Low and high frequency stimulation tests to characterize the effects of edrophonium on vecuronium-induced neuromuscular block

M. J. Baurain, B. S. Dernovoï, A. A. d'Hollander, D. A. Hennart and F. R. Cantraine

Summary
We recorded adductor pollicis mechanical activity in response to low (0.1 Hz and 2 Hz) and high (50 and 100 Hz) frequency stimulation 15 min after edrophonium 250, 500 and 1000 μg kg⁻¹, given to antagonize vecuronium-induced block at 10, 25 and 50% pre-reversal twitch height. We studied 54 ASA class I and II anaesthetized (methohexitone, fentanyl, nitrous oxide) young adult patients allocated randomly to nine groups of six patients each. The greater sensitivity of train-of four (TOF) ratio and residual force after 100-Hz, 5-s tetanic stimulation (RF100) to residual deficit allowed discrimination more readily between the effects of edrophonium dose and pre-reversal twitch height (P < 0.001, two-way analysis of variance). The highest reversal scores (approximately 0.9 TOF ratio and 0.6 RF100) were obtained when edrophonium 500–1000 μg kg⁻¹ was given at 50% twitch height (P < 0.05, Duncan's test). (Br. J. Anaesth. 1995; 74: 12–15)

Key words

Edrophonium has been advocated for antagonism of neuromuscular block because of its rapid onset, similar duration of action and less persistent muscarinic effects compared with other anticholinesterases [1–3]. Despite these potential advantages, numerous recent studies have shown that the effects of edrophonium on neuromuscular transmission were influenced markedly either by pre-reversal twitch height, or by the dose selected (ranging from 28 to 1500 μg kg⁻¹) [4–14] or even both, as suggested in a recent review article [15]. Previous studies on the reversal properties of edrophonium are difficult to compare because of numerous differences in methodology.

The purpose of this study was to characterize recovery of neuromuscular transmission 15 min after administration of edrophonium with different stimulation patterns, including low stimulation rates (twitch height (TH) 0.1 Hz train-of-four (TOF) 2 Hz) but also tetanic stimulations at 50 and 100 Hz. The use of high stimulation rates is desirable because of the limitations of low frequency stimulation rates for the detection of residual neuromuscular block in several clinical situations [16–22]. The second purpose was to study the effects of different doses of edrophonium given at various pre-reversal twitch heights on recovery of neuromuscular transmission. Three doses of edrophonium (250, 500 and 1000 μg kg⁻¹) were given at each of three pre-determined pre-reversal twitch heights (10, 25 and 50%) in normal adult patients.

Patients and methods
We studied 54 adult patients, ASA I and II, undergoing elective lower limb surgery. The study was approved by the hospital Ethics Committee for Human Research and written informed consent was obtained from all subjects. None of the patients had clinical or routine biochemical evidence of hepatic or renal damage. All were devoid of neuromuscular disease and drugs that could interfere with neuromuscular transmission. Patients with a weight smaller than (the patient's height (cm) – 100, –15%) kg and larger than (the patient’s height (cm) – 100, +15%) kg were excluded. Mean age was 38 (range 18–60) yr and mean weight 69 (46–90) kg.

The patients received diazepam 0.2 mg kg⁻¹ orally, 1 h before anaesthesia, which was induced with methohexitone 1.5 mg kg⁻¹ i.v. After loss of consciousness, ventilation was controlled manually (50% oxygen in nitrous oxide) until the trachea was intubated after administration of vecuronium. Thereafter, ventilation was controlled mechanically with 65% nitrous oxide in oxygen and adjusted to produce an end-tidal carbon dioxide concentration of 4.4±0.3 kPa. The 54 patients allocated randomly to nine groups of six patients each received vecuronium 100 μg kg⁻¹, the recommended intubation dose (2 × ED₉₀) [23]. To measure isometric contraction of the adductor pollicis, a force displacement transducer (UC3 cell Statham TM), fitted with tension attenuator (UL4-20, Statham TM) and incorporated in a hand grip, was secured.
Antagonism of vecuronium by edrophonium after administration of edrophonium. Analysis of were limited to one measurement, performed 15 min cause high frequency stimulation produces marked a random fashion. The degree of residual force after TOF ratio, 50- and 100-Hz tetanic stimulations, 5-s twitch height and TOF ratio (2 Hz every 3 min) arms was controlled using a water warming mattress (autoregulation on 37 °C rectal temperature) and surgical sheets (monitored hypothenar temperature > 35 °C).

