Edrophonium and human plasma cholinesterase combination for antagonism of mivacurium-induced neuromuscular block

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Summary

We have compared the reversal characteristics of mivacurium after administration of an edrophonium–plasma cholinesterase (PCHE) combination with that produced by each antagonist alone. Forty ASA I adults were given mivacurium 0.15 mg kg⁻¹ during fentanyl–thiopentone–nitrous oxide–isoflurane anaesthesia. TOF stimulation was applied to the ulnar nerve every 12 s, and the force of contraction of the adductor pollicis muscle was recorded. When spontaneous recovery of first twitch height (T1) reached 10% of its initial control value, patients were allocated randomly to one of four groups (n=10 in each). Neuromuscular function in patients in group 1 (control group) was allowed to recover spontaneously. Patients in groups 2–4, respectively, received edrophonium 1 mg kg⁻¹ (group ED), exogenous PCHE equivalent to activity present in 25 ml kg⁻¹ of human plasma (group PCHE) or edrophonium 1 mg kg⁻¹ with exogenous human PCHE equivalent to the activity present in 25 ml kg⁻¹ of human plasma (combination group). The time to attain a TOF ratio of 0.75 in the combination group was 4.6 (SD 0.9) min. This was shorter (P<0.01) than that observed in patients in the control (16.8 (3.3) min), ED (8.9 (3.6) min) and PCHE (9.3 (1.6) min) groups. There was no difference in recovery indices between groups ED and PCHE. We have demonstrated that the edrophonium–PCHE combination significantly accelerated recovery of mivacurium-induced block compared with that observed with the use of individual antagonists. (Br. J. Anaesth. 1996;77:424–426)

Key words


Mivacurium chloride is a bis-benzylisoquinolinium non-depolarizing neuromuscular blocking agent¹. Spontaneous recovery from 90% mivacurium block to 95% twitch height and train-of-four (TOF) of 0.75 normally occurs within 15 min². We noted that these recovery times can be shortened by administration of edrophonium, neostigmine or human plasma cholinesterase (PCHE)² ³.

Although both PCHE and edrophonium produce dose-dependent antagonism of mivacurium-induced block² ⁴, each drug acts by a different mechanism. PCHE is an enzyme that enhances hydrolysis of mivacurium in plasma, whereas edrophonium (an anticholinesterase) acts mainly by increasing the concentration of acetylcholine in the end-plate region of the muscle. These differences in pharmacodynamic characteristics might confer some advantages in combining the two drugs in clinical practice. Accordingly, we have compared the reversal characteristics of mivacurium after PCHE and edrophonium in combination with that produced by each drug alone.

Methods and results

After obtaining institutional approval and informed consent, we studied 40 ASA I patients of both sexes, aged 16–51 (mean 34) yr, weighing 52–85 kg (mean 68.8 (SD 8.9) kg). All patients were undergoing elective procedures, had no neuromuscular, renal or hepatic disease, and were not receiving any drug known to interfere with neuromuscular function.

All patients received lorazepam 2 mg orally, 90 min before operation. An infusion of lactated Ringer’s solution was given i.v. before induction of anaesthesia. The electrocardiogram, haemoglobin oxygen saturation by pulse oxymetry and arterial pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5±0.5 °C. Anaesthesia was induced with fentanyl 2 µg kg⁻¹ and thiopentone 3–5 mg kg⁻¹, and maintained with 70% nitrous oxide and 0.5% inspired isoflurane in oxygen. Concentrations of isoflurane, nitrous oxide, oxygen and carbon dioxide were measured continuously by a multiple-gas analyser (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide pressure 4.8–5.3 kPa).

Isoflurane was administered for 30 min before control twitch height was recorded. The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant
contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer International, Odense, Denmark). Preload tension on the thumb was maintained at 300 g throughout the study.

After a stable neuromuscular response was obtained for 10 min, the patient received mivacurium 0.15 mg kg\(^{-1}\) i.v. as a bolus dose. Tracheal intubation was performed when neuromuscular response was abolished. Additional increments of mivacurium 0.1 mg kg\(^{-1}\) were given to patients who required continued neuromuscular block whenever the first twitch recovered to 10% of the control value.

