Residual Block after Mivacurium with or without Edrophonium Reversal in Adults and Children

Joan C. Bevan, M.D., F.R.C.A.**

Background: The rapid recovery from mivacurium-induced neuromuscular block has encouraged omission of its reversal. The purpose of this study was to determine, in children and in adults, whether failure to reverse mivacurium neuromuscular block was associated with residual neuromuscular block on arrival in the postanesthesia care unit.

Methods: In 50 children, aged 2–1.2 yr, and 50 adults, aged 20–60 yr, anesthesia was induced and maintained with propofol and fentanyl, and neuromuscular block was achieved by an infusion of mivacurium, to maintain one or two visible responses to train-of-four (TOF) stimulation of the ulnar nerve. At the end of surgery, mivacurium infusion was stopped, and 10 min later, reversal was attempted with saline or 0.5 mg·kg⁻¹ edrophonium by random allocation. On arrival in the postanesthesia care unit, a blinded observer assessed patients clinically and by stimulation of the ulnar nerve with a Datex electromyogram in the uncalkibrated TOF mode.

Results: Children arrived in the postanesthesia care unit 8.2 ± 3.4 min after reversal of neuromuscular block and showed no sign of weakness, either clinically or by TOF stimulation. Although TOF ratio was greater in children who had received edrophonium (1.00 ± 0.05 vs. 0.93 ± 0.01, P < 0.01), TOF was >0.7 in all children. Adults arrived in the postanesthesia care unit 12.9 ± 5.3 min after reversal of neuromuscular block (P < 0.01 vs. children). Six in the saline group demonstrated weakness (two required immediate reversal of neuromuscular block, and TOF was <0.7 in four others), compared with TOF <0.7 in only one of the edrophonium group (P < 0.05).

Conclusions: This study demonstrated that, in adults, failure to reverse mivacurium neuromuscular block was associated with an increased incidence of residual block. Such weakness was not observed in children receiving similar anesthetic and neuromuscular blocking regimens. (Key words: Anesthesia: adult; pediatric. Antagonists, neuromuscular relaxants: edrophonium. Complications: residual neuromuscular blockade. Neuromuscular relaxants: mivacurium.)

The major difference between mivacurium and other nondepolarizing relaxants is the rapid spontaneous recovery of neuromuscular function after its use. In adults, the recovery index (RI; time from 25% to 75% recovery of adductor pollicis twitch tension in response to ulnar nerve stimulation) is 6–8 min,¹ compared with 11–14 min for atracurium² and vecuronium³ and 25–40 min for pancuronium,⁴ pipercuronium,⁵ or doxacurium.⁶ In children, the RI for mivacurium is 4–6 min,⁷ which is less than that for atracurium,⁸ vecuronium,⁹ or pancuronium.¹⁰ It has been suggested that the rate of spontaneous recovery is so rapid that reversal of the block rarely is necessary.¹¹ If this could be substantiated, the hemodynamic¹² and intestinal¹³ side effects of anticholinesterases could be avoided. Ding et al. have shown that, when anticholinesterases are avoided after the use of mivacurium in laparoscopic surgery, the incidence of postoperative nausea and vomiting is reduced.¹⁴ It is recognized that one of the most severe postanesthetic complications is ventilatory inadequacy as a result of residual neuromuscular blockade.¹⁵ It has been shown previously in adults that the incidence of residual block, defined as a train-of-four (TOF) ratio of <0.7, occurs in 30–40% of patients after anesthesia when long-acting relaxants, such as pancuronium or d-tubocurarine, have been administered. This occurs despite the use of clinical neuromuscular monitoring during surgery and after the administration of reversal agents,¹⁶ but this incidence can be reduced if atracurium or vecuronium is used as agents.¹⁷ In children, the incidence is much reduced¹⁸ but may increase with pharmacologic reversal of mivacurium block can be reduced.¹⁹ It is important to demonstrate that reversal of mivacurium was associated with residual neuromuscular block during nitrous oxide anesthesia. At the end of surgery, edrophonium or saline was infused to maintain an adequate TOF. The presence of any weakness in postoperative patients arrived in the postanesthesia care unit was detected by clinical examination.

