Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles

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Summary
We have studied the pattern of blood flow and pharmacodynamic profile of mivacurium-induced block at the adductor pollicis and orbicularis oculi muscles. We studied 30 adult patients anaesthetized with fentanyl, thiopentone, nitrous oxide–isoflurane, and mivacurium 0.2 mg kg$^{-1}$. Neuromuscular transmission was monitored with accelerometry (TOF Guard, Biometer, Denmark). Blood flow was measured at the two muscles with the use of a laser Doppler flowmeter (Laserflo BPM$^2$, Vasamedics, USA). All patients developed 100% neuromuscular block at the adductor pollicis muscle. Mean maximum neuromuscular block at the orbicularis oculi was 96.4 (SD 3.5) % (ns). Onset time, time required for 25% and 75% recovery of the first twitch in the train-of-four (T1), and a train-of-four ratio (T4/T1) of 90% at the orbicularis oculi were respectively, mean 130.4 (SD 28.5) s, 9.1 (3.2) min, 16.2 (3.9) min and 20.2 (4.3) min and were significantly shorter than the corresponding values at the adductor pollicis: 202.7 (37.2) s, 12.9 (3.9) min, 21.1 (5.1) min and 30.8 (7.4) min. For a given T1, there was significantly less train-of-four fade (T4/T1) at the orbicularis oculi than at the adductor pollicis muscle during recovery. Blood flow was comparable at the two muscles before induction of anaesthesia. Thiopentone significantly increased thenar muscle blood flow from 2.9 (1.5) to 12.3 (6.8) ml 100 g$^{-1}$ min$^{-1}$, with a further increase to 22.7 (8.0) ml 100 g$^{-1}$ min$^{-1}$ after isoflurane (P<0.001). Blood flow at the orbicularis oculi was not altered by thiopentone or isoflurane and was consistently lower than that at the adductor pollicis muscle. We conclude that the different pharmacodynamic profiles of mivacurium-induced block at the orbicularis oculi and adductor pollicis muscles were not related primarily to a difference in blood flows. (Br. J. Anaesth. 1997; 79: 24–28).

Key words

The response to a bolus dose of a neuromuscular blocking drug depends on which muscle is examined.$^1$ There can be differences in both onset time and sensitivity between various muscles. For example, the orbicularis oculi tends to require a larger dose for the same degree of paralysis compared with the adductor pollicis muscle. However, onset of paralysis is faster at the former.$^2$–$^4$ These two apparently contradictory effects depend on different factors. The dose required for a given effect in a specific muscle depends largely on the concentration required to block the receptors.$^1$ On the other hand, onset time is determined to a great extent on the rate at which the drug gains access to the receptors.$^1$ In dogs, the onset time of gallamine-induced neuromuscular block in the tibialis anterior muscle was found to be shortened by increasing blood flow to the muscle.$^5$

Human studies correlating neuromuscular response at different muscles with blood flow are lacking. With the recent availability of laser Doppler flowmeters, continuous monitoring of microcirculatory blood flow has become possible.$^6$ Using this technique we have compared blood flow at the orbicularis oculi and adductor pollicis muscles in patients during fentanyl, thiopentone, nitrous oxide–isoflurane anaesthesia. The pharmacodynamic profile of mivacurium-induced neuromuscular block was also evaluated at the two muscles using accelerometry.

Patients and methods
We studied 30 adult male patients, ASA I or II, aged 20–50 yr (mean 36.7 yr), weighing 61–82 kg (mean 68 (sd 9.4 kg), undergoing diagnostic endoscopic surgery, for example knee arthroscopy. This study was approved by the Hospital Ethics Committee and all patients gave written informed consent. We excluded any patient suffering from cardiac, vascular, respiratory, hepatic, renal or neuromuscular disorders. Chronic smokers, patients with previous head and neck surgery, history of small joint arthritis or those receiving medications known to affect normal neuromuscular transmission were also excluded.

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All patient were premedicated with oral diazepam 10–15 mg, approximately 90 min before surgery. In the operating room, lactated Ringer’s solution with 5% glucose was administered 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 using an electronic oscillotonometer. Anaesthesia was induced in all patients with midazolam 2–3 mg, fentanyl 2 \(\mu\)g kg\(^{-1}\) and thiopentone 4–5 mg kg\(^{-1}\). The airway was maintained with an appropriately sized laryngeal mask. For the first 5 min after induction, anaesthesia was maintained with 70% nitrous oxide in oxygen. This was followed by addition of 0.5–1% isoflurane endtidal concentration to the anaesthetic mixture. Ventilation was controlled to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.6–5.3 kPa). Nasopharyngeal temperature was monitored and maintained at 36–37 °C using warm blankets and heated i.v. fluids. Skin temperature over the thenar eminence and the forehead was monitored also and maintained at 32–33 °C. Concentrations of isoflurane, nitrous oxide, carbon dioxide and oxygen saturation were measured continuously by a multiple-gas analyser (Capnomac Ultima-SVI, Datex Instrumentarium Corporation, Helsinki, Finland).

