Influence of metoclopramide on plasma cholinesterase and duration of action of mivacurium†

H. J. Skinner¹, K. J. Girling¹, A. Whitehurst² and M. H. Nathanson³

¹University Department of Anaesthesia, Queen’s Medical Centre and Nottingham City Hospital, Nottingham NG7 2UH, UK. ²Department of Clinical Chemistry, Nottingham City Hospital, Nottingham NG5 1PB, UK. ³Department of Anaesthesia, Queen’s Medical Centre, Nottingham NG7 2UH, UK

Mivacurium is metabolized by plasma cholinesterase (PCHE). Metoclopramide inhibits PCHE in vitro and in vivo. We have assessed the effect of metoclopramide on duration of action of mivacurium and measured PCHE at baseline and at the time of maximal block. In a randomized, double-blind study, 30 patients received metoclopramide 0.15 mg kg⁻¹ i.v. or saline, followed by propofol anaesthesia and mivacurium 0.15 mg kg⁻¹. Using a TOF-Guard accelerometer, times to recovery of T1 to 25%, 75% and 90% were 13.4, 19.3 and 21.9 min in the saline group and 17.8, 25.3 and 28.8 min in the metoclopramide group (P<0.01, P<0.05, P<0.05, respectively). There were no differences in onset time or recovery index between the groups. PCHE activity at the time of maximum block decreased within each group (P<0.01) but there was no difference between groups. In a second biochemical study of eight patients, a small decrease in PCHE activity was detected after metoclopramide 0.15 mg kg⁻¹, but before administration of mivacurium (P<0.025). We conclude that metoclopramide prolongs the duration of action of mivacurium.

Br J Anaesth 1999; 82: 542–5

Keywords: interactions (drug); neuromuscular block, mivacurium; pharmacology, metoclopramide; enzymes, cholinesterase

Accepted for publication: November 18, 1998

Mivacurium is a non-depolarizing neuromuscular blocking drug that is recommended for use in short procedures.¹ It has been shown to be metabolized rapidly by plasma cholinesterase (PCHE)² and anticholinesterases are not usually required for antagonism of residual neuromuscular block produced by mivacurium. Metoclopramide has been shown to inhibit PCHE in vitro.³⁻⁵ It can be estimated from data in these in vitro studies that metoclopramide 10 mg inhibits PCHE in vivo by 10–20%. In one in vivo study, PCHE activity decreased by 25% after administration of metoclopramide 0.4 mg kg⁻¹ i.v.⁶ Neuromuscular block caused by succinylcholine, which is also metabolized by PCHE, has been shown to be prolonged by 23% after metoclopramide 10 mg i.v., 1–2 h before operation.⁷ Currently, there are no published data on the effect of metoclopramide on neuromuscular block produced by mivacurium. Drugs that unexpectedly delay recovery from neuromuscular block may compromise respiratory effort and airway integrity during emergence from anaesthesia. In this randomized, double-blind, placebo-controlled study, we aimed to assess the effect of metoclopramide on the duration of action of mivacurium and confirm the mechanism biochemically by measuring PCHE levels in vivo.

Patients and methods

Data collection

After obtaining approval from the Hospital Ethics Committee and informed consent, we studied 30 ASA I or II patients, aged 18–70 yr, undergoing elective surgery. Patients were excluded if they had a body mass index >30 kg m⁻², family history suggestive of succinylcholine apnoea or a neuromuscular disorder. An initial blood sample for PCHE assay was obtained at insertion of a venous cannula. Patients were randomized (closed envelope technique) to receive either metoclopramide 0.15 mg kg⁻¹ i.v. made up to 5 ml (n=15) or saline 5 ml (n=15). Anaesthesia was induced with fentanyl 2 µg kg⁻¹ and propofol 2.5 mg kg⁻¹ and maintained by a propofol infusion (6–10 mg kg⁻¹ h⁻¹) and 66% nitrous oxide in oxygen. The lungs were ventilated to maintain normocapnia and forearm skin temperature was kept greater than 32°C.

Using a TOF-Guard accelerometer (Biometer, Denmark), the ulnar nerve of the non-cannulated arm was stimulated

in a train-of-four (TOF) sequence at 15-s intervals, recording the first evoked response in the adductor pollicis muscle (T1). After a 5-min stable baseline period, mivacurium 0.15 mg kg⁻¹ was administered over 5 s (approximately 10 min after metoclopramide or saline). All drugs were flushed into the circulation by a free running saline infusion. The time to 95% suppression of T1 (onset time), times to recovery of T1 to 25%, 75% and 90%, and recovery index (25–75% T1) were noted. Another venous blood sample was obtained at the time of maximal twitch suppression. The study ended after T1 recovered to 90% and surgery was then commenced. The PCHE phenotype was determined for all patients, as described by Kalow and Genest. Data from patients with an atypical phenotype were excluded from further analysis as were data from patients in whom T1 failed to recover to 90%.