At the end of surgery, when first twitch height (T1) (the first response in the TOF) had recovered to 10% of control, patients were allocated randomly to one of four groups (\(n = 10\) in each). Neuromuscular function in patients in group 1 (control) was allowed to recover spontaneously, whereas patients in groups 2–4, respectively, received edrophonium 1 mg kg\(^{-1}\) (group ED), exogenous human PCHE equivalent to activity present in 25 ml kg\(^{-1}\) of human plasma (group PCHE) or edrophonium 1 mg kg\(^{-1}\) with exogenous human PCHE equivalent to activity present in 25 ml kg\(^{-1}\) of human plasma (combination group). All drugs were given simultaneously into two separate i.v. catheters inserted into one arm. Atropine 0.02 mg kg\(^{-1}\) was given to all patients who received edrophonium.

Serum cholinesterase P Behring was used in this study, which is a dry concentrate of highly purified enzyme. The contents of each vial (27–83 mg) are equivalent in activity to 500 ml of fresh normal human plasma. However, cholinesterase activity is standardized by the manufacturer. The purified human PCHE is derived from donor plasma, that is hepatitis B surfactant antigen-negative and anti-HIV-1-negative. It is pasteurized at 60 °C to inactivate DNA viruses. The risk of treatment with purified human PCHE is considered comparable with administration of human albumin.

The TOF ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response: T4/T1) was recorded continuously in all patients until the TOF ratio recovered to 0.75 or more. Isoflurane was continued during this observation period. All patients were assessed in the recovery room, on admission and 10 min later, for signs of residual weakness by their ability to maintain 5-s head-lift, tongue protrusion and cough.

In all patients, two venous blood samples were obtained from an antecubital vein in the contralateral arm to that used for i.v. fluid administration for measurement of plasma cholinesterase activity. The first sample was obtained before induction of anaesthesia and the second when the TOF ratio had recovered to 0.75. Plasma cholinesterase activity was measured by the change in absorbance at 600 nm after hydrolysis of butyrylthiocholine to thiocholine, using Du Pont Dimension, Clinical Chemistry System (Wilmington, DE, USA).

Recovery times of the first twitch from 25% to 75% (recovery index) and from 10% to 95% of control, and time to a TOF ratio of 0.75 were compared using analysis of variance. Dunnett’s test was used to compare the spontaneous recovery group with each of the other groups. Comparisons between groups that received different antagonists (groups 2–4) were carried out using Tukey’s Studentized range method. All statistical analyses were carried out using BMDP statistical package, release 7.01 (University of California Press, Berkeley, CA, 1993). Unless otherwise specified, results are expressed as mean (SD). \(P < 0.05\) was considered statistically significant.

Baseline activity of PCHE was similar and within the normal range in all groups (reference range 7–19 IU ml\(^{-1}\)) (table 1). The activity in the second assay was greatest (\(P < 0.01\)) in patients who received exogenous PCHE (groups 3 and 4) compared with those in groups 1 and 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>Antagonist</th>
<th>PCHE activity (first assay)(^{2}) (ref. range = 7–19 IU ml(^{-1}))</th>
<th>PCHE activity (second assay)(^{2}) (IU ml(^{-1}))</th>
<th>Percent change in PCHE activity</th>
<th>T1 at 10 min (T1 in control)</th>
<th>TOF ratio at 10 min</th>
<th>Time to T1 recovery (min)</th>
<th>Time to TOF = 0.75 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>—</td>
<td>13.3 (1.9)</td>
<td>13.3 (1.9)</td>
<td>0% (0%)</td>
<td>72.4 (13.7)</td>
<td>0.50 (0.11)</td>
<td>8.4 (3.0)</td>
<td>10–95%</td>
</tr>
<tr>
<td>Group 2</td>
<td>Edrophonium 1 mg kg(^{-1})</td>
<td>13.6 (2.2)</td>
<td>12.5 (1.6) (\dagger)</td>
<td>-7% (6.3)</td>
<td>90.2 (12.7)</td>
<td>0.77 (0.13)</td>
<td>5.3 (3.4)</td>
<td>8.5 (3.5)</td>
</tr>
<tr>
<td>Group 3</td>
<td>PCHE 25 ml kg(^{-1})</td>
<td>11.7 (2.5)</td>
<td>21.6 (3.9) **</td>
<td>+86.4 (20)</td>
<td>98.8 (3.2)</td>
<td>0.76 (0.06)</td>
<td>3.9 (1.0)</td>
<td>7.3 (1.5)</td>
</tr>
<tr>
<td>Group 4</td>
<td>PCHE 25 ml kg(^{-1}) + edrophonium 1 mg kg(^{-1})</td>
<td>12.1 (1.2)</td>
<td>21.5 (1.5) ** (\dagger)</td>
<td>+80.1 (23)</td>
<td>100 (0) **</td>
<td>0.88 (0.5) ** (\dagger)</td>
<td>-1</td>
<td>5.7 (0.9) **</td>
</tr>
</tbody>
</table>
patients in groups ED and PCHE. There was no difference in recovery indices between groups ED and PCHE (table 1).

