and 54 children (aged 2–12 yr) were studied. All were healthy patients. ASA physical status 1 or 2, who were scheduled for elective surgical procedures anticipated to last for at least 1 h. None had neurologic, respiratory, renal, or hepatic disease or were taking medication that might interfere with normal neuromuscular function.

In children of either sex, and was in adults, spontaneous recovery is accelerated by increasing the dose of edrophonium or neostigmine in required, doses of atropine were given. However, previous studies used historical data for adult comparisons.

propofol (1.5–3 mg·kg⁻¹ in adults and 5 mg·kg⁻¹ in children), 0.3 mg·kg⁻¹ lidocaine, and 1–2 μg·kg⁻¹ fentanyl intravenously. Tracheal intubation was accomplished without the use of muscle relaxants, and anesthesia was maintained with oxygen and nitrous oxide inhalation and an infusion of propofol (50–300 μg·kg⁻¹·min⁻¹). Incremental doses of fentanyl were given, and the propofol infusion was titrated to provide satisfactory levels of anesthesia that maintained cardiovascular stability without the addition of volatile agents. A blood sample was taken for estimation of plasma cholinesterase concentration and dibucaine number before administration of mivacurium. Neuromuscular monitoring was performed using a Puritan Bennett Datex Relaxograph (Helsinki, Finland) to record the electromyographic response of the adductor pollicis to TOF supramaximal stimulation of the ulnar nerve at 10-s intervals. The arm free of the intravenous infusion was selected for monitoring and was wrapped in blankets to minimize local cooling. Skin temperature over the adductor pollicis was recorded and maintained >32°C. When the baseline electromyographic record had stabilized, after at least 1 min of recording, neuromuscular blockade was established using 0.2 mg·kg⁻¹ intravenous mivacurium. If necessary, incremental doses of 25% of the initial dose were given to produce 90–100% depression of first twitch (T1) height. When T1 had recovered spontaneously to 5–10% of control height, an infusion of mivacurium was commenced at initial infusion rates of 10 μg·kg⁻¹·min⁻¹ in adults and 20 μg·kg⁻¹·min⁻¹ in children. The rate was adjusted at intervals (no shorter than 3 min) as needed to maintain 90–95% neuromuscular blockade for the duration of the procedure.

At the completion of surgery, patients in each of the two age groups were treated similarly. Mivacurium administration was discontinued, and they were randomized into nine groups. At spontaneous recovery of T1 to 10% of control height, six patients in each group were allocated randomly to receive no reversal (control group) or one of four doses of neostigmine (5, 10, 20, and 50 μg·kg⁻¹) or edrophonium (100, 200, 400, and 1,000 μg·kg⁻¹) with atropine (2, 4, 8, or 20 μg·kg⁻¹).
Values of T11% and TOF ratio% (ratio of fourth to first twitch height) were noted every minute for the next 10 min. A second dose of the reversal agent was given to complete the total dose of neostigmine to 50 μg·kg⁻¹ or edrophonium to 1,000 μg·kg⁻¹ for each patient, but measurements are reported only in response to the initial dose of reversal agent.

Demographic data were expressed as mean ± SD for the two age groups. Recovery data were recalculated with reference to the maximum height of T1 achieved after the second dose of reversal agent (which was taken as the control height as long as TOF was >70%). The rate of spontaneous recovery was demonstrated by the values of T1 and TOF ratio in the control patients who did not receive any reversal agent as the first dose. In each group, recovery of T1 and TOF for each dose of reversal agent was compared with control values at 5 and 10 min using analysis of variance, Student's t-test, and Bonferroni's correction. Comparisons were made using analysis of covariance. Results are expressed, except where stated, as mean and standard deviation (SD). Comparisons of demographic and neuromuscular recovery data were made using Student's t-test. Values of P < 0.05 were considered to show significant differences.

Results

The demographic data of the two age groups of patients studied are shown in table 1. The sex composition of the two groups differed, with a preponderance of female (80%) adults and male (54%) children. Estimations of plasma cholinesterase concentrations (laboratory normal values 3–10 kU·L⁻¹) and dibucaine numbers (normal values 0.7–1.0) confirmed that none of the patients was homozygous for atypical cholinesterase. In ten children (M:F 6:4), plasma cholinesterase concentrations were high (two in the control group and four in each of the neostigmine and edrophonium groups), with a maximum value of 14.8 kU·L⁻¹. The duration of action (from administration of mivacurium to 5% T1 recovery) in patients in whom the initial bolus of 0.2 mg·kg⁻¹ produced >90% blockade was longer in adults (15.5 ± 4.4 min, n = 43) than in children (6.4 ± 2.0 min, n = 45, P < 0.01).