A second study was conducted to investigate inhibition of PCHE by metoclopramide per se. Eight patients were anaesthetized under similar conditions except that all patients received metoclopramide 0.15 mg kg⁻¹ i.v, and all study drugs were flushed into the circulation with 5 ml of saline instead of a running saline infusion. In this part of the study, three venous blood samples were obtained: at insertion of the venous cannula, 10 min after administration of metoclopramide (before mivacurium) and 5 min after mivacurium. Neuromuscular function was not monitored in these patients.

**PCHE assays**

After collection, blood samples were stored in a refrigerator. The serum component was separated and frozen as soon as possible. PCHE activity was determined using benzoylcholine as substrate by a modification of the method of Kalow and Lindsay. The serum sample (100 µl) was diluted to 10 ml with phosphate buffer (0.133 mol litre⁻¹, pH 7.4) and 2 ml of the diluted sample was added to 1 ml of benzoylcholine 0.2 mmol litre⁻¹ plus 1 ml of deionized water. Hydrolysis of benzoylcholine was measured by following the decrease in absorbance of light (240 nm) for 5 min at 25°C. Enzyme activity was expressed as µmol litre⁻¹ (µmol litre⁻¹ min⁻¹). The normal range is 630–1480 iu litre⁻¹.

Acetylthiocholine, unlike benzoylcholine, is not a substrate specific for PCHE. As acetylthiocholine was used in the only previous in vivo study, we chose to repeat all assays with this substrate (at 37°C) using a modification of the method of Lewis, Lowing and Gompertz. Acetylthiocholine is hydrolysed by plasma cholinesterase to yield acetic acid and thiocholine. Thiocholine then reacts with 5,5'-dithiobis-2-nitrobenzoic acid (DTNB) to produce 5-thio-2-nitrobenzoic acid, the formation of which can be followed spectrophotometrically. Using a FARA analyser, 5 µl of serum were diluted with DTNB/phosphate buffer 270 µl and incubated for 290 s. The reaction was started by the addition of 20 µl of acetylthiocholine 7.3 mmol litre⁻¹ and the change in absorbance of light (410 nm) followed for 18 s. Enzyme activity was expressed as iu litre⁻¹. The lower limit for this assay is 1620 iu litre⁻¹.

**Statistical analysis**

Twelve patients were needed in each group to give an 80% chance of demonstrating a 15% difference between the two groups in the time to recovery of T1 to 25% at P<0.05. Data on neuromuscular function and PCHE activity between groups were compared using unpaired t tests. Paired t tests were used to compare PCHE activity within each group. P<0.05 was considered statistically significant.

**Results**

Patient characteristics of the two groups are presented in Table 1. There was no difference in age, sex, weight or body mass index between groups. Data from three patients with phenotype UA were excluded from analysis. Mean maximum block was 99.2% in the saline and 99.8% in the metoclopramide group. A maximum block >95% was recorded in every patient. T1 recovered to 90% in all patients except one in the saline group in whom T1 reached a plateau at 78% (data excluded). The change in T1 is presented in Figure 1. Times to recovery of T1 to 25%, 75% and 90% were significantly prolonged in patients who received metoclopramide (Table 2, Fig. 1). There were no significant differences in onset times or recovery index between the two groups.
Table 2 Onset times, recovery of T1 to 25%, 75% and recovery index (25–75% T1) after mivacurium 0.15 mg kg⁻¹ (mean (SD)). P values are for unpaired t tests

<table>
<thead>
<tr>
<th></th>
<th>Saline (n = 12)</th>
<th>Metoclopramide (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time (min)</td>
<td>3.2 (1.0)</td>
<td>2.6 (0.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>T1 25% (min)</td>
<td>13.4 (3.7)</td>
<td>17.8 (3.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T1 75% (min)</td>
<td>19.3 (5.3)</td>
<td>25.3 (6.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>T1 90% (min)</td>
<td>21.9 (6.2)</td>
<td>28.8 (8.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Recovery index (min)</td>
<td>5.8 (2.1)</td>
<td>7.5 (3.5)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 3 PCHE activity (iu litre⁻¹) measured at baseline and at maximal block (mean (SD)). Assays were performed with two different substrates. P values are for unpaired t tests between groups and paired t tests within each group

<table>
<thead>
<tr>
<th></th>
<th>Saline (n = 11)</th>
<th>Metoclopramide (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate: benzoylcholine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1150 (250)</td>
<td>1130 (210)</td>
<td>0.9</td>
</tr>
<tr>
<td>Maximum block</td>
<td>1000 (200)</td>
<td>990 (200)</td>
<td>0.9</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Substrate: acetylthiocholine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3307 (557)</td>
<td>3435 (723)</td>
<td>0.6</td>
</tr>
<tr>
<td>Maximum block</td>
<td>2914 (530)</td>
<td>3009 (605)</td>
<td>0.7</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 PCHE activity (iu litre⁻¹) at baseline, after metoclopramide and after mivacurium (mean (SD)). P values are for paired t tests compared with baseline

<table>
<thead>
<tr>
<th></th>
<th>Saline (n = 8)</th>
<th>Metoclopramide (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate: benzoylcholine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1050 (180)</td>
<td>1020 (170)</td>
<td>0.025</td>
</tr>
<tr>
<td>After metoclopramide</td>
<td>980 (160)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>After mivacurium</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Three post-mivacurium blood samples were haemolysed and could not be analysed. PCHE activity within each group decreased (P < 0.01) but there was no significant difference between groups (Table 3). In the second study, there was a small but significant decrease in PCHE activity after metoclopramide with a further decrease after mivacurium (Table 4).

