In non-obese patients, duration of action of rocuronium is directly correlated with body mass index

Chez les patientes non obèses, la durée d'action du rocuronium est directement corrélée à l'indice de masse corporelle

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Received: 7 November 2012 / Accepted: 26 February 2013 / Published online: 6 March 2013
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Abstract

Background Administration of neuromuscular blocking agents using a dose calculated on actual body weight carries a risk of prolonged duration of action in obese patients whose body mass index (BMI) is $> 30 \text{ kg}\cdot\text{m}^{-2}$. In the present study, we hypothesized that there could be a correlation between BMI and the duration of action of rocuronium administered according to actual body weight in non-obese patients, in particular, overweight (BMI 25–30 $\text{kg}\cdot\text{m}^{-2}$) and underweight patients (BMI $< 18.5 \text{ kg}\cdot\text{m}^{-2}$).

Methods Sixteen female patients (BMI 15–30 $\text{kg}\cdot\text{m}^{-2}$, aged 45–60 yr) scheduled for elective surgery under total intravenous anesthesia were included in this study. Rocuronium $0.9 \text{ mg}\cdot\text{kg}^{-1}$ was administered, and adductor pollicis train-of-four responses following ulnar nerve stimulation were monitored every minute with acceleromyography. The times from the injection of rocuronium until spontaneous recovery of first twitch to 5% (5% Duration) and 25% (25% Duration) of baseline were measured, and the correlation with BMI was analyzed.

Author contributions Masafumi Fujimoto designed and conducted the study, collected and analyzed the data, and prepared the manuscript. Chiyoko Tanahira, Masaaki Nishi, and Tatsuo Yamamoto helped design the study. Chiyoko Tanahira and Masaaki Nishi helped with data collection. Masaaki Nishi and Tatsuo Yamamoto helped with the data analysis and helped prepare the manuscript. Tatsuo Yamamoto helped conduct the study. Chiyoko Tanahira, Masaaki Nishi, and Tatsuo Yamamoto attest to the integrity of the original data and the analysis reported in this manuscript.

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Results A significant correlation between 5% Duration and BMI ($r^2 = 0.56$; $P < 0.001$) was found by linear regression analysis. A significant correlation was also found between 25% Duration and BMI ($r^2 = 0.49$; $P = 0.003$).

Conclusion In adult female patients with a BMI in the range of 15–30 $\text{kg}\cdot\text{m}^{-2}$, the duration of action of rocuronium increases with BMI when the drug is administered on the basis of mg per actual kg body weight.

Résumé

Contexte L'administration de curares à une dose calculée en fonction du poids réel comporte le risque d'une durée d'action prolongée chez les patients obèses dont l'indice de masse corporelle (IMC) est $> 30 \text{ kg}\cdot\text{m}^{-2}$. Dans cette étude, nous avons émis l'hypothèse qu'il pourrait exister une corrélation entre l'IMC et la durée d'action du rocuronium administré selon le poids réel chez les patients non obèses, en particulier chez les patients en surcharge pondérale (IMC 25–30 $\text{kg}\cdot\text{m}^{-2}$) et en insuffisance pondérale (IMC $< 18,5 \text{ kg}\cdot\text{m}^{-2}$).

Méthode Seize patientes (IMC 15–30 $\text{kg}\cdot\text{m}^{-2}$, âgées de 45–60 ans) devant subir une chirurgie non urgente sous anesthésie intraveineuse totale ont été incluses dans cette étude. On leur a administré $0,9 \text{ mg}\cdot\text{kg}^{-1}$ de rocuronium et, après stimulation du nerf ulnaire, les réponses au train-de-quatre de l'adducteur du pouce ont été enregistrées toutes les minutes par accéléromyographie. Les temps entre l'injection de rocuronium et la récupération spontanée de la première réponse à 5 % (durée 5 %) et 25 % (durée 25 %) des valeurs de base ont été mesurés, et la corrélation de ces temps avec l'IMC a été analysée.

