学位論文

Predictive performance of six compartmental pharmacokinetic models of rocuronium delivered by bolus followed by continuous infusion: Assessment of parameter sets determined using samples obtained after bolus infusion only

（ロクロニウム単回投与から得られた薬物動態モデル６種類の単回・持続投与時における予測性能）

旭川医科大学大学院医学系研究科博士課程医学専攻

笹川　智貴

（増井　健一、風間　富栄、岩崎　寛）

Predictive performance of six compartmental pharmacokinetic models of rocuronium delivered by bolus followed by continuous infusion: Assessment of parameter sets determined using samples obtained after bolus infusion only

Tomoki Sasakawa[1], Kenichi Masui[2*], Tomiei Kazama[2], Hiroshi Iwasaki[1]

[1] Department of Anesthesiology, Asahikawa Medical University, Midorigaoka higashi 2-1-1-1, Asahikawa, Hokkaido, Japan

[2] Department of Anesthesiology, National Defense Medical College, Namiki 3-2, Tokorozawa, Saitama, Japan

*Corresponding author

Address electronic mail to: kenichi@masuinet.com

Tel: +81-4-2995-1692; Fax: +81-4-2992-1215

Author Contributions

Tomoki Sasakawa: Designed the study, conducted the study, analyzed the data, and composed the manuscript.

Kenichi Masui: Designed the study, conducted the study, analyzed the data, and composed the manuscript.

Tomiei Kazama: Helped in conducting the study and composing the manuscript.

Hiroshi Iwasaki: Helped in conducting the study and composing the manuscript.

Short title: Pharmacokinetic model for bolus followed by continuous rocuronium infusion

Conflicts of interest

None declared

Funding

Support for this study was solely provided by departmental and institutional funding.

Previous presentation

This report was previously presented, in part, at the Anesthesiology 2013 Annual Meeting held in San Francisco on October 13, 2013.

Abstract

BACKGROUND: Rocuronium concentration prediction using pharmacokinetic (PK) models would be useful to control rocuronium effects because neuromuscular monitoring throughout anesthesia is occasionally difficult. This study assessed whether six different compartmental PK models developed from data obtained after bolus administration only could predict the measured plasma concentration (Cp) values of rocuronium delivered by bolus followed by continuous infusion.

METHODS: Rocuronium Cp values from 19 healthy subjects who received a bolus dose followed by continuous infusion in a phase III multicenter trial in Japan were used retrospectively as validation datasets.

Six different compartmental PK models of rocuronium were used to simulate the time course of rocuronium Cp values, which were compared with measured Cp values. Prediction error (PE) derivatives of median absolute PE (MDAPE), median PE (MDPE), wobble, divergence of the absolute PE, and divergence of PE were used to assess inaccuracy, bias, intra-individual variability, and time-related trends in APE and PE values.

RESULTS: MDAPE and MDPE values were acceptable only for the Magorian and Kleijn models. Divergence PE values for the Kleijn model were lower than −10%, indicating unstable prediction over time. In contrast, the Szenohradszky model had the lowest divergence PE (−2.7%) and wobble (5.4%) values, indicating the capability of stable prediction during long continuous infusion. The Magorian model showed superior PE derivatives among the six models assessed.

CONCLUSIONS: This study suggests that 1 of the 6 PK models developed from data obtained after single bolus dose alone can predict Cp values during bolus and continuous infusion.

Key words: rocuronium, neuromuscular blocking agent, drug delivery, pharmacokinetics

Introduction

Rocuronium is a nondepolarizing neuromuscular blocking agent administered by intermittent bolus and continuous infusion. Because it is an intermediate-acting agent with a large interindividual variability,[1] neuromuscular monitoring can be used to ensure optimal rocuronium administration. Acceleromyography is one of the most popular quantitative monitoring techniques because it is comparatively inexpensive, practical, and easy to use.[2] However, in some cases, intraoperative measurements with acceleromyography can be influenced by artefacts, patient movements, and unstable twitch responses.[2] In such cases, appropriate prediction of rocuronium concentration may be a useful clinical aid in conjunction with neuromuscular monitoring. Once the relationship between the predicted rocuronium concentration and the effects of rocuronium in a patient is determined, the effects of this drug could be controlled using the predicted concentration. Currently, drug advisory displays show the predicted rocuronium concentration.[3]