Methods

After institutional approval, material consent from the patients (20–60 yr) and 50 children (2–12 yr) and the related physical status,¹¹ respiratory, renal, or hepatic dysfunction,¹² receiving drugs that could affect neuromuscular function. The patients were randomly allocated to surgical procedures with a 1:1 ratio.

Premedication was atropine and midazolam, and pediatric inhalation anesthetic was inhaled with 70% nitrous oxide and 30% oxygen. After anesthesia was induced with d-tubocurarine or vecuronium, the surgical procedures were performed. The end-tidal carbon dioxide concentration was monitored in all patients. Neuromuscular monitoring was maintained using a Datex electromyogram in the uncalkibrated TOF mode. The surgical procedures were terminated when the TOF ratio returned to >0.7, and the agents were discontinued when the patient was hemodynamically stable and cooperative. The patients were transferred to the postanesthesia care unit 10 min later, and 10 min after discontinuation of the neuromuscular blocking agent, the patients were transferred to the recovery room. The postoperative period was characterized by the administration of reversal agents for up to 10 min, and the patients were discharged from the recovery room when the TOF ratio returned to >0.7. The patients were transferred to the postanesthesia care unit 10 min after the reversal agents were discontinued, and the TOF ratio was assessed 10 min later. The patients were discharged from the recovery room when the TOF ratio returned to >0.7. The patients were transferred to the postanesthesia care unit 10 min after the reversal agents were discontinued, and the TOF ratio was assessed 10 min later. The patients were discharged from the recovery room when the TOF ratio returned to >0.7.

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Address correspondence to Dr. D. Bevan, Department of Anesthesia, 5th Floor, 910 West 10th Avenue, Vancouver, British Columbia, Canada V5Z 4E5. Address electronic mail to: bevan@unixg.ubc.ca.

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curium or vecuronium is substituted for long-acting agents. In children, the incidence of residual block is much reduced but may occur. Thus, before omission of pharmacologic reversal of mivacurium neuromuscular block can be recommended with confidence, it is important to demonstrate that such a practice will not result in residual neuromuscular block.

The purpose of this study was to determine whether avoidance of reversal of neuromuscular block after mivacurium was associated with residual block. Mivacurium was administered to adults and children by infusion to maintain an intense level of neuromuscular block during nitrous oxide/fentanyl/propofol anesthesia. At the end of surgery, the infusion was stopped, and in half the patients in each age group, the block was reversed with edrophonium and atropine. The presence of residual block when the patients arrived in the postanesthesia care unit (PACU) was detected by clinical evaluation and electromyography.

Methods

After institutional approval and written, informed consent from the patient or parent, 50 adults (20–60 yr) and 50 children (2–12 yr) were studied. All were ASA physical status 1 or 2 and free of neurologic, respiratory, renal, or hepatic disease and were not receiving drugs that could interfere with normal neuromuscular function. They were scheduled for elective surgical procedures with anticipated durations of at least 1 h.

Premedication was at the discretion of the anesthesiologist, and pediatric patients had local anesthetic cream (EMLA) applied to the dorsum of the hand preoperatively to facilitate intravenous cannulation. Anesthesia was induced with 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. Blood was sampled before administration of mivacurium for estimation of plasma cholinesterase activity and dibucaine number. Tracheal intubation was facilitated with 0.2 mg·kg⁻¹ intravenous mivacurium, and an infusion of mivacurium was commenced as soon as a twitch response of the thumb was elicited by TOF stimulation of the ulnar nerve using a Dualstim III Nerve Stimulator (Lifetech, Houston, TX) or other clinical peripheral nerve stimulator. The initial infusion rates were 10 μg·kg⁻¹·min⁻¹ in adults and 20 μg·kg⁻¹·min⁻¹ in children. Adjustments to the rate were made at 2–5-min intervals to maintain a level of neuromuscular blockade at which one or two twitch responses to TOF stimulation were visible. 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 titrated to provide satisfactory levels of anesthesia, which maintained cardiovascular stability without the addition of volatile anesthetic agents.