Résultats Une corrélation significative entre la durée 5 % et l'IMC ($r^2 = 0,56$; $P < 0,001$) a été observée lors de l'analyse par régression linéaire. Une corrélation significative

a également été observée entre la durée 25 % et l'IMC ($r^2 = 0,49$; $P < 0,003$).

Conclusion *Chez des patientes adultes avec un IMC se situant entre 15 et 30 kg·m⁻², la durée d'action du rocuronium augmente avec l'IMC lorsque le médicament est administré en mg par kg de poids corporel réel.*

Obesity is a worldwide concern, and clinicians increasingly have difficulties calculating appropriate dosages for obese patients. The internationally recommended classification of obesity is based on the body mass index (BMI). The World Health Organization (WHO) defines patients with a BMI > 30 kg·m⁻² as obese, those with a BMI in the range of 25–30 kg·m⁻² as overweight,¹ and those with a BMI < 18.5 kg·m⁻² as underweight. Some reports suggest that dosing neuromuscular blocking agents according to actual body weight carries a risk of prolonging the duration of action in obese patients.^{2–5} Nevertheless, only a few studies have assessed the duration of action of neuromuscular blocking agents in overweight and underweight patients,⁵ and it is unknown whether there is a correlation between BMI and the duration of action of neuromuscular blocking agents in this patient population.

The aim of the present study was to investigate whether a correlation exists between duration of action of rocuronium and BMI in patients with a BMI in the range of 15–30 kg·m⁻² when rocuronium is administered at a dose calculated according to actual body weight.

Methods

Ethics approval

This study was approved by the Ethics Committee of Kumamoto University Hospital and registered with UMIN Clinical Trials Registry (UMIN 000006766) on November 24, 2011. This study was conducted in accordance with the Helsinki Declaration. Prior written informed consent was obtained from all patients.

Inclusion and exclusion criteria

Female patients undergoing elective surgery under general anesthesia in the supine position were enrolled in the study from December 2011 to July 2012. Inclusion criteria included females aged 45–60 yr, BMI 15–30 kg·m⁻², and American Society of Anesthesiologists physical status class I or II.

Patients with cirrhosis, hepatitis, hepatoma, cholestasis, heart failure or arrhythmia, renal dysfunction (defined by a

creatinine clearance of ≤ 30 mL·min⁻¹), water-electrolyte disturbances, acid-base imbalances, or neuromuscular disorders were excluded from the study. Patients receiving medications known to interfere with neuromuscular blocking agents, such as antibiotics and anticonvulsants, were also excluded.

Anesthesia

Premedication was not given. After the patients were admitted to the operating room, their electrocardiogram, oxygen saturation measured by pulse oximetry, noninvasive blood pressure, and bispectral index (BIS®; Aspect Medical Systems, Norwood, MA, USA) were monitored. An intravenous cannula was placed into a forearm vein. General anesthesia was induced and maintained with an intravenous opioid (i.e., remifentanyl and fentanyl or remifentanyl only) and propofol. The rate of infusion of propofol was adjusted using a target-controlled infusion technique (TCI pump®; Terumo Corporation, Terumo, Japan) with a target concentration of 3.0–5.0 µg·mL⁻¹ to maintain a BIS value in the range of 40–60. A remifentanyl infusion was adjusted in the range of 0.1–0.5 µg·kg⁻¹·min⁻¹, and the anesthesiologists adjusted the anesthetic agents and doses as necessary to provide optimal patient care and to keep blood pressure within 20% of baseline values.

