Edrophonium antagonism of intense mivacurium-induced neuromuscular block in children

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Summary
We have studied the time course of recovery after administration of edrophonium during intense mivacurium block in children aged 2–10 yr, using thumb acceleration in response to train-of-four (TOF) stimulation. Forty-three children receiving alfentanil, propofol, nitrous oxide, isoflurane anaesthesia and mivacurium 0.2 mg kg\(^{-1}\) were allocated randomly to one of three groups. Patients in group 1 \((n = 15)\) received edrophonium 1 mg kg\(^{-1}\), 2 min after maximum block (intense block group). At the time of administration of edrophonium in this group, there was no response to TOF stimulation (100 % block) and the post-tetanic count was 10.7 (range 0–20). Patients in group 2 received the same dose of edrophonium after 10 % recovery of the first twitch (T1) in the TOF (conventional reversal). Patients in group 3 \((n = 13)\) recovered spontaneously. All patients developed complete suppression of twitch height in response to the bolus dose of mivacurium. All recovery times were measured from the point of maximum block after mivacurium. Mean time for 25 % recovery of T1 (clinical duration) was 3.8 (SD 1.1) min in the intense block group. This was significantly shorter than the conventional reversal (8.3 (2.4) min) and spontaneous recovery (9.2 (3.5) min) groups \((P < 0.001)\). The times for 75 % and 90 % recovery of T1 were shorter in the intense block group (9.4 (2.8), 12.3 (4.2) min) compared with the conventional (13.1 (3.8), 17.3 (4.8) min) and spontaneous recovery (14.9 (4.5), 17.9 (5.2) min) groups \((P < 0.01)\). Total recovery time required for 70 % recovery of the TOF ratio (T4/T1) was 8.8 (2.4) min in the intense block group. This was significantly shorter than the conventional reversal (11.9 (3.2) min) \((P < 0.05)\) and spontaneous recovery (17.1 (4.0) min) groups \((P < 0.001)\). Conventional reversal was associated with a shorter total recovery time compared with spontaneous recovery \((P < 0.01)\). The recovery index (time interval between T1 25 % and 75 %) was comparable in groups 1–3 (5.5 (2.0), 4.8 (2.1) and 5.7 (1.4) min respectively). Ten minutes after development of maximum block, the numbers of patients who recovered adequately (TOF ratio 70 % or more) were, respectively, 12 (80 %), 8 (53 %) and 1 (8 %) in groups 1–3. We conclude that edrophonium antagonized intense (no response to TOF stimulation) mivacurium-induced block in children, with significant reduction in the recovery times of T1 and TOF ratio compared with conventional reversal and spontaneous recovery. \((Br. J. Anaesth. 1996; 76: 239–244)\)

Key words

Mivacurium, a short-acting, non-depolarizing neuromuscular blocking agent, has been studied in children to create dose–response curves and to maintain adequate neuromuscular block with a continuous infusion [1–4]. A common finding was that children have increased dose requirements and faster spontaneous recovery than adults under comparable conditions. Recent evidence also suggests that, compared with adults, children have different responses to antagonist-assisted recovery of mivacurium-induced block. When the reversal agents were given at a defined point of recovery, antagonism occurred more rapidly and the dose required to produce an equivalent effect was less in children than in adults [5].

Conventional antagonism of residual non-depolarizing neuromuscular block is usually attempted at the conclusion of surgery after detection of a variable degree of spontaneous recovery. In clinical practice, however, anaesthetic or surgical requirements for neuromuscular block can change suddenly, leaving the anaesthetist in the awkward situation of needing to reverse intense non-depolarizing block, for example failed tracheal intubation after a full paralysing dose of a non-depolarizing neuromuscular blocking agent. Several investigators have tried to antagonize intense non-depolarizing neuromuscular block in adults [6–8] and children [9]. At this depth of block, administration of neostigmine or edrophonium failed to shorten the total recovery time of atracurium- or vecuronium-induced block.

In a recent report [10], we demonstrated that in adults, edrophonium antagonized intense miva-

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curium block with a reduction in clinical duration. In the present study, we have examined the time course of recovery after early administration of edrophonium during intense (no response to train-of-four (TOF) stimulation) mivacurium-induced block in children.

**Patients and methods**

We studied 43 children, ASA I or II, aged 2–10 yr (mean 5.1 yr) and weighing 10–30 kg (mean 17.4 (sd 5.1) kg). All patients were undergoing low risk, short, elective ear and throat surgery, for example tonsillectomy, adenoidectomy or myringotomy. This study was approved by the Hospital Ethics Committee and all parents gave written informed consent. We excluded any patient suffering from cardiac, vascular, respiratory, hepatic, renal or neuromuscular disorders. Patients receiving medications known to affect the activity of plasma cholinesterase enzyme or normal neuromuscular transmission were also excluded.