The 54 patients received atropine 15 μg kg⁻¹ mixed with edrophonium 250 μg kg⁻¹ (n = 18), 500 μg kg⁻¹ (n = 18) or 1000 μg kg⁻¹ (n = 18). In each of these three groups, edrophonium was administered when maximum block was reached. Thereafter, when twitch height regained 25% of control, the patients received two additional doses of 20 μg kg⁻¹. For maintenance of anaesthesia, patients received fentanyl 5 μg kg⁻¹ and dehydrobenzperidol 100 μg kg⁻¹ i.v., followed by bolus doses of fentanyl 2 μg kg⁻¹ if there was clinical evidence of inadequate analgesia. Heat loss from the body surface and the arms was controlled using a water warming mattress with adhesive tape in 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 DigitStim 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). After a 3-min recording of control twitch height, vecuronium 100 μg kg⁻¹ was given i.v. The trachea was intubated when maximum block was reached. Thereafter, mean twitch height regained 25% of control, the patients received two additional doses of 20 μg kg⁻¹.

Results
The effects of edrophonium 250 μg kg⁻¹ were too small to give clinically adequate recovery of TOF ratio by the criterion of Eriksson and colleagues [27] (0.9 TOF ratio). On the other hand, with edrophonium 500–1000 μg kg⁻¹, twitch height and RF50 were always higher than 0.9 and 0.8, respectively, at all levels of pre-reversal twitch height (two-way analysis of variance, ns) (table 1).

Fifteen minutes after administration of edrophonium, mean TOF ratio and residual force after 100-Hz, 5-s tetanic stimulation (RF100) varied according to either pre-reversal twitch height or dose of edrophonium (two-way analysis of variance, P < 0.001). There were no statistically significant interactions between pre-reversal twitch height and dose of edrophonium.

Mean values for TOF ratio of approximately 0.9 were observed in three situations: edrophonium 500 μg kg⁻¹ with a pre-reversal twitch height of 50% (0.88) or edrophonium 1000 μg kg⁻¹ with 25% and 50% pre-reversal twitch height (0.91 and 0.93, respectively) (fig. 1). These combinations represent the highest subset selected by Duncan’s multiple classification range test (P < 0.05) (table 1).

Mean RF100 values in the highest subset selected by Duncan’s multiple classification range test (P <

<table>
<thead>
<tr>
<th>Dose (μg kg⁻¹)</th>
<th>Pre-reversal TH</th>
<th>TH (%)</th>
<th>TOF (%)</th>
<th>RF50 (%)</th>
<th>RF100 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>10%</td>
<td>80 (6)</td>
<td>67 (11)</td>
<td>69 (12)</td>
<td>26 (8)</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>91 (3)</td>
<td>77 (5)*</td>
<td>72 (8)</td>
<td>29 (8)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>93 (4)</td>
<td>81 (4)*</td>
<td>81 (4)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>500</td>
<td>10%</td>
<td>92 (7)</td>
<td>68 (3)</td>
<td>92 (3)</td>
<td>43 (15)*</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>96 (3)</td>
<td>73 (3)</td>
<td>94 (2)</td>
<td>53 (11)*</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>100 (1)</td>
<td>88 (2)*</td>
<td>93 (1)</td>
<td>61 (9)*</td>
</tr>
<tr>
<td>1000</td>
<td>10%</td>
<td>93 (3)</td>
<td>68 (4)</td>
<td>85 (5)</td>
<td>31 (11)</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>95 (3)</td>
<td>91 (2)*</td>
<td>82 (6)</td>
<td>41 (8)*</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>100 (1)</td>
<td>93 (2)*</td>
<td>91 (1)</td>
<td>58 (5)*</td>
</tr>
</tbody>
</table>
possible to observe high responses (0.8) to 100-Hz vecuronium-induced neuromuscular block, it was high TOF ratio [20-22]. During antagonism of impairment of neuromuscular transmission, as neuromuscular block and dose of edrophonium. The more sensitive tests varied according to depth of sensitivity of RF100 permitted evidence of residual twitch height. Recovery of responses to these two effects of dose of edrophonium and pre-reversal deficit provided greater discrimination between the apparent recovery by these measures was complete at because with the higher doses of edrophonium, combination, or both, to select good reversal conditions, recovering of sustained neuromuscular transmission as depressed ventilatory agents are used [20-22]. A TOF ratio of 0.9 has been suggested as a good test of recovery of sustained neuromuscular transmission as depressed ventilatory response to hypoxaemia was observed at a TOF ratio of 0.7 in awake volunteers after vecuronium and a normal response was observed at a TOF ratio of 0.9 [27].