The predicted rocuronium concentration is calculated using pharmacokinetic (PK) models of rocuronium. As rocuronium can be administered by both intermittent bolus and continuous infusion, a rocuronium PK model should ideally predict the concentration not only during a bolus dose regimen but also during a continuous infusion regimen. Most published PK models of this drug have been developed using samples obtained after bolus infusion only.[4-9] Therefore, the predictive performance of these PK models may be limited. Previously, we confirmed the possibility that a PK model of propofol developed on the basis of samples obtained after bolus infusion underpredicted plasma concentration (Cp) values during continuous infusion.[10]

This study aimed to assess the predictive performance of six published compartmental PK models of rocuronium developed using sequential samples obtained after bolus infusion. For the assessment, we used a dataset including rocuronium Cp values measured during continuous infusion following initial bolus infusion in 19 patients included in a phase III trial in Japan. We hypothesized that the assessed PK models provide biased predictions for the applied dataset.

Materials and Methods

Selected Pharmacokinetic Models

For the assessment, we selected six published PK models developed by Wierda et al,[4] Szenohradszky et al,[5] Alvarez-Gomez et al,[6] Cooper et al,[7] Magorian et al,[8] and Kleijn et al,[9] called the "Wierda," "Szenohradszky," "Alvarez-Gomez," "Cooper," "Magorian," and "Kleijn" models, respectively (Table 1). These models were developed using samples obtained after bolus infusion of rocuronium without continuous infusion in patients with normal renal and hepatic function. We excluded published PK models in which the structures for all individuals were not unique.

Detailed descriptions of how the models were developed can be found in the published articles. Briefly, the Wierda model was developed using samples from 10 healthy patients (7 female and 3 male, 18–60 years, 56–75 kg) who received a 1 $mg \cdot kg^{-1}$ bolus of rocuronium over 10 s. Venous samples were collected before and during a period of 1–480 min after the administration of rocuronium. Szenohradszky et al developed their model using samples from 20 patients with normal renal function or renal failure (6 female and 14 male, 21–65 years, 45–107 kg) who received a rapid bolus of 0.6 $mg \cdot kg^{-1}$ rocuronium. Venous samples were obtained from the contralateral arm before and during a period of 2–360 min after rocuronium bolus administration. We used the PK parameter set for normal renal function as the Szenohradszky model in our study. For the development of the Alvarez–Gomez model, the authors analyzed the concentration data from 7 patients (3 female and 4 male, 30 ± 6 years, 70 ± 9 kg) who received a 0.6 $mg \cdot kg^{-1}$ bolus of rocuronium. Venous samples were obtained from the contralateral arm before and during a period of 1–300 min after rocuronium injection. The Cooper model was based on data from 9 patients (5 female and 4 male, 27–64 years, 53–94 kg) without renal

failure who received a 0.6 mg·kg^{-1} fast bolus of rocuronium. Venous samples were obtained before and during a period of 1–390 min after rocuronium administration. Magorian et al developed their PK model from 20 patients with normal hepatic function or liver disease (5 female and 15 male, 23–67 years, 50–110 kg) who received a rapid bolus of 0.6 mg·kg^{-1} rocuronium. Venous or arterial samples were obtained from the contralateral arm before and during a period of 2–360 min after rocuronium bolus infusion. We used the PK parameter set for normal hepatic function as the Magorian model in our study. The Kleijn model was developed from 426 patients and 20 healthy volunteers (157 female and 289 male, 1–91 years, 9.6–139 kg, 393 non-Asians and 53 Asians) who received a 0.6-, 0.9-, or 1.2-mg·kg^{-1} bolus. The Kleijn model or the other models were developed as two- or three-compartmental models, respectively. The mixed-effects modeling approach was used while developing the Szenohradszky, Magorian, and Kleijn models, while the standard two-stage approach was used while developing the other three PK models.[11-13]

