Rocuronium-induced Neuromuscular Block Is Affected by Chronic Carbamazepine Therapy

Anna Spacek, M.D.*, Franz X. Neiger, M.D.,† Claus G. Krenn, M.D.,‡ Klaus Hoerauf, M.D.,* Hans G. Kress, M.D.§

Background: Patients on chronic anticonvulsant drugs are relatively resistant to certain nondepolarizing neuromuscular blockers such as pancuronium, vecuronium, pipocuronium, doxacurium, or metocurine, but not resistant to mivacurium and atracurium. This study investigated the influence of chronic carbamazepine therapy on the neuromuscular block induced by the new muscle relaxant rocuronium.

Methods: Twenty-two otherwise healthy individuals scheduled for neurosurgical operations were studied: 11 of them were on chronic treatment with carbamazepine; the others served as control subjects. The median duration of carbamazepine therapy was 9 weeks (range, 4–512 weeks). After premedication with oral diazepam, anesthesia was induced with fentanyl and thiopental and maintained with nitrous oxide/oxygen and 0.5% inspired isoflurane. Rocuronium, 0.6 mg/kg (2 × ED₉₅), was given for intubation. The ulnar nerve was stimulated, and the evoked electromyogram recorded using a Datex NMT monitor.

Results: Based on the response to the first of four stimuli, neither the lag time nor the onset-time differed between the two groups. However, the intervals of recovery to 10%, 25%, 50%, and 75% of the baseline response and the recovery index (RI, 25%–75%) were significantly shorter in patients on chronic carbamazepine therapy.

Conclusions: The authors conclude that the duration of the rocuronium-induced neuromuscular block is significantly shortened by preceding chronic carbamazepine therapy. (Key words: Anticonvulsant; drug interaction; long-term therapy; muscle relaxant.)

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Received from the Departments of Anesthesia and General Intensive Care, University of Vienna, Vienna, Austria. Submitted for publication April 17, 1998. Accepted for publication August 12, 1998. Supported by the Division of Organon Teknika, Austria. Presented in part at the 1997 Annual Meeting of the American Society of Anesthesiologists, October 18–22, 1997, San Diego, California.

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Anesthesiology, V 90, No 1, Jan 1999

PATIENTS on chronic anticonvulsant therapy have been reported to be relatively resistant to certain nondepolarizing neuromuscular blockers, such as vecuronium,1–3 pancuronium,4–6 doxacurium,7 metocurine,8,9 and pipercuronium.10 On the other hand, recent reports could not find such a resistance to mivacurium,11,12 and this seems also to be true for atracurium,11,13 although there is a contradictory report.14 The underlying mechanisms of this phenomenon, however, are still not clear. Based on the fact that atracurium and mivacurium differ from the other relaxants with respect to their metabolic pathways, a possible pharmacokinetic origin of the observed differential effects of chronic carbamazepine therapy has been suggested.11,13 Thus, we investigated the effect of chronic carbamazepine therapy on the duration of action of rocuronium, a nondepolarizing muscle relaxant that is thought to be mainly eliminated by the liver.15,16 To date, only two case reports point to a resistance to rocuronium: one in a patient on chronic phenytoin therapy,17 and another one in an epileptic patient on long-term carbamazepine therapy.18 Although data in patients under miscellaneous anticonvulsants have recently been published,19 this is the first report focusing systematically on the influence of chronic carbamazepine therapy on the action of rocuronium.

