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Geographic Regional Differences in Rocuronium Bromide Dose–Response Relation and Time Course of Action

An Overlooked Factor in Determining Recommended Dosage

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Background: **Geographic location is not acknowledged as a stratifying factor that can directly affect drug potency, because drugs are still licensed with the same recommended dose for different geographic regions. The aim of the current study was to compare the potency and duration of action of rocuronium bromide in 54 patients in three countries with different life habits, diet, and ambient conditions, namely white Austrians, white North Americans, and Han Chinese in China.**

Methods: **Neuromuscular block of six consecutive 50-μg/kg rocuronium incremental doses followed by 300 μg/kg was evaluated using the Relaxometer mechanomyograph (Groningen University, Groningen, Holland). Dose–response curves were created using log-dose-probit transformation. The authors compared rocuronium bromide ED_{50}, ED_{90}, and ED_{95} (effective doses required for 50%, 90%, and 95% first twitch depression, respectively) as well as Dur_{25} and $Dur_{0.8}$ (times from last incremental dose administration until 25% first twitch and 0.8 train-of-four ratio recovery, respectively) in patients of the three countries.**

Results: **Rocuronium ED_{50}, ED_{90}, and ED_{95} were significantly higher in Austrian patients (258 ± 68, 530 ± 159, and 598 ± 189 μg/kg) and Chinese patients (201 ± 59, 413 ± 107, and 475 ± 155 μg/kg) compared with American patients (148 ± 48, 316 ± 116, and 362 ± 149 μg/kg, respectively). Dur_{25} and $Dur_{0.8}$ were significantly shorter in Austrian patients (22.3 ± 5.5 and 36.9 ± 12.8 min) and Chinese patients (30.4 ± 7.5 and 45.7 ± 15.9 min) compared with American patients (36.7 ± 8.5 and 56.2 ± 16.7 min, respectively).**

Conclusions: **The authors demonstrated a significant difference in rocuronium potency and duration of action among patients in the three countries. Larger studies are required for determining dosage recommendations for different geographic regions.**

VARIABILITY of drug responsiveness could result from several factors. However, geographic location is not acknowledged as a stratifying factor that can directly affect drug potency. This has been a relatively neglected area of investigation, and drugs are still licensed with the same recommended dose for different geographic locations. In 1969, Ronald Katz[1] described how, during the course of a 1-year sabbatical, he was surprised to observe clinically that the dose of tubocurarine that regularly abolished the twitch response to stimulation of the ulnar nerve in white patients in New York, New York, did not do so in white patients in London, England. He was fascinated by the fact that American anesthesiologists routinely used doses of tubocurarine that seem "homeopathic" to their English colleagues. What he found even more intriguing was the fact that the manufacturing company, in response to demand, prepared tubocurarine in two different concentrations, one for each country on both sides of the Atlantic Ocean. Recently, Fiset *et al.*[2] demonstrated a similar transatlantic difference in vecuronium potency between Montreal, Quebec, Canada, and Paris, France.

The absence of apparent regional differences in various studies assessing potencies of other neuromuscular blocking drugs such as pancuronium, atracurium, mivacurium, and cisatracurium could be simply attributed to the fact that, to date, no structured study specifically aiming at examining regional difference was conducted for these neuromuscular blocking drugs. Investigations to elucidate the extent of such differences among different regions are confronted by many obstacles that were taken into consideration while designing our study, because we used mechanomyography that can precisely quantify the neuromuscular block; rocuronium was obtained from the same European production line (Organon, Oss, Holland), was transported under the strict transport instructions of the manufacturer, and was given within the shelf life; and one primary investigator (A.A.D.) supervised the strict implementation of the same study protocol in all three countries with use of the same equipment.

The aim of our study was to compare the potency and duration of action of rocuronium bromide in 54 patients in three countries with different life habits, diet, and ambient conditions, namely white Austrians, white North Americans, and Han Chinese of second-generation Han Chinese descent in China.