Validation Dataset

To assess the predictive performance of the six PK models, we used a dataset obtained from a phase III multicenter clinical trial conducted in Japan that examined the effectiveness, safety, and side effects of rocuronium.[14] In the trial, rocuronium Cp was measured in 19 of 38 patients (13 female and 6 male, 20–62 years, 44–72 kg) scheduled for elective surgery with an estimated duration of general anesthesia of 2–5 hours. The exclusion criteria were neuromuscular disorders, renal or hepatic failure, pregnancy, or any medication or disease that could potentially interfere with neuromuscular transmission. Following the induction of general anesthesia using a propofol bolus, sevoflurane (n = 10) or propofol (n = 9) was administered for the maintenance of anesthesia. Neuromuscular blockade was monitored using acceleromyography (TOF watch

SX; MSD K.K., Tokyo, Japan). Supramaximal train-of-four stimulation was applied to the ulnar nerve at the wrist. Continuous infusion of rocuronium was initiated at 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ following rapid bolus infusion of 0.6 or 0.9 $mg \cdot kg^{-1}$ rocuronium. The dose was adjusted to maintain the single-twitch response at 3%–10% during surgery. Venous samples were obtained immediately before the initiation of rocuronium infusion, at 60 and 90 min after the initiation of continuous infusion and immediately before the end of continuous infusion. Rocuronium Cp values were determined by liquid chromatography mass spectrometry. The lower limit of quantification was 0.2 $ng \cdot mL^{-1}$.

Assessment of Pharmacokinetic Models

Measured/predicted Cp was described to clarify the bias of prediction by the PK models. To show the time-related changes in prediction and clarify the intraindividual variability in prediction errors, we depicted the individual time course of $PE_{ij} - MDPE_i$ ($j = 1,...,N_i$), where N_i is the number of prediction error (PE) values obtained for the *i*-th subject. We also illustrated a linear regression line to show the tendency of the percentage PEs to increase or decrease over time in each patient.

The predictive performances of the six PK models were analyzed using the following five PE derivatives (%) calculated as (measured Cp − predicted Cp)/predicted Cp × 100.[15, 16] The median PE (MDPE) reflects the bias in Cp prediction. In the *i*-th subject,

$$MDPE_i = median\left\{PE_{ij}, j = 1, \cdots, N_i\right\},$$

where N_i is the number of PE values obtained for the *i*-th subject. Hereby, an MDPE value of 0 indicates no bias. The median absolute PE (MDAPE) value indicates the inaccuracy of Cp prediction. In the *i*-th subject,

$$MDAPE_i = median\left\{\left|PE_{ij}\right|, j = 1, \cdots, N_i\right\},$$

where N_i is the number of PE values obtained for the *i*-th subject. The closer the MDAPE value is to 0, the more accurate is the model. MDPE values ranging between −20% and 20% and MDAPE values below 30% are regarded as acceptable.[17] The wobble value measures the total intraindividual variability in PEs. In the *i*-th subject,

$$Wobble_i = median\left\{\left|PE_{ij} - MDPE_i\right|, j = 1, \cdots, N_i\right\},$$

where N_i is the number of PE values obtained for the *i*-th subject. The closer the value is to 0, the lesser is the intraindividual variability. Divergence APE_i, which is the original divergence defined by Varvel *et al*,[15] and divergence PE_i, which is proposed by Glen *et al*,[16] are calculated for the *i*-th individual as the slope obtained from linear regression of an individual's PE_{ij}s and $|PE_{ij}|$s against time, respectively. Divergences show time-related trends in PE and APE. An absolute value of divergence that is close to 0 means that prediction is stable over time. MDPE, MDAPE, wobble, divergence PE, and divergence APE (PE derivatives) values were calculated as averages of corresponding individual values, according to Varvel *et al*.[15]

Calculation and Statistics

NONMEM VII (GloboMax LLC, Hanover, MD) was used to simulate the time course of the predicted Cp values, which were represented by the concentrations in the central compartment. A paired t-test was used to compare $wobble_i$s values among the PK models. The one-sample t-test was used to test the hypothesis that the mean of a divergence is significantly different from 0. P-values were adjusted using the Beyer–Hardwick (BH) method.[18] P = 0.05 was considered statistically significant. All statistical analyses were conducted using Prism 6.04 (GraphPad Software, La Jolla, CA) and R version 3.0.2 (http://www.R-project.org).