All patients were premedicated with oral midazolam 0.5 mg kg\(^{-1}\) 20–30 min before surgery. In the operating room, an i.v. infusion of 5% glucose in 0.225% NaCl solution was given at a rate of 4–6 ml kg\(^{-1}\) h\(^{-1}\) through a peripheral arm vein. The ECG was monitored continuously and arterial pressure was measured every 5 min using an automatic oscillotonometer (Dinamap). Anaesthesia was maintained at 32–33°C. Concentrations of isoflurane, nitrous oxide, carbon dioxide and oxygen in the inspired fraction were determined from the computer printout of the TOF Guard machine: (1) onset of mivacurium block: time interval between the end of injection of mivacurium and development of maximum block; (2) mivacurium antagonist time: time interval between development of maximum block and edrophonium administration; (3) PTC at the time of administration of edrophonium in the intense block group; (4) time interval between development of maximum block and edrophonium administration; (5) PTC at the time of administration of edrophonium in the intense block group; (6) total recovery time: time interval between the end of injection of mivacurium and recovery of TOF ratio (T4/T1) to a value of 70%; (7) T1 and TOF ratio every minute for at least 20 min after development of maximum block; and (8) number of patients in each group who were adequately recovered (TOF of 70% or more) after 10 min from the development of maximum block after mivacurium.

All patients continued to receive 0.5–1% isoflurane throughout the investigation. Antagonism was considered adequate at a TOF ratio of 70%. After tracheal extubation, patients were kept in the recovery room for at least 1 h. Patients were assessed frequently for clinical signs of adequate recovery.

Statistical analyses were performed by one-way analysis of variance (ANOVA) and Student–Newman–Keuls test was used when multiple comparisons between different groups were required. Differences were considered significant at \(P < 0.05\).
Results

All patients developed complete ablation of the TOF response (100 % block) after administration of the bolus dose of mivacurium. Onset time was comparable in all groups (mean 2.1 (range 1–3.3) min). At the time of antagonist administration, there was no response to TOF stimulation (100 % block) in the intense block group with a mean PTC of 10.7 (0–20). Mivacurium antagonism time was significantly shorter in the intense block group compared with the conventional reversal group (table 1, fig. 1).

The times taken for T1 to reach 25 %, 75 % and 90 % of control and for the TOF ratio to recover to 70 % were significantly shorter in the intense block group compared with the conventional reversal and spontaneous recovery groups (table 1, figs 1–3). However, the rate of recovery of T1, reflected by the duration of the RI, was comparable in all groups and was not affected by the method of recovery or the timing of edrophonium administration (table 1, figs 1, 2). There was no difference in the times to recovery of T1 between the spontaneous recovery and conventional reversal groups. Total recovery time was shorter in the conventional reversal group compared with the spontaneous recovery group (table 1).

Ten minutes after the development of maximum block, the numbers of patients adequately recovered were 12 (80 %), 8 (53 %) and 1 (8 %) in groups 1–3, respectively.

No patient manifested clinical signs of muscle weakness in the recovery room.

![Figure 1](image-url) Mean times for recovery of the first twitch of the TOF (T1) after spontaneous or edrophonium-assisted recovery of two levels of mivacurium-induced block. Mivacurium antagonist time (□) = interval between development of maximum block after mivacurium and edrophonium administration; clinical duration (□) = interval between development of maximum block after mivacurium and recovery of T1 to 25 % of its control; recovery index (□) = interval between 25 % and 75 % recovery of T1. For the two groups of patients who were given edrophonium, the clinical duration includes the mivacurium antagonist time. For all groups, the time required for 75 % recovery of T1 is the sum of clinical duration and recovery index.
Mivacurium is unique among non-depolarizing neuromuscular blockers in that it is metabolized by plasma cholinesterase [13]. The activity of butyrylcholinesterase is inhibited by neostigmine [14]. A recent study in children receiving mivacurium for neuromuscular block demonstrated that neostigmine decreased plasma cholinesterase activity by about 85% but edrophonium had no effect [15]. Earlier reports suggested that spontaneous recovery from mivacurium-induced block may be preferable to the routine use of antagonists [13]. However, later studies showed that in adults, when evidence of spontaneous recovery was present at the end of surgery, antagonism of residual block by neostigmine or edrophonium was superior to spontaneous recovery [16, 17]. The time saved by conventional reversal of mivacurium-induced block in adults is in the range of 7–9 min [13, 16]. In children, when anticholinesterases were given at a twitch height equivalent to 25% of control during recovery from mivacurium-induced block, the time saved by antagonist-assisted compared with spontaneous recovery of mivacurium block was short and clinically unimportant [15]. This was also the case with conventional reversal in the present study. Compared with spontaneous recovery, conventional reversal was not associated with any time saving with respect to T1 recovery. The difference between total recovery time in the conventional and spontaneous recovery groups was only 5 min. In contrast, edrophonium antagonism of intense mivacurium block was associated with significant reduction in the recovery times of T1 and total recovery time compared with spontaneous recovery. This time saving may be particularly beneficial in a busy day-care facility where the use of mivacurium may be especially indicated.