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Materials and Methods

A prospective controlled clinical consecutive study was conducted in three centers—Englewood Medical Center (Englewood, New Jersey), Dalian Medical University (Dalian, People's Republic of China), and Graz Medical University (Graz, Austria)—in conformity with the guidelines of the "Consolidated Standards of Reporting Trials (CONSORT) Statement,"[3] "Good Clinical Research Practice (GCRP) in Pharmacodynamic Studies of Neuromuscular Blocking Agents,"[4] and editorial recommendations.[5] After approval was obtained from Englewood Medical center institutional review board, Graz Medical University ethics committee, and Dalian Medical University ethics committee, all patients who agreed to participate in the study gave written informed consent. Potential participants with a history of neuromuscular disease, small joint arthritis, or body mass index < 20 or > 26 kg/m^2,[6] and patients receiving treatment with drugs thought to interfere with neuromuscular transmission were excluded from the study.

Eighteen white patients, nine males and nine females, with American Society of Anesthesiologists physical status I or II, aged 30–50 yr, and undergoing general anesthesia for scheduled elective surgery were first recruited at Englewood Medical Center. Shortly after that, each recruited patient was matched for sex, American Society of Anesthesiologists physical status, approximate age, and approximate body weight with 18 white patients in Graz University Hospital, followed by 18 matched Han Chinese patients in Dalian University Hospital.

Anesthesia was induced with 1.5 μg/kg fentanyl and 2–3 mg/kg propofol until the eyelash reflex was obtunded. A laryngeal mask airway was inserted, and mechanical ventilation was adjusted to maintain 25–35 mmHg end-tidal carbon dioxide. Anesthesia was maintained with 100- to 150-$\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol and 0.1- to 0.3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil infusions. Patients were warmed using a forced-hot-air blanket to maintain core temperature above 36°C and skin temperature above 32°C. Estimated fluid and blood losses were replaced by Ringer's solution.

The neuromuscular block at the adductor pollicis muscle was evaluated using the Relaxometer mechanomyograph (Groningen University, Groningen, Holland).[7] After anesthesia induction, the force transducer was attached to the thumb, and the ulnar nerve was stimulated supramaximally at the wrist (pulse width 200 μs, square wave) *via* surface electrodes with train-of-four (TOF) stimuli (2 Hz for 2 s) at 12-s intervals. Data were continuously recorded using the AZG-Relaxometer 5.0 program (Groningen University, Groningen, Holland). T_1 (first twitch of the TOF), expressed as percentage of control response, and the TOF ratio (T_4:T_1) were used for the evaluation of neuromuscular block.

After T_1% baseline stabilization, six consecutive 50-μg/kg rocuronium incremental doses were administered into a rapidly running infusion. Each incremental dose was given after three consecutive T_1 responses did not register a decline. T_1% achieved after each rocuronium bolus was recorded. Rocuronium dose–response curves were created according to the cumulative dose–response method of Donlon *et al.*[8] Individual patients' dose–response relations were examined by least squares linear regression of the logarithm of each dose against a probit transformation of T_1%, from which the doses required for 50%, 90%, and 95% T_1 depression (ED_{50}, ED_{90}, and ED_{95}, respectively) were calculated. Because probit values for 0% and 100% do not exist, 0% and 100% T_1 depression were considered missing values.

After all six incremental doses, or if 100% twitch depression was achieved after any of the incremental doses, 300 μg/kg rocuronium was administered in addition to the remainder of the incremental doses. Patients were allowed to recover spontaneously from the neuromuscular block, and Dur_{25} (time from last incremental dose administration until 25% T_1 recovery), Dur_{25-75} (time from 25% to 75% T_1 recovery), $Dur_{25-0.8}$ (time from 25% T_1 to 0.8 TOF ratio recovery), and $Dur_{0.8}$ (time from last incremental dose administration until 0.8 TOF ratio recovery) time-course-of-action variables[4] were calculated.

Statistical Analysis

Because ED_{95} is the basis for determining the recommended dosage for neuromuscular blocking drugs, comparing rocuronium ED_{95} among patients of the three groups was considered the primary end point of our study. Based on data from a previous study[2] of transatlantic difference in vecuronium dose response, where the mean ED_{95} was 44.2 ± 10.9 μg/kg in Montreal compared with 71.9 ± 30.5 μg/kg in Paris, our *a priori* power analysis for one-sided *t* test ($\alpha = 0.025$ to accommodate for two comparisons according to Bonferroni correction) showed that a group size of 17 patients would be required to reveal a statistically significant difference between the groups with more than 80% power. One-way analysis of variance was used for statistical analysis. The Tukey-Kramer *post hoc* test was used to determine which intergroup differences were statistically significant. Data were expressed as mean ± SD. $P < 0.05$ was considered statistically significant.