Results

The individual time courses of the measured Cp values of rocuronium are depicted in Figure 1. All the rocuronium Cp values were used for the assessment. This dataset includes a venous Cp (n = 72) of 0.6–3.3 $\mu g \cdot mL^{-1}$ up to 292 min after the start of drug administration.

The individual time courses of measured/predicted Cp are shown in the left column in Figure 2. Visual inspection revealed clear overprediction with the Szenohradszky model and underprediction with the Wierda, Alvarez–Gomez, and Cooper models. These results are confirmed by the MDPE values presented in Table 2. The MDPE value for the Szenohradszky model was −25.7%, which was below the acceptable range, whereas those for the Wierda (20.7%), Alvarez–Gomez (42.9%), and Cooper models (31.3%) were above the acceptable MDPE range.

The middle column in Figure 2 depicts the individual time courses of $PE_{ij} - MDPE_i$ values. These figures indicate that the Szenohradszky model has the least degree of variation in predicted Cp values for each patient compared with the other PK models. Similarly, the wobble value for the Szenohradszky model was significantly smaller than that for the other four models, indicating a smaller total intraindividual variability in PEs (Table 2).

Regression lines for $PE_{ij} - MDPE_i$ values for each individual are illustrated in the right column in Figure 2. The slopes of the linear regression line were negative in more patients when the Wierda, Alvarez–Gomez, Cooper, and Kleijn models were used than when the Szenohradszky and Magorian models were used. This indicated a tendency of the former four models to predict

lower Cp values in the early phase and higher Cp values in the late phase after the start of rocuronium administration. The divergence PE values summarize the tendency of the regression lines. The divergence PE values for all models except the Szenohradszky and Magorian models were below −10%/h, which were significantly lower than 0 (Table 2).

The divergence APE values are shown in Table 2. Only the value for the Cooper model was −21.8%, which was significantly lower than 0.

Discussion

We investigated the predictive performance of six published PK models of rocuronium developed using sequential Cp values obtained after bolus infusion. We used published Cp data that originated from a clinical trial in which the rocuronium dosing scheme included both bolus and continuous infusion in 19 patients. In the assessment of bias and inaccuracy, the Magorian and Kleijn models showed acceptable performance. The Szenohradszky model exhibited less intraindividual variability. The Szenohradszky and Magorian models showed stable prediction over time. Among the six models, the Magorian model showed an acceptable predictive performance for a dosing scheme that included continuous infusion.

Predicted concentrations of intravenous drugs, particularly propofol and opioids, are frequently used while administering anesthesia in daily practice and offer various advantages that result in better patient care,[3] such as the prevention of overdosing or insufficient dosing to avoid unexpected effects. The predicted rocuronium concentration obtained using a good PK model can also improve daily anesthesia practice. The combination of predicted rocuronium concentration and neuromuscular monitoring will help in predicting the effects of rocuronium over time. However, for appropriate prediction, one should select a validated PK model.

MDPE and MDAPE values are the primary factors for assessing the external validity of PK models in some studies.[19, 20] Assessment using these two indices in our study revealed that the Magorian and Kleijn models were acceptable, whereas the other PK models were unacceptable (Table 2). In addition, the divergence PE of −15.1%/h for the Kleijn model, which was significantly lower than 0, indicated unstable prediction of the PK model over time. Although

the wobble values showed that the intraindividual variability of the Magorian model was larger than that of the Szenohradszky model (Table 2), the wobble values for propofol PK models generally used in clinical practice are ≥10%, which are larger than those for the Magorian model.[16] These results indicate that the predictive performance of the Magorian model was acceptable overall.

