Mivacurium-induced prolonged neuromuscular block

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Summary
We report a case of prolonged neuromuscular block after administration of mivacurium 0.2 mg kg\(^{-1}\) to a 16-yr-old patient where the duration of block was 2.5 h. The interesting points in this case were that the patient had homozygous atypical plasma cholinesterase deficiency (both parents had a normal phenotype) following liver transplantation. Investigations showed low plasma cholinesterase activity (343 iu litre\(^{-1}\); normal 600-1400) and dibucaine number was 25 (normal 76-83). Despite possessing atypical enzyme normally associated with markedly prolonged duration of suxamethonium, on two occasions the patient received suxamethonium and responded normally. This had not previously been reported. The patient demonstrated prolonged block with mivacurium as a result of atypical enzyme (despite normal metabolism of suxamethonium). (Br. J. Anaesth. 1995; 74: 234-236)

Key words
Neuromuscular block, mivacurium. Enzymes, cholinesterase.

Mivacurium is a synthetic bisbenzoylisoquinolinium diester non-depolarizing neuromuscular blocker. It is metabolized by plasma cholinesterase which ensures that the duration of action is approximately half that of the intermediate-acting neuromuscular blockers atracurium and vecuronium [1].

The rate of hydrolysis of mivacurium in vitro has been found to be approximately 70-88 % of that of suxamethonium [2, 3]. As rapid recovery and termination of clinical effect is dependent on plasma cholinesterase, it is to be expected that the neuromuscular blocking effect of mivacurium might be prolonged in patients with quantitative or qualitative defects of the enzyme [4, 5].

We present a case of prolonged neuromuscular block after mivacurium in a young liver transplant patient who presented for elective oesophagogastro-duodenoscopy.

Case report
A 16-yr-old girl presented as an inpatient for oesophagogastro-duodenoscopy. Her medical history was significant in that she had a Kasai operation (hepaticoportoenterostomy) for biliary atresia when she was 12 weeks old. She continued to have biliary atresia for which she had a liver transplant at the age of 8 yr. One month after her first liver transplant, she had acute infarction of the liver as a result of hepatic vein thrombosis and therefore had a second liver transplant which was successful. Five months later she had melaena and haematemesis for which a diagnostic oesophagogastro-duodenoscopy was performed; she was diagnosed as having oesophagitis and oesophageal stricture because of hiatus hernia, but no oesophageal varices were seen. Liver function remained normal. General anaesthesia was uneventful apart from the fact that on one occasion (January 1987) suxamethonium 40 mg (1.5 mg kg\(^{-1}\)) had a duration of action of 20 min. Subsequently she required many oesophagogastro-duodenoscopies for dilatation of the oesophageal stricture without any anaesthetic problems, and suxamethonium did not have a prolonged effect in February or October 1987. There was no known history of any other significant illness in the family. Medication included antacids (ranitidine and omeprazole) and immunosuppressants (azathioprine and cyclosporin).

Review of other systems was negative. The patient weighed 50 kg, and physical examination revealed no abnormal findings apart from abdominal incisions resulting from previous surgery. Results of preoperative liver function tests, biochemistry and haematology investigations were normal.

General anaesthesia was induced with propofol 170 mg and maintenance of anaesthesia was provided with 2 % isoflurane and 66 % nitrous oxide in oxygen. Monitoring consisted of electrocardiography, non-invasive arterial pressure, oxygen saturation, end-tidal capnography and peripheral nerve stimulation. After confirming correct placement of electrodes in the distribution of the ulnar nerve at the wrist, mivacurium 0.2 mg kg\(^{-1}\) was given to facilitate tracheal intubation. Two minutes after administration of mivacurium there was no response to train-of-four (TOF) stimulation indicating that the neuromuscular block was adequate for intubation. Tracheal intubation was carried out and the conditions were satisfactory. Ventilation was controlled to maintain end-tidal carbon dioxide concentration at about 5 %.