Neuromuscular monitoring

All neuromuscular monitoring was conducted in accordance with the guidelines established by *Good clinical research practice in pharmacodynamic studies of neuromuscular blocking drugs*.⁶ Neuromuscular function was monitored with the train-of-four (TOF)-Watch® SX (Organon, Swords, Co. Dublin, Ireland) on the patient's arm contralateral to the blood pressure cuff irrespective of the position of the intravenous cannula. The patient's study arm was immobilized during neuromuscular monitoring. Stabilization and calibration of the acceleromyograph were performed after induction of anesthesia and before administration of rocuronium. A 50-Hz tetanic stimulation of the ulnar nerve, induced via surface electrodes at the wrist, was applied for five seconds and followed by five minutes of TOF stimulation every 15 sec. When the response to TOF was stable, calibration and supramaximal stimulation were performed by the built-in calibration function. A stable baseline in response to TOF was documented for at least two minutes before rocuronium was administered. Neuromuscular data were collected via a transducer fixed on the distal part of the patient's thumb and transferred online to a computer using the TOF-Watch SX monitoring program version 1.2. A preload was applied to the thumb with the hand adapter. Rectal or oral

temperature was measured and maintained at $\geq 35^{\circ}\text{C}$. Additionally, peripheral body temperature was measured continuously with a thermistor at the thenar eminence of the palm and maintained at $\geq 32^{\circ}\text{C}$ with a Bair Hugger® forced-air warming device (Arizant Healthcare, Inc. Eden Prairie, MN, USA) during neuromuscular monitoring.

After calibration and stabilization of the TOF-Watch® SX, a single dose of rocuronium $0.9\text{ kg}\cdot\text{m}^{-2}$ was administered according to actual body weight, followed by TOF stimulation every minute. The duration from the injection of rocuronium until the spontaneous recovery of T1 to 5% and 25% of baseline height was determined (5% Duration and 25% Duration). The 95% effective dose (ED_{95}) of rocuronium has been reported to be $0.3\text{ mg}\cdot\text{kg}^{-1}$,⁷ and we selected a $3 \times \text{ED}_{95}$ of rocuronium because this dosage is used routinely at our hospital to obtain rapid onset of neuromuscular block.

Statistical analysis

The relationship between duration of action of rocuronium and BMI was analyzed using linear regression analysis. Patients were also divided into three groups according to BMI: a low BMI group ($< 20\text{ kg}\cdot\text{m}^{-2}$), a normal BMI group ($20\text{--}25\text{ kg}\cdot\text{m}^{-2}$), and a high BMI group ($> 25\text{ kg}\cdot\text{m}^{-2}$). Duration in these three groups was compared using one-way analysis of variance (ANOVA) and Tukey's *post-hoc* test. A *P* value < 0.05 was considered statistically significant. The sample size was calculated to detect a correlation between duration and BMI with a risk of type I error $\alpha = 0.05$ and type II error $\beta = 0.20$ using a power analysis based on a pilot study with ten patients. According to the pilot study, correlation between duration 5% and BMI did not reach statistical significance ($f^2 = 0.59$; $r^2 = 0.37$; $P = 0.06$). A power analysis based on the pilot study indicated that the sample size required for this study was 16. Statistical analysis was performed with GraphPad Prism version 5.0 (GraphPad software, San Diego, CA, USA).

Results

Sixteen consecutive patients were eligible and all patients completed the study protocol. The demographic data about the study population are shown in Table 1. There were no abnormalities in preoperative laboratory examinations (aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, total protein, albumin, blood urea nitrogen, creatinine, sodium, potassium, chlorine, calcium). There were no underweight patients who seemed malnourished and/or had lost weight due to disease. One patient with a

BMI of $21.0\text{ kg}\cdot\text{m}^{-2}$ had a history of hyperthyroidism, but all her preoperative examinations were within normal limits. No patient received antibiotics and/or anticonvulsants known to interfere with neuromuscular blocking agents.

A significant correlation between 5% Duration and BMI was found for the whole cohort by linear regression analysis ($Y = 2.27X - 2.80$; Y : 5% Duration [min]; X : BMI [$\text{kg}\cdot\text{m}^{-2}$]; $r^2 = 0.56$; $P < 0.001$; Figure A). A similar correlation was identified between 25% Duration and BMI ($Y = 3.01X - 5.25$; Y : 25% Duration [min]; X : BMI [$\text{kg}\cdot\text{m}^{-2}$]; $r^2 = 0.49$; $P = 0.003$; Figure B).