There was no indication of residual weakness in the recovery room after anaesthesia.

Comment

We have demonstrated that the time to attain a TOF ratio of 0.75 (after return to 10% first twitch height) was shorter ($P<0.01$) with a combination of edrophonium 1 mg kg$^{-1}$ and exogenous human PCHE equivalent to activity present in 25 ml kg$^{-1}$ of human plasma than that observed in patients in the control (16.8 (3.3) min), ED (8.9 (3.6) min) and PCHE (9.3 (1.6) min) groups. Further, both PCHE and edrophonium (in the doses used in this study and in patients with normal PCHE activity) had similar efficacy as antagonists of mivacurium-induced neuromuscular block (table 1).

The results of this study confirm our recently published data that administration of either edrophonium or exogenous PCHE equivalent to activity present in 25 ml kg$^{-1}$ of human plasma results in reliable antagonism of mivacurium-induced neuromuscular block. We have also demonstrated that when antagonism of mivacurium was attempted with edrophonium or PCHE alone, at 90% twitch depression, the time saved to return to TOF = 0.75 compared with control was < 8 min. However, with the use of the PCHE–edrophonium combination, mean time saved was > 12 min.

Our data suggest that when recovery is established, residual mivacurium block is sensitive to both increases in PCHE activity and inhibition of acetylcholinesterase at the neuromuscular junction. The relative importance of both components cannot be determined from our study. Although the magnitude of recovery was similar after administration of either PCHE or edrophonium, the PCHE–edrophonium combination proved to be superior than any of the individual drugs alone. Each drug acts by a different mechanism. Increasing PCHE activity enhances hydrolysis of mivacurium in plasma. As the plasma concentration of mivacurium declines, there is net movement of mivacurium from the neuromuscular junction back into the blood. This accelerates recovery of neuromuscular function. In addition, inhibition of acetylcholinesterase at the neuromuscular junction facilitates recovery further. It should be noted, however, that the pharmacological action of edrophonium is not limited to inhibition of acetylcholinesterase. Evidence suggests that the direct influences of the acetylcholinesterase drugs on neuromuscular transmission involve at least three distinct, although possibly interacting mechanisms: (a) weak agonist action, (b) formation of desensitized receptor complex intermediates, and (c) alteration of the conductance properties of active channels.

The dose of PCHE equivalent in activity to 25 ml kg$^{-1}$ of human plasma in a 65-kg patient represents, on average, the equivalent of PCHE activity of 1625 ml of adult human plasma. Serum cholinesterase PCHE Behring concentrate is expensive, at approximately $US 300 for one vial, and the shelf-life is 2 yr. Therefore, the average cost of PCHE administered per patient in groups 3 or 4 is more than $US 1000. Nevertheless, because of the prohibitive cost of this compound, this reversal modality is unlikely to have a routine practical application at this time. A possible exception might be the individual who is homozygous for atypical butyrylcholinesterase.

References