Materials and Method

The study was approved by the Institutional Ethics Committee at the University Hospital of Vienna. Written informed consent was obtained from 22 patients (American Society of Anesthesiologists physical status I-III) who were free of cardiac, renal, pulmonary, and hepatic diseases. All patients were scheduled for various neurosurgical procedures. Individuals receiving medications thought to potentially affect neuromuscular transmission were excluded from the study, as were patients undergoing deliberate intraoperative hypotension. Patients with neuromuscular disorders or psychiatric diseases and those with a recent history of alcohol or drug abuse
were also not eligible. Eleven patients (group I) were on continuous anticonvulsant therapy with carbamazepine because of seizure disorders for a minimum of at least 4 weeks. Plasma concentrations of carbamazepine, measured by radioimmunoassay, were determined before surgery and were within the therapeutic range (15–40 \( \mu \)M). Group II patients (n = 11) did not receive any anticonvulsant and served as control subjects. All patients were premedicated with oral diazepam (10 mg) 1 h before surgery. Anesthesia was intravenously induced with 3–4 \( \mu \)g/kg fentanyl and 4–6 mg/kg thiopental and maintained with 70% nitrous oxide and 0.5% inspired isoflurane in oxygen using supplemental doses of fentanyl. After intubation, the lungs were mechanically ventilated keeping the continuously measured end-tidal carbon dioxide partial pressure between 30 and 35 mmHg. Esophageal temperature was kept above 36°C with convective heating (Bair Hugger, Augustine Medical, Inc., SA, USA). Routine patient monitoring included continuous electrocardiography (ECG), invasive measurement of arterial blood pressure, pulse oximetry, end-tidal capnography, esophageal, and surface temperature probe.

Neuromuscular block was monitored with the Datex Neuromuscular Transmission Monitor NMT (Datex Instrumentarium Corp., Helsinki, Finland). The ulnar nerve was stimulated at the wrist, and the evoked compound electromyogram (EMG) was recorded from the abductor digiti minimi muscle. Every 20 s, the NMT delivered trains-of-four supramaximal stimuli at a rate of 2 Hz, each with a pulse width of 100 \( \mu \)s. The heights of the EMG responses (in percent of baseline) were recorded by a printer connected to the monitor. The patient’s hand was carefully secured to a padded board to minimize movement and was kept warm (above 32°C measured with a surface probe). The system was calibrated for each patient after induction of anesthesia but before the administration of rocuronium. The control EMG was recorded for a 3-min period, and a stable baseline was obtained in each patient. Thereafter, a single bolus dose of rocuronium (0.6 mg/kg = 2 \( \times \) ED<sub>50</sub>) was administered intravenously. The time from the start of injection required for the first response to decrease noticeably below the control level (lag time), the time from beginning of injection to 95% depression of the first twitch (onset time), as well as the times for T1 from start of injection of the bolus dose to recover to 10%, 25%, 50%, and 75% of baseline value were measured in all patients. The recovery index (RI) was calculated as the time required for the response to the first stimulus to recover from 25% to 75% of the baseline.²⁰

**Statistical Analysis**

Comparisons were made between the carbamazepine group and the control group using analysis of variance (ANOVA) and the two-tailed \( t \) test for independent samples at the nominal 5% level of significance.

**Results**

The control group and the carbamazepine group did not differ in terms of age, weight, or gender distribution (table 1). The durations of the preoperative carbamazepine treatment ranged between 14–312 weeks (90.6 ± 119.7; mean ± SD) with a median duration of 9 weeks. Daily doses ranged from 300 mg to 1800 mg. The mean preoperative plasma concentration of carbamazepine was 23.3 ± 9.2 \( \mu \)M (mean ± SD). The EMG response to the intubation dose of rocuronium in both groups is shown in table 2. Every patient responded with an at least 95% depression of the baseline EMG. Based on the response to the first of four stimuli, the lag times, and onset-times did not differ between the two groups. In contrast, the times of recovery to 10%, 25%, 50%, 75% of the baseline response as well as the recovery index (RI, 25%–75%) were significantly shorter in patients on chronic carbamazepine therapy (table 2).