The number of patients in the low, normal, and high BMI groups was six, six, and four, respectively. Duration time in each group is shown in Table 2. A significant difference was found between groups by one-way ANOVA; duration was found to be significantly longer in the high BMI group compared with the low and normal BMI groups by Tukey's *post-hoc* analysis. A difference in duration was not found between the low and normal BMI groups.

Discussion

In the present study, a correlation was found between duration of action and BMI when rocuronium was administered at a dose according to actual body weight in middle-aged female patients with a BMI in the 15–30 $\text{kg}\cdot\text{m}^{-2}$ range.

The prolonged neuromuscular block previously reported in obese patients has been observed when the rocuronium dose was calculated according to actual body weight.^{4,5} This was attributed to differences between obese and normal weight patients with respect to distribution, protein binding, and elimination of drugs.⁸ Leykin *et al.* reported that the duration of action of rocuronium $0.6\text{ mg}\cdot\text{kg}^{-1}$ was significantly prolonged in morbidly obese patients with BMI $> 40\text{ kg}\cdot\text{m}^{-2}$ compared with normal weight patients whose mean BMI was $22\text{ kg}\cdot\text{m}^{-2}$.⁴ Meyhoff *et al.* reported that the dose of rocuronium should be calculated according

Table 1 Demographic data of the patients ($n = 16$)

Age (yr)	53.6	(5.3)	45–60
Height (cm)	159.5	(5.4)	149.1–167.0
Weight (kg)	55.6	(10.4)	41.4–76.8
BMI ($\text{kg}\cdot\text{m}^{-2}$)	21.9	(3.9)	15.8–29.6
Types of surgery			
Upper abdominal	3	(19%)	
Lower abdominal	8	(50%)	
Orthopedic (lower limb)	5	(31%)	

Data were expressed as mean (standard deviation) range or number of patients (%)

Figure Linear correlation between either duration to 5% (A) or 25% (B) first twitch spontaneous recovery (as % of baseline) after rocuronium $0.9 \text{ kg} \cdot \text{m}^{-2}$ and body mass index (BMI). Broken lines indicate 95% confidence interval

to ideal body weight to prevent the prolonged rocuronium-induced neuromuscular block in morbidly obese patients.⁹ The findings of the present study suggest that the higher the BMI, the longer the duration of rocuronium-induced neuromuscular block, even in non-obese patients. Thus, even if the patient is not categorized as “obese” according to the WHO classification, the higher the BMI of the patient, the more carefully rocuronium should be administered with neuromuscular monitoring to prevent prolonging neuromuscular block.

Our study also showed that patients with low BMI recover rapidly from rocuronium-induced neuromuscular block, suggesting that underweight patients may move unexpectedly during surgery if rocuronium is administered at a dose based on actual body weight. Thus, additional administration of rocuronium may be required early in underweight patients. Thus, neuromuscular monitoring during anesthesia is important, especially in underweight patients.

While BMI is a simple concept and the most popular index of obesity, it has some limitations. The BMI values

are the same for both sexes and are age-independent; therefore, BMI may not correspond with the same level of obesity in different populations due to different body proportions. For example, individuals who are heavily muscled would be classified as obese, and we would expect that there would be fewer such individuals found among females than among males. It is also known that sex can influence both the pharmacodynamic and pharmacokinetic responses to neuromuscular blocking agents due to physical and metabolic differences, such as muscle and fat distribution.¹⁰ The guidelines established by *Good clinical research practice in pharmacodynamic studies of neuromuscular blocking drugs* recommend taking the potential impact of sex into account in the study design.⁶ Therefore, in the present study, the subjects were limited to female patients.