Spontaneous recovery from neuromuscular block in patients who had received no reversal agents was more rapid in children than in adults (figs. 1 and 2 and table 2). Five minutes after 10% T1 recovery was reached spontaneously (i.e., 5 min after the time when reversal was administered in the other groups), T1 had achieved 37 ± 11% in adults, compared with 74 ± 8% in children (P < 0.0001), with corresponding TOF recoveries of 14 ± 4% and 53 ± 5%, respectively (P < 0.0001). By 10 min, T1 had increased to 69 ± 11% in adults, compared with 97 ± 2% in children (P < 0.01), with TOF of 50 ± 13% in adults and 84 ± 5% in children (P < 0.00001). Mean values of T1 ≥90% and TOF ≥70% were achieved within 7 min of spontaneous recovery to 10% T1 in children but had not been reached in adults by the end of the 10-min observation.

The mean values for recovery of T1 and TOF for the different doses of neostigmine and edrophonium in adults and children are shown in figures 1 and 2. Five minutes after reversal in adults, T1 and TOF recovery were greater than control after all doses of edrophonium and after the two higher doses of neostigmine. In children, recovery after reversal was greater than control after three of the four doses of edrophonium and after one dose of neostigmine. By 10 min, T1 and TOF recovery in adults was greater than control after all doses of edrophonium and after two of the doses of neostigmine. However, in children at 10 min, assisted recovery was never greater than control after edrophonium and was statistically greater after neostigmine in two of the eight groups, but the difference was of no clinical significance.

Discussion

The major findings in this study were: first, the duration of action of mivacurium was shorter and the rate of recovery from neuromuscular blockade was more rapid in children than in adults. Mean TOF exceeded 70% within 7 min of the time of anticipated reversal in children but had not reached this value by 10 min in adults. Second, 10 min after administration of edrophonium or neostigmine, recovery of neuromuscular function in children was not clinically significantly greater than that observed in control subjects. However,
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Fig. 1. Recovery of T1 after reversal with edrophonium and neostigmine in adults and children.

in adults, two doses of neostigmine (20 and 50 μg·kg⁻¹) and all doses of edrophonium accelerated recovery. Thus, it is anticipated that, from these levels of neuromuscular block, reversal of mivacurium-induced relaxation in unlikely to be necessary in children but may be indicated in adults.

The results of this study are in agreement with previous studies. Using a similar experimental design in adults, Naguib et al. constructed dose-response curves every minute for 10 min after reversal and calculated the doses of neostigmine or edrophonium necessary to produce 50% and 70% recovery of T1 and TOF, respectively. They demonstrated that, compared with previous studies examining the reversal of atracurium and vecuronium and of pancuronium and d-tubocurarine, to achieve adequate return of neuromuscular activity, smaller doses of reversal agent were required with mivacurium than after the intermediate or longer-acting agents. This finding was anticipated because of the more rapid rate of spontaneous recovery with mivacurium. Naguib et al. also calculated the ratio of edrophonium/neostigmine required to produce equivalent T1 or TOF recovery. They found that the E:N ratio was less for mivacurium than for the previously investigated longer acting agents. Thus, they argued that neostigmine was less effective than edrophonium in reversing mivacurium neuromuscular blockade. We elected not to calculate potency ratios, in part because, by 10 min after reversal, neuromuscular function was seldom in children and inconsistently in adults, different from values seen in control patients. Also, dose-response curves and their derived potency ratios, constructed 5 min after administration of reversal agents, may be misleading because of the more rapid course
Fig. 2. Recovery of TOF after reversal with edrophonium (ED; 100, 200, 400, and 1,000 µg/kg) and neostigmine (NEO; 5, 10, 20, and 30 µg/kg) in adults and children.

of recovery induced by edrophonium than by neostigmine. Potency ratios calculated at this time are likely to favor edrophonium. In addition, the derived values, ED<sub>50</sub> and ED<sub>50</sub>, in Naguib et al.'s study were extrapolated beyond the data sets, as would have been required in the current investigation, thus limiting their reliability.

There is mounting evidence that reversal of mivacurium-induced neuromuscular block is less effective with neostigmine than with edrophonium. Abdulatif compared the recovery of neuromuscular function at intense levels of neuromuscular block. Either edrophonium or neostigmine was given 5 min after mivacurium, as a 0.15 mg·kg<sup>-1</sup> bolus, when there was complete suppression of twitch response even to posttetanic stimulation. He found that reversal time was prolonged considerably by neostigmine but not by edrophonium. Similarly, Kao et al. reported that, when 70 µg·kg<sup>-1</sup> neostigmine was given to antagonize profound neuromuscular block, twitch tension recovered more slowly than if no antagonist was administered. The difference is probably because neostigmine but not edrophonium decreases the activity of plasma cholinesterase. Thus, neostigmine but not edrophonium decreases the metabolism and slows the rate of spontaneous recovery from mivacurium.