Our previous experience with antagonism of intense mivacurium block in adults demonstrated that edrophonium reduced the clinical duration but not the total recovery time to a TOF ratio of 70% [10]. In contrast, in the present study early administration of edrophonium during intense mivacurium-induced block in children was associated with shorter times for T1 and TOF recovery. The times to 25%, 75% and 90% recovery of T1 were reduced compared with conventional reversal and spontaneous recovery. Compared with the adult study, edrophonium antagonism of intense mivacurium block in children was also associated with reduction in total recovery time. Ten minutes after development of maximum block, most patients (80%) who received edrophonium during intense mivacurium-induced block had recovered adequately (TOF ratio 70% or more). A general observation was that most of the recovery times of T1 and the TOF ratio in the intense and conventional reversal groups were markedly shorter (50% or less) in children compared with adults. Spontaneous recovery in children was also faster than antagonist-assisted conventional reversal in adults. The discrepancy between adults and children with respect to recovery after edrophonium antagonism of intense mivacurium block may be an age-related variation in the response to mivacurium, methodological differences, or both, between the two studies.

Spontaneous recovery from neuromuscular blocking drugs is more rapid in children aged 1–10 yr than in adults [18]. This is especially the case with neuromuscular blocking drugs that are largely metabolized in plasma, for example atracurium and mivacurium [19]. An inverse relationship was found.
between plasma cholinesterase activity and time to first response to TOF stimulation with the use of mivacurium [20–22]. Mean cholinesterase activity in children is about 30% above that in adults [23]. Therefore, faster recovery from the effects of mivacurium in children could be related to increased clearance secondary to changes in the function of its excretory pathways, including plasma esterases. It has been suggested also that the rapid rate of spontaneous recovery from mivacurium-induced block in children may be related to rapid redistribution from the biophase [19]. Beemar and co-workers [24] pointed out that reversal time is determined by two processes: direct antagonism by the anticholinesterase and spontaneous recovery from the effects of the neuromuscular blocking agent, with the latter becoming the major determinant at profound levels of block.

The main differences between the two studies were in the method of recording of the evoked adductor pollicis response and the depth of block at which antagonism was attempted in the intense block group. Force displacement and piezoelectric acceleration transducers were used in the adult and children studies, respectively. A good level of accuracy and correlation between the two types of transducers have been reported by several investigators [25–27]. Therefore, the differences in neuromuscular monitoring equipment do not seem to be sufficient to explain the marked discrepancy between the two age groups.

There was no response to TOF stimulation at the time of administration of edrophonium in the intense block groups in the adult and children studies. However, mean PTC recorded at the time of edrophonium administration in children was 10.7. Mean PTC recorded after the initial detection of post-tetanic response in adults was 3 [10]. This finding confirms the relative resistance of children to mivacurium-induced block and may partly explain the difference in recovery characteristics.

Mangat and co-workers [28] reported that in children aged 2–12 yr, receiving halothane anaesthesia, mean clinical duration of neuromuscular block was 3.2 (range 2.9–3.6) min and 10.25 (9–11.6) min during spontaneous recovery from intubating doses of suxamethonium 1 mg kg⁻¹ and mivacurium 0.2 mg kg⁻¹, respectively. The clinical duration of mivacurium-induced block in the spontaneous recovery group in the present study was 9.2 (3.5) min and was comparable with that reported by Mangat and colleagues. However, with early administration of edrophonium during intense mivacurium-induced block, the clinical duration was reduced markedly (3.8 (1.1) min) to approach that of suxamethonium. This finding may be particularly beneficial if the indication for antagonism of intense block was failed tracheal intubation after a bolus dose of mivacurium. In this clinical situation, resumption of adequate breathing may be life saving. Mangat and co-workers [28] demonstrated that in children receiving mivacurium 0.2 mg kg⁻¹ and monitored with the use of an acceleration transducer, there was obvious disparity between recovery of respiratory muscles and the adductor pollicis brevis muscle. Spontaneous ventilation was present when T1 had recovered to only 10% of control. This suggests that early antagonism of intense mivacurium-induced block in children can restore spontaneous breathing within 3–4 min after development of maximum block.

An alternative approach to accelerate recovery from intense mivacurium-induced block might be to administer human plasma cholinesterase in the form of either whole blood or a highly purified human plasma cholinesterase preparation. Experimental studies in anaesthetized cats have indicated that antagonism of intense mivacurium-induced block could be achieved with purified human plasma cholinesterase enzyme [29]. However, Bevan [30] pointed out that the use of plasma cholinesterase preparations to antagonize intense mivacurium-induced block in humans may be considered inappropriate as it may increase the risk of serious viral infections related to transfusion of blood products. The results of the present study also indicate that this approach is not only hazardous but unnecessary in children, as edrophonium can antagonize intense mivacurium block within a clinically acceptable recovery time.

References


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