Results

Patient demographics are presented in table 1. There were no significant differences among the three groups regarding the duration of T_1 stabilization, skin temperature, core temperature, mean arterial pressure, estimated fluid and blood losses, and propofol and remifentanil doses during the neuromuscular monitoring period of the study.

Table 1. Patient Demographics

	Austrian Group	Chinese Group	American Group
Age, yr	37.7 ± 13.2	44.8 ± 6.9	40.8 ± 12.9
Weight, kg	74.4 ± 8.0	68.1 ± 13.1	71.9 ± 12.7
Height, cm	176 ± 8	168 ± 10	177 ± 9
Body mass index, kg/m^2	24 ± 1.1	24.1 ± 0.6	24.5 ± 1.2

No significant differences between the three groups. Data are mean ± SD; n = 18.

Table 2. Rocuronium Effective Doses

	Austrian Group	Chinese Group	American Group
ED_{50}, μg/kg	258 ± 68*	201 ± 59‡	148 ± 48†
ED_{90}, μg/kg	530 ± 159*	413 ± 107§	316 ± 116†
ED_{95}, μg/kg	598 ± 189*	475 ± 155§	362 ± 149†

Tukey-Kramer *post hoc* test. Data are mean ± SD; n = 18.

* $P < 0.001$ compared with the American group. † $P < 0.05$ compared with the Chinese group. ‡ $P \leq 0.01$ compared with the Austrian group. § $P \leq 0.05$ compared with the Austrian group.

ED_{50}, ED_{90}, and ED_{95} = effective doses required for 50%, 90%, and 95% first twitch of train-of-four depression.

Compared with the American patients, the dose–response curve was shifted to the right in the Chinese patients and further shifted to the right in the European patients (fig. 1). Our study showed that there was a statistically significant difference in ED_{50}, ED_{90}, and ED_{95} among the three groups. Rocuronium ED_{50}, ED_{90}, and ED_{95} were significantly higher in the European and Chinese patients compared with the American patients (table 2). There was a statistically significant difference in Dur_{25} and $Dur_{0.8}$ among the three groups. Dur_{25} and $Dur_{0.8}$ were significantly shorter in the European and Chinese patients compared with the American patients (table 3).

Discussion

Our results demonstrated that rocuronium potency was significantly higher in American patients than in similar European patients. A transatlantic difference in sensitivity of neuromuscular blocking drugs was previously reported. Katz *et al.*[1] showed that tubocurarine resulted in significantly more intense neuromuscular block with duration of action that lasted almost twice as long in American patients in New York compared with a similar group of British patients in London. Fiset *et al.*[2] demonstrated that vecuronium was more potent, with a significantly lower ED_{90}, in Montreal patients compared with similar patients in Paris.

The difference in rocuronium sensitivity among the three countries of our current study raises the question of whether "native" sensitivity could be acquired. Collins *et al.*[9] compared rocuronium potency in 18 white patients and 18 second-generation Han Chinese subjects living in Vancouver for a mean of 10 yr. They showed that the difference in ED_{50} did not reach statistical significance between the Chinese and white patients living in Vancouver. Interestingly, our results were quite different, because the ED_{50} in our Chinese subjects living in Dalian, People's Republic of China, were significantly higher than our white subjects in New Jersey. This suggests that the ethnic Chinese subjects of the Collins *et al.*[9] study, who lived in Vancouver for an average of 10 yr, could have acquired the same sensitivity as the native Vancouver white patients.[9] Similarly, in the Fiset *et al.*[2] study that demonstrated a significant difference in vecuronium potency between patients in Paris and Montreal, paradoxically half of the Montreal patients were born in Europe but were living in Montreal for more than 10 yr;