**Discussion**

Metoclopramide is used commonly in anaesthetic practice both as an antiemetic and prokinetic agent. We have shown that times to recovery of T1 to 25%, 75% and 90% after mivacurium were increased by more than 30% in patients who received metoclopramide. The likely cause for the increase in the duration of action of mivacurium in patients who received metoclopramide is inhibition of PCHE,1–6 producing further potentiation of the neuromuscular blocking drug. Metoclopramide 10 mg i.v., administered 1–2 h before operation, produced an increase of 23% in the time to recovery of T1 to 25% after succinylcholine.7 We have found a greater increase in the duration of action of mivacurium after a similar dose of metoclopramide.

However, we administered metoclopramide immediately before induction of anaesthesia, resulting in higher plasma concentrations when the neuromuscular blocking drug is being metabolized.11 The effect of metoclopramide on recovery from mivacurium may have been even more pronounced if the two drugs were administered simultaneously.

From previous work in humans, it can be expected that PCHE activity should be inhibited by 10–20% after metoclopramide 10 mg.3–6 In particular, Rao, Kaveeshwar and Mishra demonstrated in vivo reduction in PCHE activity after metoclopramide.6 However, we found no difference between PCHE activity in patients who received metoclopramide and those who received saline. There are three possible explanations for this finding. First, Rao, Kaveeshwar and Mishra used acetylthiocholine as substrate in their in vivo study. We planned initially to use only benzoylcholine as substrate as it is specific for PCHE. However, we repeated all assays using acetylthiocholine and still found no difference between the groups. Second, the samples obtained at maximal block may not represent the true state of PCHE activity at that time. Metabolism of mivacurium in the samples would continue until enzyme activity was sufficiently inhibited. We attempted to minimize continuing hydrolysis by prompt cooling of the samples. However, mivacurium present in the sample could still compete for PCHE with substrate in the assay and account for the lower measured activity in both groups. This effect may mask small inhibition by metoclopramide per se. Finally, in the methods used to determine PCHE, plasma is diluted in the substrate/buffer mixture. With benzoylcholine and acetylthiocholine, dilution was 200 and 59 times, respectively. Inhibition by metoclopramide is thought to be reversible and this dilution may cause its true inhibitory effect in plasma to be underestimated.12

In the initial protocol, the second sample was obtained at maximal block, as we wanted to study any inhibitory effect at this particular time. In the second study, we took an additional sample after metoclopramide but before mivacurium. A decrease of 3% in PCHE activity was detected after metoclopramide; we believe this decrease in activity is unlikely to account for the 30% increase in duration of action of mivacurium. These findings emphasize the limitations of studying enzyme inhibition by reversible inhibitors using an in vivo technique.

It may have been anticipated that if metoclopramide inhibited PCHE significantly, the time to peak effect of mivacurium may have been faster in patients who received metoclopramide. Within the limitations of the number of patients studied, we could not detect a significant difference in onset times or in the recovery indices between the two groups. Retrospective power analysis suggested that approximately 40–45 patients would be required in each group to demonstrate a significant difference in these parameters.

We selected a dose of metoclopramide 0.15 mg kg⁻¹,
Influence of metoclopramide on mivacurium approximating to the dose used commonly in anaesthetic practice. The dose of mivacurium used was 2×ED₉₅ which has been shown to result in 100% twitch suppression. We consider that a 30% increase in the duration of action of mivacurium may be clinically significant. Even though the absolute increase in neuromuscular block was only a few minutes, this may be relevant in short procedures when the duration of neuromuscular block could outlast the duration of surgery.

There is a good correlation for onset and recovery times between the TOF-Guard and mechanomyograph but the limits of agreement precludes the interchangeable use of information obtained from the two methods. Accelergraphy has been described as a convenient alternative for quantitative monitoring of neuromuscular block and has been used by other workers to assess the pharmacodynamic effects of neuromuscular blocking drugs. We used the TOF-Guard accelerometer for all patients and it is unlikely that the difference in the recovery profiles between the groups could be attributed to this aspect of the methodology.

In summary, metoclopramide significantly prolonged the duration of action of mivacurium. This effect was seen even though only marginal inhibition of PCHE by metoclopramide could be demonstrated in vivo.

Acknowledgement
This study was supported by the Nottingham University Hospital Special Trustees.

References
1 Pino RM, Ali HH, Denman WT, Barrett PS, Schwartz A. A comparison of the intubation conditions between mivacurium and rocuronium during balanced anesthesia. Anesthesiology 1998; 88: 673–8