Monitoring either twitch height or residual force after 5-s, 50-Hz tetanic stimulation (RF50) was moderately helpful in discriminating any pre-reversal twitch heights or edrophonium dose combination, or both, to select good reversal conditions, because with the higher doses of edrophonium, apparent recovery by these measures was complete at all levels of pre-reversal twitch height. The greater sensitivity of TOF ratio and residual force after 100-Hz, 5-s tetanic stimulation (RF100) to residual deficit provided greater discrimination between the effects of dose of edrophonium and pre-reversal twitch height. Recovery of responses to these two more sensitive tests varied according to depth of neuromuscular block and dose of edrophonium. The sensitivity of RF100 permitted evidence of residual impairment of neuromuscular transmission, as reported previously, even in the presence of a very high TOF ratio [20-22]. During antagonism of vecuronium-induced neuromuscular block, it was possible to observe high responses (0.8) to 100-Hz, 5-s tetanic stimulations under normal clinical conditions, 15 min after neostigmine 40 μg kg⁻¹ was administered at 25 % pre-reversal twitch height [20-22]. Therefore, this test should not be considered as too sensitive or even as “unphysiological” in assessing neuromuscular transmission, as previous electrophysiological recordings in humans have revealed some motor units firing at 100 HZ in tibialis anterior muscle [28].

Despite numerous, well designed clinical studies [4-14] assessing antagonism of edrophonium on neuromuscular block, there are no data in the absence of drugs such as enflurane, isoflurane and halothane [20] on the combined effects of standardized pre-reversal paralysis levels and edrophonium doses. Isoflurane produces a dose-dependent “flickering” of the nicotinic acetylcholine-activated ion channel, causing it to vary rapidly between the open and closed states under conditions in which a drug-free channel would otherwise remain open [29]. Consequently, isoflurane potentiation of neuromuscular block induced by non-depolarizing neuromuscular blocking agents appears to be a non-competitive phenomenon and is reversible only poorly with classic anticholinesterase agents, as was reported also for enflurane and halothane [15, 20]. Moreover, in addition to anticholinesterase effects, edrophonium may also impair neuromuscular transmission: postsynaptic ion channel open time was decreased at edrophonium plasma concentrations similar to those observed during antagonism of neuromuscular block [30].

The design of our study permits a description of the relationships between dose of edrophonium and pre-reversal twitch height in nine different conditions for each studied variable (twitch height, TOF ratio, RF50 and RF100). The effects of edrophonium are defined by edrophonium dose (X axis), pre-reversal twitch height (Y axis) and mechanical activity of the adductor pollicis in response to a stimulus (Z axis), recorded 15 min after administration of edrophonium. With this approach we observed that the highest recovery scores (about 0.9 TOF ratio and 0.6 RF100) were present when edrophonium 500–1000 μg kg⁻¹ was administered at 50 % pre-reversal twitch height.

We conclude that both dose of edrophonium and depth of neuromuscular block significantly influenced the degree of recovery of neuromuscular transmission observed 15 min after administration of edrophonium, when neuromuscular transmission was assessed by the two most sensitive tests of our study (TOF and 100-Hz tetanic stimulation). Nevertheless, our data suggest that there is no advantage in modifying the dose of edrophonium according to depth of neuromuscular block, as proposed by Bevan, Donati and Kopman [15] because both the 500- and 1000-μg kg⁻¹ doses need to be given at about 50 % pre-reversal twitch height to ensure clinically adequate recovery, as assessed by a TOF ratio of at least 0.9 [27] and by the highest recovery in response to 100-Hz, 5-s tetanic stimulation (0.6 RF100).

In contrast with recent recommendations [15], we suggest that even in the absence of halogenated agents, the dose of edrophonium (500–1000 μg kg⁻¹)
should be given at a high (about 50%) pre-reversal twitch height level to provide the greatest recovery of neuromuscular transmission. Without adequate monitoring of neuromuscular transmission, such high levels are difficult to define clinically (even with the use of a peripheral nerve stimulator). Moreover, our results differ substantially from those obtained after administration of neostigmine in similar clinical conditions, with a mean TOF ratio of 0.9 and a mean RF100 of 0.8 were obtained 15 min after administration of neostigmine, administered at 25% pre-reversal twitch height. The role of edrophonium in antagonizing neuromuscular block remains debatable.

References