Augmentation of the Rocuronium-induced Neuromuscular Block by the Acutely Administered Phenytoin

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Background: The effects of an acute administration of phenytoin on the magnitude of the rocuronium-induced neuromuscular block were evaluated.

Methods: Twenty patients (classified as American Society of Anesthesiologists physical status I or II) scheduled for craniotomy were studied:

15 received rocuronium during operation (10 mg/kg), and the others served as controls. Anesthesia was induced with thiopental and fentanyl and maintained with nitrous oxide (65%) in oxygen and end-tidal isoflurane (1%). The ulnar nerve was stimulated supramaximally and the evoked electromyography was recorded using a neuromuscular transmission monitor. Continuous infusion of rocuronium maintained the neuromuscular block with first twitch (T1) between 10 and 15% for 45 min before the start of an infusion of either phenytoin or NaCl 0.9%. Twitch recordings continued for 60 min thereafter. Arterial blood samples were collected at the predefined time points (four measurements before and four after the start of the infusion) to determine the concentrations of phenytoin and rocuronium and the percentage of rocuronium bound to plasma proteins.

Results: The first twitch produced by an infusion of rocuronium remained constant during the 15 min before and the 60 min after the start of the saline infusion. After the phenytoin infusion, the twitch decreased progressively, but the plasma concentrations and the protein-bound fraction of rocuronium did not change.

Conclusion: Phenytoin acutely augments the neuromuscular block produced by rocuronium without altering its plasma concentration or its binding to plasma proteins. (Key Words: Acute administration; anticonvulsant; drug interaction; muscle relaxant.)

THE acute effects of phenytoin on the neuromuscular block produced by a nondepolarizing muscle relaxant apparently differ from those after long-term administration of anticonvulsant drugs. In humans, the acute administration of phenytoin enhanced1 and the long-term intake shortened2,3 the neuromuscular block produced by vecuronium. If the acute effects reported by Gray et al.1 could be reproduced with yet another nondepolarizing muscle relaxant, the argument for an acute pharmacodynamic interaction between phenytoin and the nondepolarizing muscle relaxants would be strengthened. The goal of the current study was to evaluate the effect of acutely administered phenytoin on the pre-established neuromuscular block produced by an infusion of rocuronium.

Materials and Methods

The study was approved by the Institutional Review Board of the University Hospital of Regensburg, Germany, and written informed consent was obtained from each patient. Twenty patients scheduled to undergo elective craniotomy for tumors or a cerebrovascular anomaly were evaluated. Fifteen patients required intra-
operative anticonvulsant prophylaxis with phenytoin (group 1), whereas five patients did not require phenytoin prophylaxis and served as controls (0.9% saline infusion, group 2). All 20 patients (classified as American Society of Anesthesiology physical status I or II) had normal cardiac, renal, pulmonary, and hepatic function. Patients with neuromuscular disease or who were taking drugs known to alter the neuromuscular transmission were excluded from the study. Also excluded were patients with psychiatric diseases and those with a recent history of alcohol or drug abuse.

The patients were premedicated with 20 mg oral chlorpromazine 1 h before surgery. After preoxygenation, anesthesia was induced with 3–5 mg/kg thiopental and 3–5 μg/kg fentanyl injected intravenously. After tracheal intubation, the lungs were mechanically ventilated to keep the end-tidal carbon dioxide level between 30 and 35 mmHg. Anesthesia was maintained with 65% nitrous oxide in oxygen and 1% end-tidal isoflurane and supplemented with fentanyl as judged by clinical criteria. The esophageal temperature was maintained at more than 36°C using convective heating. Patient monitoring included electrocardiography, invasive measurement of arterial blood pressure, pulse oximetry, end-tidal capnography, and esophageal and skin temperatures.

Neuromuscular transmission was monitored using the Datex Neuromuscular Transmission Monitor (Datex Instrumentarium Corp., Helsinki, Finland). Every 20 s the monitor delivered to the ulnar nerve via surface electrodes a train-of-four supramaximal stimuli at a rate of 2 Hz, with each stimulus lasting 100 μs. The patient’s hand was secured carefully to a padded board to minimize movement and was kept warm (>32°C as measured using a skin thermistor). Electromyographic data from the abductor digitii minimi muscle were recorded in each patient for a 3- to 5-min period after anesthesia was induced, but before rocuronium was administered. A stable baseline was obtained in each patient. Thereafter, a bolus dose of rocuronium (0.9 mg/kg = 3 × ED₉₀) was injected intravenously to facilitate tracheal intubation.