The mivacurium infusion was stopped at the end of surgery, and spontaneous recovery of neuromuscular blockade was allowed to proceed for 10 min. The patients in both of the age groups were randomized to receive 0.5 mg·kg⁻¹ edrophonium with 0.02 mg·kg⁻¹ atropine or saline for reversal of residual neuromuscular blockade. The reversal agent and placebo were identical in appearance and made up to standard volumes, so that the anesthesiologist who administered the drugs was unaware of the randomization choice. The anesthesiologist in charge of the patient decided on the times for tracheal extubation and transfer of the patient to the recovery room, based solely on clinical criteria, which might include use of a peripheral nerve stimulator. Further doses of edrophonium and atropine could be administered at any time if considered necessary on clinical grounds. On arrival in the recovery room, neuromuscular monitoring was performed using a Puritan Bennett Datex Relaxograph (Helsinki, Finland) to record three consecutive responses of the electromyographic response of the adductor pollicis to TOF supramaximal stimulation of the ulnar nerve at 10-s intervals. The electromyogram was used in the uncalibrated mode to obtain TOF ratios only. The arm free of the intravenous infusion was selected for monitoring, and skin temperature over the adductor pollicis at the recording site was measured and maintained above 32°C by use of warming blankets.

The duration of anesthesia and the total dose of mivacurium administered were noted. Time from the administration of edrophonium or saline to the beginning of electromyogram monitoring in the recovery room was recorded. The three TOF ratios measured were averaged for statistical analysis. Data were expressed as mean ± SD. In each age group, comparisons were made between the TOF ratios on arrival in the recovery room after edrophonium or saline using Student’s t-test and the incidence of postoperative residual blockade, clinical weakness, or TOF ratio ≤0.7 in the adults and children was compared using Fisher’s exact test. Values of...
Results

Adults Versus Children

The mean ages were 4.5 ± 2.2 and 37.6 ± 9.2 yr, and the mean weights were 19.2 ± 8.0 and 66.0 ± 13.1 kg, of children and adults, respectively. The duration of neuromuscular block was similar in adults and children, 66.0 ± 13.1 versus 73.3 ± 30.4 min, but the mivacurium infusion rate required to maintain constant block was greater in children, 0.017 ± 0.005 versus 0.006 ± 0.003 mg·kg⁻¹·min⁻¹, and the time interval from reversal to PACU assessment was longer in adults, 12.9 ± 5.3 versus 8.2 ± 3.4 min (P < 0.01). Plasma cholinesterase activity was greater in children than in adults, 8.8 ± 1.6 versus 7.0 ± 2.1 kU/l (P < 0.01).

Adults

The mean ages and weights and sex distribution were similar in the reversal and saline groups (table 1). The duration of neuromuscular block was greater in patients who had received edrophonium (P < 0.01), but the infusion rate was similar (table 2). The times from reversal to PACU assessment and the mean TOF ratios on assessment were similar in the saline-treated and edrophonium-treated patients. However, in the saline group, four had a TOF ratio <0.7, and two others were so weak on arrival in the PACU (small tidal volume, inability to head-up, weak hand-grip) that edrophonium was administered to restore ventilation and muscle tone before assessments could be made (table 2). Thus, six of the saline-treated patients demonstrated residual neuromuscular block in the PACU compared with one patient in the edrophonium group who had a TOF ratio <0.7 (P < 0.05). In five of these seven patients, recovery to TOF >0.7 occurred spontaneously within 10 min, but two from the saline group required additional edrophonium before adequate recovery was achieved. The seven adults who demonstrated residual neuromuscular block did not appear to differ from their cohorts with respect to age, duration of infusion, mivacurium requirement, plasma cholinesterase activity, or in the times from reversal to assessment (table 3).

Children

There were no significant differences in age, weight, sex distribution, duration of infusion, infusion dose, or time from reversal to PACU assessment between the saline- and edrophonium-treated children (table 1). Although all had TOF >0.7, the mean TOF ratio was less in the saline than in the edrophonium group (P < 0.01; table 2).