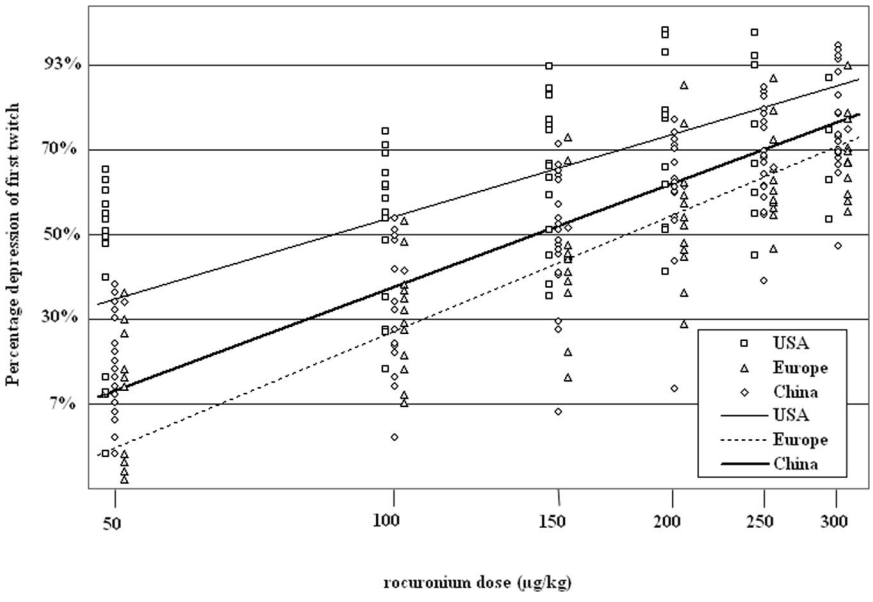

Fig. 1. Rocuronium dose–response curves in Englewood, New Jersey; Dalian, China; and Graz, Austria.

Table 3. Rocuronium Time-course-of-action Variables

	Austrian Group	Chinese Group	American Group
Onset time, min	13.1 ± 3.1	12.5 ± 2.9	12.2 ± 1.3
Dur_{25}, min	22.3 ± 5.5*	30.4 ± 7.5‡	36.7 ± 8.5†
$Dur_{25–75}$, min	11.3 ± 3.1	12.7 ± 3.3	13.2 ± 4.7
$Dur_{25–0.8}$, min	14.6 ± 9.3	15.3 ± 8.3	19.5 ± 9.4
$Dur_{0.8}$, min	36.9 ± 12.8*	45.7 ± 15.9	56.2 ± 16.7†

Tukey-Kramer *post hoc* test. Data are mean ± SD; n = 18.

* $P < 0.001$ compared with the American group. † $P < 0.05$ compared with the Chinese group. ‡ $P \leq 0.01$ compared with the Austrian group.

Onset time = time from beginning of incremental doses administration until first response of train-of-four (T_1) maximum suppression; Dur_{25} = time from last incremental dose administration until 25% T_1 recovery; $Dur_{25–75}$ = time from 25% to 75% T_1 recovery; $Dur_{0.8}$ = time from last incremental dose administration until 0.8 train-of-four ratio recovery; $Dur_{25–0.8}$ = time from 25% T_1 to 0.8 train-of-four ratio recovery.

hence, they manifested a different sensitivity than the European subjects.

However, Katz *et al.*[1] in addition studied a third group of American citizens, operated on at the US Air Force Hospital in London, who lived in London and its environs for periods of 13–36 months. Interestingly, these American citizens demonstrated sensitivity that was similar to that seen in the New York patients and not the British subjects of the study.[1] This probably implies that 3 yr was not a sufficient period to acquire the "native" sensitivity.

Pharmacogenetic studies have shown that ethnic or racial variations in hepatic metabolizing isoenzymes are important demographic variables that may account for differences in drug response among different populations.[10] However, rocuronium is eliminated mostly unchanged *via* biliary excretion,[11] whereas the difference in rocuronium potency between the two European and American white groups in our study was much wider than the difference between the ethnic Chinese and white groups, clearly indicating that ethnic or racial difference was not the most influential factor in our results; rather a multifactorial interaction of environmental factors such as pollution, life habits, diet, ambient conditions, and others could be the most likely explanation.

Because the aim of our study was to compare the dose–response relation between different regions and was not intended as an absolute potency estimate, we used the cumulative dose technique rather than the single-dose method, the accepted standard for creating dose–response curves[4] that would have required a far larger sample size of 108 patients. The cumulative dose technique could be used for intermediate-acting neuromuscular blocking drugs such as rocuronium, provided that the incremental doses were given within a brief period of time,[4,8] such as the 36 s of three consecutive T_1 responses that we used in our study. This allowed no significant recovery between the incremental doses as indicated by the short incremental doses onset time among the three groups (table 3).

In conclusion, our results demonstrated a significant difference in rocuronium potency and duration of action among patients in the three countries. Larger studies are required for determining dosage recommendations for different geographic regions.

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