While the correlation between age and obesity is not clear, it is already known that the duration of rocuronium-induced neuromuscular block increases in elderly patients as a result of a decrease in the elimination of the drug.¹¹⁻¹³ According to the above guidelines, individuals aged 18-65 yr are categorized as adults;⁶ however, it is unreasonable to include those individuals as a single group in the investigation of a drug's duration of effect. As a result, to exclude the influence of age on the duration of action of neuromuscular blocking agents, we also limited the subjects to 45-60-yr-old senior adult female patients.

Although a significant correlation between BMI and the duration of action of rocuronium was shown in these populations, it is unclear whether this correlation exists in other populations. Pühringer *et al.* reported no differences in the duration of action of $0.6 \text{ mg} \cdot \text{kg}^{-1}$ of rocuronium (a lower dose than the one used in this study) between underweight (BMI $< 20 \text{ kg} \cdot \text{m}^{-2}$), normal weight (BMI $20\text{--}24 \text{ kg} \cdot \text{m}^{-2}$), and overweight (BMI $24\text{--}28 \text{ kg} \cdot \text{m}^{-2}$) patients;

Table 2 Duration of action in three different BMI groups

	5% Duration (min)			25% Duration (min)		
	Mean Range	(SD)	95% CI	Mean Range	(SD)	95% CI
Low BMI group ($n = 6$)	42.3 33-53	(6.7)	35.3 to 49.4	56.8 43-72	(9.9)	46.4 to 67.2
Normal BMI group ($n = 6$)	40.7 33-51	(6.8)	33.5 to 47.8	49.0 39-60	(8.8)	39.8 to 58.2
High BMI group ($n = 4$)	63.0 49-71	(9.8)*	47.5 to 78.5	83.3 65-91	(12.3) [§]	63.7 to 102.8

Data are expressed as mean (standard deviation) range

One-way ANOVA showed a significant difference in both 5% and 25% duration between the three groups ($P < 0.01$). *[§] Tukey's *post-hoc* analysis revealed significant longer duration compared with the low and middle BMI groups ($P < 0.05$)

5% Duration and 25% duration = time from the injection of rocuronium until spontaneous recovery of first twitch to 5% and 25% of its baseline height, respectively; BMI = body mass index; Low BMI = BMI $15\text{--}20 \text{ kg} \cdot \text{m}^{-2}$; Normal BMI = BMI $20\text{--}25 \text{ kg} \cdot \text{m}^{-2}$; High BMI = BMI $25\text{--}30 \text{ kg} \cdot \text{m}^{-2}$; SD = standard deviation; CI = confidence interval; ANOVA = analysis of variance

however, with the exception of BMI, no other characteristics of the subjects were described in their report.⁵ Given the variability of the duration of action of rocuronium due to age and sex, it may be difficult to detect a correlation between BMI and the duration of action of rocuronium in the group without restriction on the age range and sex. If the age range of the population is narrow and the study is conducted in patients of one sex, a linear regression between BMI and the duration of action of rocuronium could also be found in other populations.

In the present study, while the linear regression analysis showed a clear correlation between duration and BMI, differences in duration between low and normal BMI groups were not found. Even so, the sample size was not determined to perform multiple group comparisons and may have been too small to perform statistically appropriate multiple group comparisons. We selected the recovery time of single twitch height to 5% and 25% of baseline height as the end point. Although many clinicians are interested in the recovery time of a TOF ratio to 0.90, which represents sufficient recovery for tracheal extubation, these data could not be collected because additional rocuronium was required for the surgery.

We conclude that there is a correlation between duration of action of rocuronium $0.9 \text{ kg} \cdot \text{m}^{-2}$ and BMI when dose is calculated according to actual body weight in 45–60-yr-old female patients with a BMI in the range of 15–30 $\text{kg} \cdot \text{m}^{-2}$. Thus, rocuronium should be administered considering the differences in the duration of action associated with BMI, not only in obese patients but also in overweight and underweight patients.

Funding Supported by Kumamoto University Hospital.

Associations None.

Conflicts of interest None declared.

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