Chronic carbamazepine therapy does not influence mivacurium-induced neuromuscular block

A. SPACEK, F. X. NEIGER, C. K. SPISS AND H. G. KRESS

Summary

Patients receiving anticonvulsant drugs chronically are relatively resistant to some non-depolarizing neuromuscular blocking drugs. We investigated the influence of chronic carbamazepine therapy on neuromuscular block induced by mivacurium in 20 otherwise healthy individuals undergoing neurosurgical operations, 10 of whom were receiving chronic treatment with carbamazepine and the other 10 served as controls. The median duration of carbamazepine therapy was 22 weeks (range 4–182 weeks). After premedication with oral diazepam, anaesthesia was induced with fentanyl and thiopentone and maintained with 0.5% isoflurane and nitrous oxide in oxygen. The ulnar nerve was stimulated and the evoked electromyogram recorded using a Datex NMT monitor. Mivacurium 0.15 mg kg$^{-1}$ ($2 \times ED_{95}$) was given as a bolus i.v. Based on the response to the first of four stimuli, lag time, onset-time, times to recovery to 10%, 25%, 50% and 75% of baseline responses and recovery index (RI 25–75%) did not differ between the two groups. We conclude that mivacurium-induced neuromuscular block was not influenced by preceding chronic carbamazepine therapy. (Br. J. Anaesth. 1996;77:500–502)

Key words

Patients receiving chronic carbamazepine therapy show a relative resistance to the neuromuscular effects of vecuronium$^{1,2}$, pancuronium$^3$, doxacurium$^4$ and pipecuronium$^5$. Resistance to vecuronium was manifested as an increased $ED_{95}$. For the other non-depolarizing blockers and vecuronium, resistance was documented either by increased hourly requirements for maintenance of a constant neuromuscular block or by a shorter duration of action$^{2–5}$. Recovery time was decreased by 65% after an i.v. bolus dose ($2 \times ED_{95}$) of pancuronium$^3$.

Mivacurium chloride is a new short-acting non-depolarizing neuromuscular blocking agent. Enzymatic hydrolysis catalysed by plasma cholinesterase is the primary metabolic pathway and distinguishes mivacurium from all other non-depolarizing neuromuscular blockers$^{6,7}$. The distinct degradation pathway of mivacurium stimulated us to investigate the interaction between carbamazepine and mivacurium in neurosurgical patients. A report on a similar topic appeared recently after we had concluded our experiments$^8$.

Patients and methods

After obtaining approval from the Institutional Ethics Committee at the University Hospital of Vienna and written informed consent, we studied 20 patients, ASA I–III, undergoing various neurosurgical procedures. All patients were free of cardiac, renal, pulmonary, hepatic and neuromuscular diseases. Individuals receiving medications thought to potentially affect neuromuscular transmission were excluded, as were those undergoing deliberate hypotension during operation. Patients with psychiatric diseases, those with a recent history of alcohol or drug abuse, and those with known or suspected reduced activity of plasma cholinesterase or with an atypical form of the enzyme were also excluded. Plasma cholinesterase was measured and found to be within the normal range in all subjects. No further characterization of the enzyme was performed. Ten patients (group I) were receiving continuous carbamazepine therapy for seizure disorders for at least 4 weeks. Plasma concentrations of carbamazepine, measured by radioimmunoassay, were determined before surgery and were within the therapeutic range (15–40 μmol litre$^{-1}$). Control patients (group II) received no anticonvulsants.

All patients were premedicated with oral diazepam 10 mg, 1 h before surgery. Anaesthesia was induced with fentanyl 3–4 μg kg$^{-1}$ and thiopentone 4–6 mg kg$^{-1}$, and maintained with 0.5% inspired isoflurane and 70% nitrous oxide in oxygen, and supplementary doses of fentanyl. After tracheal intubation, the lungs were ventilated mechanically to maintain end-tidal carbon dioxide partial pressure at 4.0–4.4 kPa. Oesophageal temperature was maintained greater than 36°C with convective heating (Bair Hugger). Routine patient monitoring included continuous ECG, invasive arterial pressure, pulse oximetry, end-tidal capnography and oesophageal temperature probe.

Neuromuscular transmission was monitored with the Datex Neuromuscular Transmission Monitor...
NMT measuring the evoked electromyographic response (EMG) of the abductor digiti minimi muscle to supramaximal stimulation of the ulnar nerve at the wrist. The NMT delivered trains-of-four supramaximal square wave impulses (100 μs width) at 2 Hz. The trains were repeated every 20 s. The heights of the EMG responses to the first stimuli in the train (as percentage of baseline) were recorded by a printer connected to the monitor. To minimize movement-induced artefacts, the patient’s hand was secured carefully to a padded board and the hand kept warm. The system was calibrated for each patient after induction of anaesthesia but before administration of mivacurium. The control EMG was recorded for a 3-min period and a stable baseline was obtained in each patient. Thereafter, a bolus dose of mivacurium 0.15 mg kg⁻¹ (2 × ED₉₀) was given i.v. The time required for the first response to decrease noticeably below the control level (lag time), time to disappearance of all responses (onset time), and times for T₁ to recover to 10%, 25%, 50% and 75% of baseline were measured in all patients. Recovery index (RI) was calculated as the time required for the responses to the first stimuli to recover from 25% to 75% of baseline.

Comparisons were made between the carbamazepine and control groups using the two tailed Student’s t test for independent samples and the nominal 5% level of statistical significance. In addition, a comprehensive exploratory statistical analysis of the data was performed. A sample size of 10 patients per treatment group can be justified by the subsequent rationale: setting the nominal alpha risk (two-sided) to 5% and defining the clinically relevant difference between the means of both groups as exceeding 1.3-fold of the standard deviation, yields a power of 80% with a sample size of 10 patients per treatment group.