When the first twitch in the train (T₁) reappeared, rocuronium administration began with an intravenous infusion at an initial rate of 8 ± 3 μg · kg⁻¹ · min⁻¹. To obtain and maintain a steady state neuromuscular block of 85–90%, the infusion rate was adjusted in steps of 1 μg · kg⁻¹ · min⁻¹. The study was initiated after a stable T₁ amplitude was established at between 10 and 15% for 30 min without changes in the infusion rate or the inhaled concentration of isoflurane. During the preinfusion study period, which lasted 15 min, the magnitude of the twitch was recorded every 5 min. The four sampling times were labeled −15, −10, −5, and 0 min. At each sampling time, nine measurements of T₁ were recorded and the arterial blood samples were collected. One sample of 8 ml was placed in a heparin-prepared tube containing 2 ml NaH₂PO₄, 1 ml, and was used to measure the rocuronium concentration in plasma, whereas another sample of 6 ml blood was used to measure the protein-bound fraction of rocuronium. An infusion of either phenytoin or saline was started at time zero.

Phenytoin was administered to the patients of group 1 in a concentration of 25 mg/ml at a rate of 25–50 mg/min to a total dose of 10 mg/kg. The infusion rate was slowed when the mean arterial pressure decreased to less than 80% or when relevant changes, such as bradycardia or a block, appeared on the electrocardiogram. Patients in group 2 received an infusion of saline, 0.9% (0.4 ml/kg), at a rate of 1 ml/min. The infusions were completed within 15–30 min. The magnitude of the first twitch was recorded (nine observations at each sampling time) and arterial blood samples were collected 10, 20, 40, and 60 min after the start of the infusion. Blood samples were centrifuged immediately (4°C at 3,000 rpm for 10 min), and the plasma was stored at −70°C until the total and the protein-free concentration of rocuronium was measured using a high-performance liquid chromatography method that can distinguish the parent drug and its metabolites. No metabolites could be detected in the plasma samples. The protein-free fraction of rocuronium was obtained by centrifugation (2,000 rpm for 60 min) of serum and ultrafiltration using Centricon 1 membranes (20,000 D, Sartorius, Germany), according to the method reported by Jacob et al. The percentage of protein-bound rocuronium was calculated from the difference between total and free levels. In addition, separate blood samples (8 ml each) were collected from patients in group 1 before and 20, 40, and 60 min after the start of the phenytoin infusion to determine the phenytoin concentrations by fluorescence polarization immunoassay.

**Statistical Analyses**

The first twitch was transformed to its logit (logit T₁ = ln[T₁ / (100 − T₁)]). The nine transforms for each sampling period were averaged and the arithmetic means were used for further analysis. T₁ recorded as 0% was set to 0.1% to obtain a usable logit transform. The total plasma concentrations of rocuronium or phenytoin and the percentage of rocuronium bound to plasma proteins were first converted to their logarithms and the trans-
forms were used for statistical analyses. The transformed data were subdivided into two groups, a saline and a phenytoin group, and each group was further subdivided into two periods, that before and that after the start of infusion. The data in the four subgroups were frequently non-normally distributed as estimated by the Levene test for homogeneity of variances. In these instances, both the parametric (mean, SD, and t test) and nonparametric analyses (median, lower and upper quartiles, Mann-Whitney U test, and the Spearman rank order correlation) were performed and the results of both analyses are reported. We decided whether a result might be attributed to a chance observation based on a probability of 5% or more associated with a chance observation (i.e., \( P < 0.05 \)).

Results

Seven women and eight men who were 45.1 ± 11.4 yr old (mean ± SD) and weighed 77.6 ± 13.5 kg were studied in group 1; five patients were included in group 2, four women and one man who were 38.8 ± 16.4 yr old and weighed 74.8 ± 8.2 kg.

Figure 1 shows the magnitudes of the first twitch in individual patients as a function of time. A marked decrease in the twitch size is evident in patients receiving phenytoin but not in those receiving saline.

Table 1 is a numeric summary of the data. Before the infusions were started, the twitch sizes were within the range specified in the experimental design, albeit slightly smaller in the phenytoin than in the saline group. After the start of the infusions, the twitch size did not change in the saline group but was markedly decreased in the phenytoin group.

The wider spread of the twitch sizes in this subgroup may be explained by an association of the smaller twitch sizes with the longer times elapsed after the start of the phenytoin infusion (Spearman rank order correlation, \( P < 0.001 \)).

Figure 2 shows the time course of the total plasma concentration of rocuronium in individual patients. Inspection of the data reveals no marked differences between the saline and phenytoin groups or between the pre- and postinfusion periods within each group.

Table 2 summarizes the binding of rocuronium to plasma proteins. The extent of protein binding was not altered after the saline infusion. The bound fraction was, however, slightly decreased after the phenytoin infusion.

In most patients, the peak total plasma concentrations of phenytoin were established by 20 min after the start of the infusion, and the concentrations decreased thereafter.