Prediction of Cp values during continuous infusion using one of the assessed six PK models is equivalent to extrapolation because these PK models were developed on the basis of a dosing scheme involving bolus infusion only. A previous study showed that PK models developed on the basis of a bolus dosing scheme underpredicted Cp values.[10] However, the Magorian model showed an acceptable prediction of Cp values, which was against our hypothesis. Although the reason remains unclear, the modeling approach (discussed below) may have influenced the predictive performance of these PK models.

Previous studies compared the mixed-effects modeling approach and the standard two-stage approach to develop PK models.[11-13] The results of these studies indicated that mixed-effects modeling approach did not improve the internal validity of the PK models. In the present study, the Magorian and Kleijn models developed using the mixed-effects modeling approach showed acceptable bias and inaccuracy, whereas the Wierda, Alvarez-Gomez, and Cooper models developed using the standard two-stage approach resulted in unacceptable bias or inaccuracy for our validation dataset. The mixed-effects modeling approach may enable the development of a better PK model for the prediction of Cp values for extrapolation compared with the standard two-stage approach, i.e., a PK model developed using the mixed-effects modeling approach may predict Cp values more effectively than a model developed using the standard two-stage

approach, particularly when patients have background factors differing from those used while developing the PK model, such as dosing scheme, age, and sex. For example, a PK model developed using the mixed-effects modeling approach on the basis of data from patients aged 30–60 years old can predict Cp values for 80-year-old patients. Similarly, a model developed using data from male patients may be able to predict data for female patients.

This study was limited by the fact that the entire dataset of measured Cp values were collected from the Japanese population, while the Kleijn model includes race as a covariate for measuring intercompartmental clearance.[9] However, the influence of these racial differences was likely to be minimal because the median difference in Cp values predicted using the Kleijn model was only 0.03 (range, 0–0.13) μg/mL between Asian and non-Asian populations.

Conclusions

The results from this study showed that the Magorian model of rocuronium, developed using a bolus dosing scheme only, could predict Cp values during dosing schemes involving continuous infusion. When the data from a PK model are extrapolated to predict Cp values for a patient, the validity of the PK model should be confirmed first. For this extrapolation of data, PK models developed using the mixed-effects modeling approach may be superior to those developed using the standard two-stage approach.

Acknowledgment

The authors are grateful to MSD K.K. (Tokyo, Japan), a subsidiary of Merck & Co., Inc. (Whitehouse Station, NJ, USA), for providing the validation dataset involving measured plasma concentrations of rocuronium.

References

1. Maybauer DM, Geldner G, Blobner M, Puhringer F, Hofmockel R, Rex C, et al. Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. Anaesthesia. 2007;62:12-7.

2. Fuchs-Buder T, Schreiber JU, Meistelman C. Monitoring neuromuscular block: an update. Anaesthesia. 2009;64 Suppl 1:82-9.

3. Struys MM, De Smet T, Mortier EP. Simulated drug administration: an emerging tool for teaching clinical pharmacology during anesthesiology training. Clin Pharmacol Ther. 2008;84:170-4.

4. Wierda JM, Kleef UW, Lambalk LM, Kloppenburg WD, Agoston S. The pharmacodynamics and pharmacokinetics of Org 9426, a new non-depolarizing neuromuscular blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl. Can J Anaesth. 1991;38:430-5.

5. Szenohradszky J, Fisher DM, Segredo V, Caldwell JE, Bragg P, Sharma ML, et al. Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. Anesthesiology. 1992;77:899-904.

6. Alvarez-Gomez JA, Estelles ME, Fabregat J, Perez F, Brugger AJ. Pharmacokinetics and pharmacodynamics of rocuronium bromide in adult patients. Eur J Anaesthesiol Suppl. 1994;9:53-6.

7. Cooper RA, Maddineni VR, Mirakhur RK, Wierda JM, Brady M, Fitzpatrick KT. Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (Org 9426) during isoflurane anaesthesia in patients with and without renal failure. Br J Anaesth. 1993;71:222-6.

8. Magorian T, Wood P, Caldwell J, Fisher D, Segredo V, Szenohradszky J, et al. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. Anesth Analg. 1995;80:754-9.