The ulnar and temporal branches of the facial nerves were stimulated supramaximally with single twitch square pulses of 0.2 ms duration, repeated every 10 s. An acceleration piezoelectric transducer (Biometer International, Odense, Denmark) was fastened to the volar surface of the distal phalanx of the thumb using adhesive tape or to the upper eyelid by means of double-sided adhesive tape. At the eyelid, the piezoelectric transducer was fixed such that it measured the acceleration generated by circumferential contraction of the orbicularis oculi muscle.\(^4\)

After at least 20 min of stable anaesthetic conditions and stabilization of the twitch height recordings, each patient received an i.v. bolus of mivacurium 0.2 mg kg\(^{-1}\). At maximum block, the pattern of nerve stimulation was changed to a train-of-four (TOF) sequence at 2 Hz repeated every 15 s. Recording of the evoked orbicularis pollicis or orbicularis oculi response was carried out using a TOF Guard neuromuscular monitor (Biometer International, Odense, Denmark). All graphical and numerical neuromuscular data were recorded on a memory card and subsequently a computer printout was obtained using TOF Guard Reader software (Biometer International, Odense, Denmark). The following variables were determined for each muscle: (1) maximum twitch depression after mivacurium; (2) onset of block: time interval between the end of injection of mivacurium and development of maximum block; (3) time interval between development of maximum block and recovery of T1 to a value of 25% and 75% of its control, and recovery of train-of-four ratio (T4/T1) to a value of 90%; (4) recovery index (RI): time required for recovery of T1 from 25 to 75% of its control; (5) T1 and train-of-four ratio every 1 min for at least 30 min after development of maximum block; (6) T4/T1 ratio at 10% incremental recovery of T1.

A laser Doppler flowmeter (Laserflo BPM\(^2\), Vasamedics Inc, Minnesota, USA) was used to measure blood flow at either the adductor pollicis \((n=15)\) or the orbicularis oculi muscle \((n=15)\). A sterile 19-gauge needle type laser flowmeter probe (Laserflo BPM\(^2\), Vasamedics Inc, Minnesota, USA) was inserted percutaneously in the thenar eminence or the orbital part of the orbicularis oculi muscle. The hand and eye contralateral to the site of neuromuscular monitoring were used for blood flow measurements. Blood flow monitoring started in all patients before induction of anaesthesia and 15 min were allowed for stabilization of the flow signal. The baseline awake blood flow value was obtained as the mean of three successive readings recorded at 2-min intervals. During the course of anaesthesia, muscle blood flow was monitored continuously and recorded every 1 min for the first 10 min during induction and every 5 min during maintenance of anaesthesia.

Statistical analyses were performed by analysis of variance (for repeated measures) to compare blood flow changes within each muscle, and paired Student’s \(t\) test to compare the two muscles with respect to blood flow and neuromuscular data. Differences were considered significant when \(P<0.05\).

### Table 1  Neuromuscular data (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Orbicularis oculi</th>
<th>Adductor pollicis</th>
<th>(P)</th>
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<tbody>
<tr>
<td>Maximum twitch depression (%)</td>
<td>96.4 (3.5)</td>
<td>100</td>
<td>ns</td>
</tr>
<tr>
<td>Onset (s)</td>
<td>130.4 (28.5)</td>
<td>202.7 (37.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1 25% (min)</td>
<td>9.1 (3.2)</td>
<td>12.9 (3.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T1 75% (min)</td>
<td>16.2 (3.9)</td>
<td>21.1 (5.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Recovery index (min)</td>
<td>7.1 (2.2)</td>
<td>8.2 (1.8)</td>
<td>ns</td>
</tr>
<tr>
<td>T4/T1 (90%) (min)</td>
<td>20.2 (4.3)</td>
<td>30.8 (7.4)</td>
<td>&lt;0.001</td>
</tr>
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</table>

Figure 1  Time course of first twitch recovery at the orbicularis oculi and adductor pollicis muscles after mivacurium 0.2 mg kg\(^{-1}\) (mean, s/n).
Results

All patients developed 100% neuromuscular block at the adductor pollicis muscle. In contrast, neuromuscular block at the orbicularis oculi was 85–94% in seven patients. However, overall mean maximum neuromuscular block at the orbicularis oculi was 96.4 (sd 3.5) % and was not statistically different from the adductor pollicis muscle.

Onset time, time required for 25% and 75% recovery of T1, and T4/T1 ratio of 90% were all shorter for the orbicularis oculi than the adductor pollicis muscle. Recovery indices were comparable at the two muscles (table 1, figs 1, 2).

For a given T1, there was significantly less train-of-four fade (T4/T1) at the orbicularis oculi than at the adductor pollicis muscle throughout the course of neuromuscular recovery (fig. 3).