Discussion

The results clearly show that a stable neuromuscular block produced by a constant infusion of rocuronium is augmented by an acute administration of phenytoin. Phenytoin rapidly decreases the twitch size but does not

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<th>Table 1. Twitch (T1 in %)</th>
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<tr>
<td><strong>Saline infusion</strong></td>
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<tr>
<td>Mean</td>
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<td><strong>Phenytoin infusion</strong></td>
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<td>Median</td>
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* The saline group consisted of 5 and the phenytoin group of 15 patients. The pre- and postinfusion periods consist of 4 observations each.
† The twitch is smaller in comparison with the corresponding period in the saline group (Mann-Whitney U test, \( P < 0.001 \)).
‡ The twitch is significantly smaller in comparison with the corresponding value during the preinfusion period in the same group as well as during the postinfusion period in the saline group (Mann-Whitney U test, \( P < 0.001 \)).
change either the total concentration of rocuronium in plasma or the extent of its binding to plasma proteins. The results confirm earlier findings with vecuronium in patients, and with d-tubocurarine and pancuronium or fozadinum in rats after acute administration of phenytoin, carbamazepine, or valproic acid.

Currently available information about the interaction between anticonvulsants and nondepolarizing muscle relaxants may be summarized briefly as follows: Acute administration of anticonvulsants augments neuromuscular block, whereas chronic administration reduces the duration of action of all aminosteroidal muscle relaxants (vecuronium, pancuronium, pipercuronium, and rocuronium, metocurine, and doxacurium but not of the ester benzylisoquinoline relaxants atracurium (with a possible exception) and mivacurium. Possible explanations of the opposite effects of the acute and chronic administration of anticonvulsant drugs include a pharmacodynamic or a pharmacokinetic interaction, or both. We believe that the pharmacokinetic explanation, such as through an enhanced systemic clearance of the relaxants, accounts well for the effects of chronic administration of anticonvulsants, and the pharmacodynamic explanation accounts for the acute effects of these drugs.

A plausible pharmacodynamic explanation for the clinical findings with muscle relaxants in patients treated acutely with phenytoin or carbamazepine may be based on the in vitro effects of these drugs on neuromuscular transmission. Although the precise mechanisms are still unclear, phenytoin was reported consistently to decrease the stimulus-induced release of acetylcholine from the motor nerve terminals. The extent of this acute in vitro inhibition by clinically relevant concentrations of phenytoin was estimated from the quantal content of acetylcholine. The content was decreased by approximately 20% in the frog neuromuscular junction and by 50% in a mouse muscle. A diminution of the presynaptic activity induced by phenytoin, described as membrane stabilization, also was documented in cats in vivo. Succinylcholine-induced repetitive firing of the motor nerve terminal was suppressed, whereas the equieffective doses of succinylcholine were reduced (leftward shift of the dose-response curve) by a 30-mg/kg intravenous injection of phenytoin. The findings indicate a diminished transmitter output. We suggest that our findings may be explained by postulating that phenytoin acutely reduces the stimulus-induced release of acetylcholine.

Although the decrease in the twitch size by phenytoin develops rapidly, it showed no association with the plasma concentration of the drug. The lack of correlation (hysteresis) probably indicates that the drug is only

Table 2. Percent of Rocuronium Bound to Plasma Proteins

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<th>Preinfusion</th>
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<th>Postinfusion</th>
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<tr>
<td>Saline infusion</td>
<td></td>
<td>20</td>
<td></td>
<td></td>
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<tr>
<td>Mean (mean ± SD)</td>
<td>83.1 (78.3-87.8)</td>
<td>19†</td>
<td>83.1 (78.1-88.2)</td>
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<tr>
<td>Median (lower and upper quartile)</td>
<td>82.5 (80.1-84.8)</td>
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<td>83.7 (79.5-88.1)</td>
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<tr>
<td>Phenyltoin infusion</td>
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<tr>
<td>Mean (mean ± SD)</td>
<td>76.2 (63.5-88.9)</td>
<td>51†</td>
<td>73.4 (59.8-87.0)</td>
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<tr>
<td>Median (lower and upper quartile)</td>
<td>80.7 (67.3-85.5)</td>
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<td>77.5 (66.6-84.5)</td>
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*Due to the theoretically expected and indeed experimentally observed nonnormal distribution of the percentage values, the results of both the parametric and the nonparametric analysis are presented.
†Six and nine observations are missing from the preinfusion and postinfusion periods in the phenyltoin group, respectively. In the saline group, one value is missing during the postinfusion period.
‡The percent of rocuronium bound to plasma proteins is smaller than that in the saline group during the postinfusion period (Mann-Whitney U test, P = 0.00522).
slowly distributed in the body. Thus, the peak phenytoin concentration in the muscle tissue and in the synaptic clefts might be delayed. The duration of the postulated presynaptic effect of phenytoin is not known.

In conclusion, our study clearly shows that an acute administration of phenytoin augments the steady state neuromuscular block produced by rocuronium without influencing the plasma concentration of rocuronium or the extent of its protein binding.

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References