Discussion

This study demonstrated that, in adults, after an infusion of mivacurium sufficient to maintain intense neuromuscular block, 6 of 25 patients in whom reversal was not attempted at the end of anaesthesia had residual block on arrival in the PACU. Only 1 of 25 patients in whom the block had been reversed with 0.5 mg·kg⁻¹ edrophonium demonstrated residual block. None of the children who had received a neuromuscular block of similar intensity, half of whom had received edrophonium, demonstrated residual neuromuscular block. Although the time from reversal of the block in the operating room to assessment in the PACU was less than in adults (P < 0.05), and a greater dose of mivacurium was required to maintain an equivalent degree of neuromuscular block. The incidences of residual block, clinical weakness, and/or TOF <0.7, in the adult pa-

Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Sex (M/F)</th>
<th>Weight (kg)</th>
<th>pCHE (kU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Reversed</td>
<td>37.0 ± 8.2</td>
<td>3/22</td>
<td>65.6 ± 11.2</td>
</tr>
<tr>
<td></td>
<td>Spontaneous</td>
<td>38.0 ± 10.3</td>
<td>4/21</td>
<td>66.4 ± 15.0</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Children</td>
<td>Reversed</td>
<td>4.2 ± 2.2</td>
<td>9/16</td>
<td>17.8 ± 7.0</td>
</tr>
<tr>
<td></td>
<td>Spontaneous</td>
<td>4.7 ± 2.3</td>
<td>8/17</td>
<td>20.8 ± 8.7</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

NS = not significant.
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Table 2. Characteristics of Mivacurium Neuromuscular Blockade Related to Train-of-Four Ratio Measured on Arrival in the Postanesthesia Care Unit in Adults and Children

<table>
<thead>
<tr>
<th></th>
<th>Duration (min)</th>
<th>Dose (mg·kg⁻¹·min⁻¹)</th>
<th>Time to Assessment (min)</th>
<th>TOF Ratio (%)</th>
<th>TOF &lt;0.7 or Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversed</td>
<td>81 ± 41</td>
<td>0.006 ± 0.003</td>
<td>14 ± 6</td>
<td>92 ± 11</td>
<td>1</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>52 ± 35</td>
<td>0.006 ± 0.003</td>
<td>12 ± 4</td>
<td>86 ± 26</td>
<td>6</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversed</td>
<td>71 ± 30</td>
<td>0.018 ± 0.003</td>
<td>9 ± 3</td>
<td>100 ± 5</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>75 ± 31</td>
<td>0.018 ± 0.007</td>
<td>8 ± 4</td>
<td>93 ± 10</td>
<td>0</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01 NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

TOF = train-of-four; NS = not significant.

*Assessments and TOF ratios were not included in the two patients who received edrophonium in the PACU.

tients (24%) in whom the block was not reversed were similar to rates previously described in adults after reversal of a block produced by long-acting neuromuscular blocking drugs. This suggests that failure to reverse mivacurium-induced block may lead to residual neuromuscular block. Avoidance of reversal should be limited to those patients in whom recovery from the block has been confirmed with neuromuscular monitoring.

In children, the risk of residual neuromuscular block is low. Previous studies have demonstrated that spontaneous recovery from neuromuscular block produced by several agents, including mivacurium, occurs more rapidly in children than in adults. In addition, Meakin et al. demonstrated, using the same doses of edrophonium or neostigmine to reverse pancuronium-induced block, that more rapid recovery occurred in children than in adults. Similarly, the dose of neostigmine but not of edrophonium required to antagonize d-tubocurarine-induced neuromuscular block was less in infants and children than in adults. In the latter reports, pharmacokinetic studies showed that the volumes of distribution of neostigmine and edrophonium were similar in all age groups, suggesting that the differences were not due to altered pharmacokinetic behavior. Also, in these studies, d-tubocurarine was administered by continuous infusion to maintain a constant level of neuromuscular block, rather than by bolus injection. Nevertheless, the comparisons between children and adults apply.

The overall recovery of neuromuscular activity after reversal from spontaneous recovery and its acceleration by anticholinesterases. The more rapid rate of spontaneous recovery and the much greater mivacurium infusion requirement may result, at least in part, from greater plasma cholinesterase (pCHE) activity in these children. In adults, it has been shown that the duration of mivacurium-induced neuromuscular

Table 3. Characteristics of the Seven (14%) Adult Patients Who Demonstrated Residual Block (TOF <0.7) on Arrival in the Postanesthesia Care Unit