Blood flow was comparable at the two muscles before induction of anaesthesia. Thiopentone significantly increased thenar muscle blood flow from 2.9 (1.5) to 12.3 (6.8) ml 100 g⁻¹ min⁻¹, with a further increase to 22.7 (8.0) ml 100 g⁻¹ min⁻¹ with addition of isoflurane (P<0.001). Blood flow at the orbicularis oculi was not altered by thiopentone or isoflurane and was consistently lower than that at the adductor pollicis muscle despite comparable haemodynamics in the two groups (fig. 4).

Temperature of the skin overlying the two muscles was comparable.

Discussion

We have confirmed the current view that the onset of non-depolarizing neuromuscular block is more rapid and its duration is shorter at the orbicularis oculi compared with the adductor pollicis muscle. The difference in onset time of mivacurium-induced block between the two muscles was, on average, 1.2 min. This is consistent with the recent findings of Rimaniol and colleagues and Debaene and co-workers. Onset times of neuromuscular block at the orbicularis oculi muscle reported by Rimaniol and co-workers, using accelerometry, were 235 and 90 s after mivacurium 0.15 mg kg⁻¹ and 0.25 mg kg⁻¹, respectively. In our study, onset time of an intermediate dose of mivacurium 0.2 mg kg⁻¹ at the orbicularis oculi was 130.4 s and was in general agreement with the trends in onset time reported by Rimaniol and colleagues.

Neuromuscular blocking agents can only produce neuromuscular block when they bind
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with acetylcholine receptors at the neuromuscular junction. Therefore, onset time after injection of neuromuscular blocking drugs into a peripheral vein depends on circulatory factors, notably cardiac output, circulation time to the muscle, muscle blood flow and proximity of the target muscle to the central arterial circulation. In this study the response of the orbicularis oculi and adductor pollicis muscles were determined simultaneously in the same group of patients. This clearly obviates the possible effect of cardiac output on the onset of block. A surprising finding in this study was that blood flow in the orbicularis oculi muscle was significantly lower than that in the adductor pollicis muscle during thiopentone–nitrous oxide–isoflurane anaesthesia. The underlying reasons for the differences in blood flow between the two muscles are unclear at this stage. However, Vollmar and Habazettl noted that the nature and magnitude of the vascular effects of anaesthetics vary depending on the vascular bed and type of vessels studied. Our blood flow results suggest that, at least for the orbicularis oculi muscle, blood flow was not the main mechanism of rapid onset of action of mivacurium-induced block. It is possible however that the proximity of the orbicularis oculi to the central circulation compared with the adductor pollicis may compensate for the difference in blood flow and may have a role in accelerating the onset of neuromuscular block at the former. The onset of vecuronium-induced neuromuscular block in the adductor pollicis muscle was more rapid when the drug was injected into the central circulation, via a pulmonary artery catheter, than when the drug was given into a peripheral vein on the hand.

In our study, all patients developed 100% neuromuscular block at the adductor pollicis muscle, but neuromuscular block at the orbicularis oculi was 85–94% in seven patients. These findings, coupled with a shorter duration of mivacurium-induced block at the orbicularis oculi, reflect the relative resistance of this muscle to mivacurium-induced block. Several mechanisms have been proposed to explain the unequal sensitivities of different muscles to neuromuscular blocking agents. Recent studies, however, proved that this is related mainly to mean muscle fibre diameter and the fraction of fibre circumference occupied by the motor endplate. However, the association between duration of neuromuscular block and fibre size or endplate to fibre size ratio was relatively weak suggesting that other factors may contribute to muscle response to neuromuscular blockers. Bowman suggested that single twitch depression, and tetanic or train-of-four fade, are the result of interaction of acetylcholine antagonists with different binding sites within the neuromuscular junction. Neuromuscular blockers act at presynaptic nicotinic receptors in such a way that mobilization of acetylcholine is impaired. Thus during high frequency stimulation, transmitter output becomes exhausted so that fade occurs. In this study, there was significantly less train-of-four fade (T4/T1) at the orbicularis oculi than the adductor pollicis muscle throughout the course of neuromuscular recovery. It is therefore possible that resistance of the orbicularis oculi may reflect less prejunctional effects of mivacurium at this muscle than the adductor pollicis.

Current evidence suggests that interest is increasing in monitoring the response of orbicularis oculi muscle in clinical practice. This is mainly because of the comparable neuromuscular course at this muscle, the diaphragm and laryngeal muscles. Force displacement transducers and visual assessment have been used previously to monitor the orbicularis oculi response. Mechanomyography and electromyography are used mainly for research purposes. Visual assessment is simple but lacks reliability. The recent study by Rimanioi and colleagues and our study have demonstrated that piezoelectric acceleration transducers could be used to monitor the mechanical response of the orbicularis oculi muscle. The new generations of acceleration monitors, for example TOF Guard, are as reliable as mechanomyography and electromyography and their simplicity of operation may increase interest in routine neuromuscular transmission monitoring at different sites, including the orbicularis oculi muscle.

References