**Results**

Patient data were similar in the control and carbamazepine groups (table 1). The shortest period of carbamazepine treatment was 4 weeks, the longest 182 weeks (median 22 weeks). Daily doses ranged from 300 to 1200 mg. Mean preoperative blood concentrations of carbamazepine were 27.4 (SD 9.9) μmol litre⁻¹.

The EMG response to mivacurium in both groups is shown in table 2. The EMG response to the first stimulation in the train was decreased by at least 95% in all patients. The times required for the response to recover to baseline were not significantly different between the control patients and those receiving chronic carbamazepine therapy.

**Discussion**

We have demonstrated that mivacurium-induced neuromuscular block was unaffected by chronic carbamazepine therapy. Although all measured variables of recovery were slightly shorter in the carbamazepine-treated group compared with the control group, the differences were not statistically significant. We conclude that chronic treatment with carbamazepine has no effect on neuromuscular block produced by mivacurium. Similar findings were reported recently for patients receiving chronic treatment with carbamazepine and other antiepileptic drugs. In this respect mivacurium differs from vecuronium, pancuronium, doxacurium and pipecuronium, as the duration of action of these drugs was diminished by more than 40% in patients treated with carbamazepine.

The reasons why carbamazepine treatment reduces the potency and duration of action of some non-depolarizing neuromuscular blockers while not influencing others is still unclear. Both pharmacokinetic and pharmacodynamic explanations have been proposed. The pharmacodynamic explanation is based on the assumption that treatment with anticonvulsants decreases the affinity of the acetylcholine receptor for neuromuscular blockers or increases the number of receptors on muscle fibres. This explanation could account for the increased ED₉₀ of vecuronium and, at least in part, for the shorter duration of neuromuscular block. Our study was not designed to test the potency of mivacurium in patients receiving carbamazepine therapy and, hence, the possible effect of carbamazepine on the interaction of mivacurium with receptors remains open.

The pharmacokinetic explanation for the shortened duration of action of vecuronium in patients receiving carbamazepine therapy is supported strongly by the finding of Alloul and coworkers. These authors reported that systemic clearance is markedly higher in treated than in control patients. The faster elimination of vecuronium could account for the shorter duration of action. As vecuronium concentrations at the site of action required for half-maximal neuromuscular block were similar in the control and treated patients (EC₅₀ of 151.1 (SEM 19.2) and 125.0 (11.2) ng ml⁻¹, respectively), the authors could not substantiate the hypothesis that treatment with carbamazepine lowers the affinity of the receptors for vecuronium. Increased systemic clearance of vecuronium induced by carbamazepine may be attributed to more rapid hepatic uptake and metabolism of vecuronium. As hepatic uptake and metabolism are irrelevant for mivacurium, neither its rate of degradation nor its duration of action would be expected to be altered by treatment with carbamazepine.

**Table 1** Patient data (mean (SD or range) or number). No significant differences between groups.

<table>
<thead>
<tr>
<th></th>
<th>Carbamazepine (n=10)</th>
<th>Control (n=10)</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>49.9 (19–70)</td>
<td>41.0 (18–68)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.8 (13.3)</td>
<td>70.0 (11.0)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>4/6</td>
<td>5/5</td>
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**Table 2** Lag time, onset, recovery times and recovery index (mean (SD) min) after a bolus dose of mivacurium 0.15 mg kg⁻¹ (2 × ED₉₀). No significant differences between groups.

<table>
<thead>
<tr>
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<th>Carbamazepine (n=10)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag time</td>
<td>0.7 (0.3)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td>Onset</td>
<td>3.6 (1.2)</td>
<td>3.9 (1.2)</td>
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<tr>
<td>10% recovery</td>
<td>12.7 (6.5)</td>
<td>13.0 (6.7)</td>
</tr>
<tr>
<td>25% recovery</td>
<td>16.2 (7.3)</td>
<td>16.9 (7.0)</td>
</tr>
<tr>
<td>50% recovery</td>
<td>19.5 (7.7)</td>
<td>21.6 (8.6)</td>
</tr>
<tr>
<td>75% recovery</td>
<td>24.9 (9.3)</td>
<td>26.3 (9.8)</td>
</tr>
<tr>
<td>Recovery index</td>
<td>8.7 (3.7)</td>
<td>9.3 (4.0)</td>
</tr>
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The action of atracurium was also reported not to be affected by chronic anticonvulsant therapy\textsuperscript{13-15}, although there is one contradictory report\textsuperscript{16}. We suggest that the common denominator for the different findings with mivacurium and atracurium is that their distinct degradation pathway is not influenced by carbamazepine.

Although the pharmacokinetic explanation in terms of enhanced elimination of some but not other neuromuscular blockers by carbamazepine appears plausible, pharmacodynamic mechanisms may also be involved. To elucidate these mechanisms in more detail, further pharmacokinetic, pharmacodynamic and electrophysiological studies are needed. In clinical practice, however, mivacurium may be preferred in patients receiving chronic anticonvulsant therapy when a brief but predictable duration of neuromuscular block is required or neuromuscular monitoring is unavailable.

Acknowledgement

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References

10. Kim CS, Arnold FJ, Itani MS, Martyn JA. Decreased sensitivity to metocurine during long-term phenytoin therapy may be attributable to protein binding and acetylcholine receptor changes. \textit{Anesthesiology} 1992; 77: 500–506.