The duration of surgery was 20 min but marked fade was observed in response to TOF stimulation. At this stage neostigmine 2.5 mg with glycopyr-
Prolonged mivacurium block

Table 1  Plasma cholinesterase tests in the patient and parents

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Plasma cholinesterase activity (iu litre$^{-1}$)</th>
<th>Dibucaine number (range)</th>
<th>Fluoride number (range)</th>
<th>RO-20683 (range)</th>
<th>Suxamethonium sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>UU (normal)</td>
<td>600-1400</td>
<td>80-83</td>
<td>53-63.5</td>
<td>93.5-97.5</td>
<td>Not normally sensitive</td>
</tr>
<tr>
<td>UA (heterozygous)</td>
<td>430-1100</td>
<td>58-68</td>
<td>45.5-53</td>
<td>66.5-80.0</td>
<td>Moderately sensitive</td>
</tr>
<tr>
<td>AA (homozygous)</td>
<td>180-700</td>
<td>13.5-27</td>
<td>17-31.5</td>
<td>5-22.5</td>
<td>Very sensitive</td>
</tr>
<tr>
<td>Our patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>343</td>
<td>25</td>
<td>28</td>
<td>21</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Mother</td>
<td>1193</td>
<td>79</td>
<td>59</td>
<td>98</td>
<td>Not sensitive</td>
</tr>
<tr>
<td>UU</td>
<td>900</td>
<td>80</td>
<td>63</td>
<td>97</td>
<td>Not sensitive</td>
</tr>
<tr>
<td>Parents</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Ronium 0.4 mg was administered to hasten recovery. The rate of recovery was very slow and 20 min after antagonism there was still a marked fade in response to TOF stimulation, 40 min after the initial administration of mivacurium. The patient was thus transferred to the recovery ward where controlled ventilation and monitoring was continued, and propofol infusion commenced to maintain unconsciousness.

Seventy-five minutes after initial administration of mivacurium, there was still a marked fade in response to TOF stimulation and the visually estimated TOF ratio was approximately 50%, and at 140 min 75%. Propofol infusion was discontinued and full neuromuscular recovery occurred at 150 min. Soon after the patient was awake and breathing adequately. After tracheal extubation the patient was able to sustain a head lift for more than 5 s. She was observed in the recovery ward and later discharged to the ward where she made an uneventful recovery and was discharged home the following morning.

A plasma sample was sent to Lewisham hospital for measurement of plasma cholinesterase and genotyping. Plasma cholinesterase activity was measured colorimetrically using benzoylcholine as the substrate. Plasma cholinesterase activity and dibucaine number of the blood sample were found to be very low. Genotyping was performed using differential inhibition of the enzyme by dibucaine, fluoride and the specific cholinesterase inhibitor RO-20683.

The results of these tests are summarized in table 1. They suggest that the patient is most probably homozygous for the atypical cholinesterase gene or alternatively heterozygous for the atypical and silent gene. The results of the plasma cholinesterase activity and genotyping of the parents revealed that both had a normal phenotype (table 1).

Discussion

The major advantage offered by mivacurium is rapid recovery of neuromuscular block. However, duration of drug action is increased in patients with reduced plasma cholinesterase activity [4, 5].

Children with liver disease are at risk of developing oesophageal varices, and require regular oesophago-gastroduodenoscopies to monitor progress and if necessary to inject any varices with sclerosant. This procedure may only last a few minutes and so suxamethonium is commonly used, as a non-depolarizing agent with a sufficiently short action does not exist. Unfortunately if this procedure is prolonged, repeated doses may be required, resulting in bradycardia. To prevent this, large doses of atropine or glycopyrronium must be given at induction which may result in troublesome tachycardia. The short action of mivacurium makes it a potentially useful agent for this procedure.