Two studies suggested that factors other than anticholinesterase activity might be considered in the return of neuromuscular activity after administration of neostigmine or edrophonium. Szénhársdzy et al. demonstrated that neostigmine was less effective in antagonizing the neuromuscular effect of mivacurium than that of vecuronium when neostigmine was administered during the course of a continuous infusion of either relaxant. Also, neostigmine increased plasma mivacurium concentration; the authors suggested these
effects were responsible for the impaired antagonism. Increases in mivacurium concentration were seen after administration of edrophonium in a similar experiment. Thus, although these results do not explain the difference in effectiveness of neostigmine and edrophonium in the reversal of mivacurium neuromuscular block, they suggest that factors that modify the concentration of relaxant may be important. The relationship between plasma concentration and the extent of neuromuscular block has been demonstrated under stable conditions for several muscle relaxants including d-tubocurarine, pancuronium, and vecuronium. If neuromuscular activity depends on the proportion of functioning receptors, plasma relaxant concentration is an indirect index of receptor occupancy that assumes a stable relationship between acetylcholine concentration and its production and metabolism and other acetylcholine receptor agonists, such as anticholinesterases. As neuromuscular relaxants are bound at sites other than the neuromuscular junction, increases in circulating concentration may occur from release from junctional and extrajunctional sites. The relationship between circulating concentration and neuromuscular blockade has not been established under such conditions. Thus, it may be premature to associate impaired antagonism to elevated circulating mivacurium concentrations. However, these are the first studies to demonstrate the release of neuromuscular relaxant from binding sites by edrophonium and neostigmine.

Previous studies have demonstrated that return of neuromuscular activity after reversal of long-acting relaxants was more rapid in children than in adults. Meakin et al. showed that, in the reversal of pancuronium neuromuscular block, for the same doses of edrophonium and neostigmine, recovery was more rapid in children than in adults. Fisher et al. demonstrated that, in the reversal of neuromuscular block maintained by an infusion of d-tubocurarine, the dose-response curves for neostigmine but not for edrophonium were shifted to the left in children compared with that seen in adults. Dose-response curves obtained when reversal agents were given during the course of spontaneous recovery from doxacurium were shifted to the left in children compared with adults. Similarly, when adults and children were given one or two doses of edrophonium or neostigmine during recovery from pancuronium, recovery was more rapid in children than in adults. Although these studies used different experimental protocols and historical data for the adult values, the conclusions were similar: Recovery of neu-

Table 2. Recovery of TOF and Train-of-Four (TOF) Spontaneously and after Neostigmine or Edrophonium in Adults and Children

<table>
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<tr>
<th>Dose (μg/kg)</th>
<th>T1</th>
<th>TOF</th>
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<th>10 min</th>
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<td>0</td>
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<td>10</td>
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<td>50</td>
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<td>0.125</td>
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<td>8.0±0.18</td>
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<tr>
<td>Control</td>
<td>9.5±1.7</td>
<td>8.0±0.18</td>
<td>8.0±0.18</td>
<td>8.0±0.18</td>
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<tr>
<td>Necostigmine</td>
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<td>8.0±0.18</td>
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<tr>
<td>Edrophonium</td>
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<td>8.0±0.18</td>
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romuscular block occurs more rapidly in children than in adults under steady-state conditions or when spontaneous recovery is prevented by administration of muscle relaxants by controlled infusions. In the current study, the extent of neuromuscular recovery after each dose of either reversal agent was greater in children than in adults. It is likely that the predominant factor was the more rapid spontaneous recovery in children.

This study was not designed to determine whether mivacurium-induced neuromuscular block should be reversed at the end of anesthesia. Separate studies to determine the presence or absence of residual block when patients arrive in the postoperative recovery room will be necessary. However, because the TOF ratio in children had reached >70% 7 min after achieving 10% T1 spontaneously, it seems unlikely that reversal will be required routinely in this age group. Because the mean TOF value had not achieved 70% at the end of the 10-min observation in adults, it is likely that reversal will be required more frequently unless low levels of neuromuscular block are maintained or the administration of mivacurium is stopped earlier at the end of surgery than in this controlled investigation. To achieve TOF ≥0.7 10 min after reversal is attempted, there seems to be no advantage in administering doses greater than 20 μg·kg⁻¹ neostigmine or 200 μg·kg⁻¹ edrophonium, a conclusion similar to that of Kopman et al. Recovery from neuromuscular block is the sum of spontaneous recovery and its acceleration by anticholinesterases. The more rapid the spontaneous recovery, the smaller the dose of reversal agent required. In children, after mivacurium, spontaneous recovery is so rapid that reversal will not likely be necessary.

In conclusion, this study confirmed that the spontaneous rate of recovery from mivacurium-induced neuromuscular block is more rapid in children than in adults. In both age groups, early recovery can be accelerated by anticholinesterases. However, 10 min after reversal, neuromuscular function after edrophonium or neostigmine in children is little different from spontaneous recovery. If reversal is considered necessary, edrophonium may be preferred to neostigmine because it does not decrease plasma cholinesterase activity, which is important for spontaneous recovery from mivacurium relaxation. Additional studies will be required to determine the incidence of residual block after unopposed mivacurium neuromuscular blockade in clinical practice.

References

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