9. Kleijn HJ, Zollinger DP, van den Heuvel MW, Kerbusch T. Population pharmacokinetic-pharmacodynamic analysis for sugammadex-mediated reversal of rocuronium-induced neuromuscular blockade. Br J Clin Pharmacol. 2011;72:415-33.

10. Miyabe-Nishiwaki T, Masui K, Kaneko A, Nishiwaki K, Nishio T, Kanazawa H. Evaluation of the predictive performance of a pharmacokinetic model for propofol in Japanese macaques (Macaca fuscata fuscata). J Vet Pharmacol Ther. 2013;36:169-73.

11. Kataria BK, Ved SA, Nicodemus HF, Hoy GR, Lea D, Dubois MY, et al. The pharmacokinetics of propofol in children using three different data analysis approaches. Anesthesiology. 1994;80:104-22.

12. Murat I, Billard V, Vernois J, Zaouter M, Marsol P, Souron R, et al. Pharmacokinetics of propofol after a single dose in children aged 1-3 years with minor burns. Comparison of three data analysis approaches. Anesthesiology. 1996;84:526-32.

13. Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, et al. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology. 1993;79:881-92.

14. Takagi S, Ozaki M, Iwasaki H, Hatano Y, Takeda J. [Effects of sevoflurane and propofol on neuromuscular blocking action of Org 9426 (rocuronium bromide) infused continuously in Japanese patients]. Masui. 2006;55:963-70.

15. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm. 1992;20:63-94.

16. Glen JB, Servin F. Evaluation of the predictive performance of four pharmacokinetic

models for propofol. Br J Anaesth. 2009;102:626-32.

17. Glass PS, Shafer S, Reves JG. Intravenous drug delivery systems. In: Miller RD, editor. Miller's anesthesia. 6 th ed. Pennsylvania, USA: Elsevier; 2004. p. 439-80.

18. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Roy Stat Soc, B. 1995;57:289-300.

19. Sepulveda P, Cortinez LI, Saez C, Penna A, Solari S, Guerra I, et al. Performance evaluation of paediatric propofol pharmacokinetic models in healthy young children. Br J Anaesth. 2011;107:593-600.

20. Masui K, Upton RN, Doufas AG, Coetzee JF, Kazama T, Mortier EP, et al. The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: a comparison using bolus, continuous, and target-controlled infusion data. Anesth Analg. 2010;111:368-79.

Titles of tables and figures

Table 1. Pharmacokinetic parameters for the assessed compartmental models

Age: (years), BW: body weight (kg), CR: creatinine clearance (mL/min), k_{10}: elimination rate constant, k: equilibration rate constant, Race: 1 for non-Asian and 0.788 for Asian, V_1: volume of central compartment

Table 2. Prediction error derivatives [mean (range)]

PE: prediction error, APE: absolute PE, MDPE: median PE, MDAPE: median APE

* $P < 0.05$ or ** $P < 0.01$ *vs* the Szenohradszky model, † $P < 0.05$ or ‡ $P < 0.01$ *vs* the Alvarez-Gomez model, § and §§ indicates that the average is different from 0 ($P < 0.05$ and $P < 0.01$, respectively).

Figure 1. Time course of measured plasma concentration (Cp) of rocuronium

The closed circles represent each measured Cp. The dotted line connects all the sampling points for each individual.

Figure 2.

Left column: Time course of measured divided by predicted plasma concentration (measured/predicted Cp) for each pharmacokinetic model

The closed circles represent each measured Cp. The thin dotted line connects all the sampling points for each individual. When the measured Cp is equal to the plasma Cp, the value of measured/predicted is 1, indicating perfect prediction.

Middle column: Time course of prediction error (PE) minus individual median PE ($MDPE_i$) (PE

− $MDPE_i$). The closed circles represent each measured Cp. The thin dotted line connects all the sampling points for each individual. These lines show the intraindividual variation in prediction versus time.

Right column: Individual regression line for PE – $MDPE_i$ (solid line)

The lines illustrate individual time-related trends of PE.