Acquired deficiency of plasma cholinesterase may be associated with liver disease which may affect metabolism of both suxamethonium and mivacurium. It has been shown in adult patients with minimal hepatic dysfunction (Child's group A) that recovery was about 50% greater than the control group after mivacurium 0.15 mg kg$^{-1}$ [6] ($T1/T0 = 75\% \; 33 \; \text{min vs} \; 24 \; \text{min in control patients}$). But duration was markedly prolonged only in patients with severe liver dysfunction (Child's group C: $T1/T0 = 75\% \; 70 \; \text{min vs} \; 24 \; \text{min in controls}$) because of lesser plasma cholinesterase activity [6]. Our patient had normal liver function tests.

Ostergård and colleagues showed that in patients heterozygous for the atypical and usual gene, the time to 90% $T1$ recovery after administration of mivacurium 0.2 mg kg$^{-1}$ was significantly longer than controls (45.5 min vs 32.1 min) [4]. In addition they also demonstrated that in patients homozygous for the atypical plasma cholinesterase gene, even a small dose of mivacurium (0.03 mg kg$^{-1}$) induced neuromuscular block, where time to reappearance of $T1$ response was 26–128 min indicating that these patients are markedly sensitive to mivacurium compared with phenotypically normal patients [4]. In our patient with a homozygous genotype for atypical plasma cholinesterase it was not surprising that mivacurium 0.2 mg kg$^{-1}$ induced prolonged neuromuscular block exceeding 2.5 h. But recovery from block in our patient was quicker than one would expect from the reports of the effect of mivacurium 0.03 mg kg$^{-1}$.

Four cases have been reported recently where there was prolongation of neuromuscular block after mivacurium in previously undiagnosed patients with atypical plasma cholinesterase gene [7–9].

It is interesting that our patient had received a liver transplant 8 yr previously. In liver transplant patients, assays of plasma cholinesterase activity are useful as a prognostic sign indicating the function of the transplant [10]. As our patient had a functioning
liver transplant and her liver functions remained normal it is possible to assume that she “acquired” the abnormal gene for atypical plasma cholinesterase from the donor transplanted liver. We have confirmed this by testing the parents for plasma cholinesterase activity and found that both parents had a normal plasma cholinesterase phenotype.

Interestingly, in spite of her homozygous atypical cholinesterase gene, she did not have very prolonged neuromuscular block after suxamethonium on two occasions, whereas mivacurium lasted for 2.5 h. This had not previously been reported. Does this imply that some of these patients with genetic cholinesterase deficiency are able to metabolize suxamethonium but not mivacurium?

Mivacurium has the advantage that it can be antagonized by anticholinesterase agents. This did not occur in our patient. Analysing the reported cases of prolonged block after mivacurium reveals that antagonizing the block with anticholinesterase may hasten recovery to a certain extent, that is a duration of 4 h and 6 h was shown in two cases, whereas the block lasted 8 h in a young patient where antagonism was not attempted [7-9]. Obviously there is a great variation in the rate of recovery from mivacurium in patients with genetically abnormal enzyme.

It could be argued that neostigmine inhibits plasma cholinesterase activity and might therefore prolong mivacurium block. However, enzymes in patients with abnormal genotype are qualitatively and quantitatively different from genotypically normal patients and the inhibiting effect of neostigmine on plasma cholinesterase may be of little concern in these patients [11].

Another method of accelerating recovery may be to administer human plasma cholinesterase in the form of purified plasma cholinesterase [12]. Nevertheless, with the increasing risks involved in transfusing blood and blood products it is probably not justifiable when spontaneous recovery is certain without transfusion [13].

When the block is prolonged, ideal management includes supporting ventilation, maintaining the patient asleep and attempting antagonism with anticholinesterase when there is evidence of return of neuromuscular recovery. Unanticipated prolonged block occurs with an approximate incidence of 1:3000 [13] and these patients will be extremely sensitive to the neuromuscular blocking effect of mivacurium, as with suxamethonium. It is important to give a warning card to these patients for both mivacurium and suxamethonium.

References