<table>
<thead>
<tr>
<th>Group/Patient No.</th>
<th>Age (yr)</th>
<th>Infusion (min)</th>
<th>pCHE (KU/l)</th>
<th>TOF</th>
<th>Assessment (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>74</td>
<td>6.7</td>
<td>0.55</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>37</td>
<td>6.6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>39</td>
<td>51</td>
<td>5.4</td>
<td>0.61</td>
<td>13</td>
</tr>
<tr>
<td>18</td>
<td>44</td>
<td>140</td>
<td>5.6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>40</td>
<td>31</td>
<td>30</td>
<td>4.7</td>
<td>0.19</td>
<td>16</td>
</tr>
<tr>
<td>42</td>
<td>24</td>
<td>36</td>
<td>7.2</td>
<td>0.25</td>
<td>11</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>38.0 ± 10.3</td>
<td>52.0 ± 35.5</td>
<td>7.2 ± 2.2</td>
<td>0.86 ± 0.26</td>
<td>11.9 ± 4.2</td>
</tr>
<tr>
<td>Edrophonium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>58</td>
<td>85</td>
<td>7.0</td>
<td>0.58</td>
<td>10</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>37.0 ± 8.28</td>
<td>6.8 ± 2.0</td>
<td>6.8 ± 2.0</td>
<td>0.92 ± 0.11</td>
<td>13.8 ± 6.0</td>
</tr>
</tbody>
</table>

TOF = train-of-four; NA = not applicable.
blockade is inversely related to pChE and is moderately prolonged in patients who are heterozygous for the usual and the atypical gene for pChE. Recovery is greatly delayed in patients homozygous for the atypical gene. Although some authors were unable to demonstrate age-related differences in pChE activity, it is possible to recognize pChE variants using techniques of molecular genetics so that previously unrecognized abnormalities of the enzyme can be identified.

The current study suffers from several of the problems associated with clinical investigations. Mivacurium was used to provide neuromuscular block for clinical indications. Anesthesia with propofol/fentanyl/nitrous oxide was chosen to prevent potentiation of the block and impairment of reversal by inhalational agents. The intensity of the block was maintained constant by appropriate monitoring and adjustment of the infusion rate. However, although the reversal agent, or saline, was given after some neuromuscular activity had been demonstrated 10 min earlier at the termination of the infusion, the interval from its administration and the subsequent arrival and assessment of neuromuscular activity in the PACU occasionally was delayed in adults. Thus, the assessment was made, as in clinical practice, at different times after reversal. Nevertheless, we believe the findings are applicable to clinical practice. It is interesting that the times from reversal to PACU assessment in the current study were similar to those found in previous investigations of residual neuromuscular block in adults but were less than was previously documented in children. Perhaps, if a longer time had elapsed from stopping the infusion until arrival in the PACU or if a less intense neuromuscular block had been produced, a greater degree of recovery would have been demonstrated in adults. However, in certain circumstances, such as after laparoscopic cholecystectomy, when surgery is terminated quickly, very rapid recovery from neuromuscular block is required.

We have shown that residual neuromuscular block may occur in adults if mivacurium-induced neuromuscular block is not reversed. We suggest that recovery, assessed by neuromuscular monitoring, be confirmed before reversal is omitted. Previous studies have demonstrated the effectiveness of both edrophonium and neostigmine in accelerating recovery from mivacurium in adults and in children. However, edrophonium is more effective in antagonizing an intense neuromuscular block when neostigmine may impede spontaneous recovery. When reversal is necessary, edrophonium is preferable to neostigmine, because the latter inhibits pChE to a greater extent. The inhibition probably is responsible both for the impaired recovery from intense block and for the lower neuromuscular edrophonium potency ratio found in the reversal of mivacurium than of other nondepolarizing relaxants. However, it has been shown that the administration of neostigmine during the course of a mivacurium infusion increased the circulating concentrations of the trans-trans and cis-trans stereoisomers of mivacurium and the authors suggested that this might be responsible for the impaired antagonism of the block. However, similar increases were observed after edrophonium, so that this is an unlikely explanation for any difference between neostigmine and edrophonium. In addition, the relationship between plasma concentrations of mivacurium and neuromuscular block have not been compared in this situation.

In conclusion, this randomized double-blind study has shown that, when mivacurium-induced neuromuscular blockade was allowed to recover spontaneously, residual block was not observed in pediatric patients. However, in adults, residual weakness was identified in 6 of 25 patients in whom edrophonium-reversal was replaced with saline. Consequently, it should not be assumed that the neuromuscular blockade produced by mivacurium does not need to be reversed.

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