**Discussion**

Chronic anticonvulsant therapy with carbamazepine significantly shortened the rocuronium-induced neuromuscular block compared with the control patients. In this respect, rocuronium does not differ from vecuronium,¹³ pancuronium,⁴–⁶ doxacurium,⁷ metocurine,⁸⁹ and pipercuronium.¹⁰ The reason is still unclear why carbamazepine treatment reduces the potency and the

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<thead>
<tr>
<th>Table 1. Biometric Data (mean ± SD)</th>
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<tbody>
<tr>
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<tr>
<td><strong>Carbamazepine Group</strong></td>
</tr>
<tr>
<td>(n = 11)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
</tr>
<tr>
<td>Age (yr) (mean ± SD)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Weight (kg) (mean ± SD)</td>
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<tr>
<td>Female</td>
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<td>Male</td>
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Table 2. Lag Time, Onset, Recovery Times, and Recovery Index after a Bolus Dose of Rocuronium (0.6 mg kg\(^{-1}\) = 2 \times ED\(_{95}\))

<table>
<thead>
<tr>
<th>Carbamazepine Group (n = 11) (min)</th>
<th>Control Group (n = 11) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag time</td>
<td>0.9 ± 0.2 (n.s.)</td>
</tr>
<tr>
<td>Onset time</td>
<td>2.8 ± 1.2 (n.s.)</td>
</tr>
<tr>
<td>10% recovery</td>
<td>19.8 ± 6.9*</td>
</tr>
<tr>
<td>25% recovery</td>
<td>25.7 ± 7.6*</td>
</tr>
<tr>
<td>50% recovery</td>
<td>30.4 ± 8.2*</td>
</tr>
<tr>
<td>75% recovery</td>
<td>36.5 ± 10.6*</td>
</tr>
<tr>
<td>Recovery index (RI)</td>
<td>10.9 ± 4.6*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

n.s. = not significant; Lag time = time from the start of injection required for the first response to decrease noticeably below the control level; Onset time = time from beginning of injection to 95% depression of the first twitch; Recovery 10%, 25%, 50%, and 75% = times for T1 from start of injection of the bolus dose to recover to 10%, 25%, 50%, and 75%, respectively, of baseline; Recovery index (RI) = time required for the response to the first stimulus to recover from 25% to 75% of the baseline.

* P < 0.05.

duration of action of some nondepolarizing neuromuscular blockers while not influencing the effects of the others, such as mivacurium\(^1\),\(^10\),\(^12\) and probably atracurium.\(^1\),\(^13\),\(^14\)

Several possible mechanisms for this interaction have been suggested: an increased metabolism or hepatic clearance via induction of specific enzymes of the cytochrome P450 system due to long-term therapy with anti-convulsant drugs such as phenytoin or carbamazepine,\(^21\) decreased sensitivity at the receptor sites, increased acetylcholinesterase activity, increased number of postsynaptic acetylcholine receptors, or increased binding of muscle relaxants to α\(_1\)-acid glycoproteins (AAG).\(^1\),\(^8\),\(^9\)

Because at least the duration of action of mivacurium was clearly shown to remain unaffected by anti-convulsant therapy,\(^1\),\(^10\),\(^12\) it is unlikely that pharmacodynamic reasons are responsible for the shorter duration of all the other nondepolarizing agents in patients on chronic anti-convulsant therapy. Mivacurium, however, has a different metabolic pathway as it is degraded \textit{in vivo} by plasma cholinesterase-catalyzed hydrolysis.\(^22\) Thus, the pharmacokinetic explanation of enhanced liver enzyme-dependent elimination of certain neuromuscular blockers by anti-convulsant drugs appears plausible. This pharmacokinetic explanation for the shorter duration of action in patients on carbamazepine therapy is strongly supported by Alloul \textit{et al.},\(^23\) who observed a markedly higher systemic clearance of vecuronium in treated patients than in control patients. In accordance with this conception, the chronic use of phenytoin was associated with a significantly shorter duration of rocuronium-induced neuromuscular block together with an increased plasma clearance of rocuronium in a patient undergoing a cadaver renal transplantation.\(^15\) Nevertheless, although the pharmacokinetic hypothesis in terms of accelerated elimination of certain neuromuscular blockers by carbamazepine-induced metabolic enhancement appears now even more plausible, additional pharmacodynamic mechanisms cannot absolutely be ruled out.

The authors thank Dr. Vladimir Nigrovic for valuable discussions and advice.

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