Aportación Clínica

Rev. Mex. Anest
1999;22:225-229

Pharmacodynamic modeling without plasma concentrations of Rocuronium administrated to children during Isoflurane anesthesia§

Elvia Yadira Velázquez-Armenta, Alejandro A. Nava-Ocampo***

ABSTRACT

Objective: To obtain pharmacodynamic parameters that could be useful to understand the time-course of the effect of rocuronium in children, by performing the pharmacodynamic modeling without plasma concentration (PDMWOPC) of neuromuscular response of the adductor pollicis to different doses of rocuronium. *Material and methods:* Forty-five children aged 2-14 yr. (ASA 1), undergoing elective surgery requiring tracheal intubation were studied. Neuromuscular response was monitored by means of a TOF-Guard. The ratio of the height of the first response to the control height (T1:T0) and the ratio of the fourth to the first response were measured. And the muscular response T1:T0 was fitted to time by using the PDMWOPC method previously described by Bragg et al. *Results:* All patients were successfully individually modeled. Three parameters (k_e, γ and IR_{50}) were similar among the three doses, and significant differences ($p<0.05$) were observed between the doses of 400 and 600, and between 600 and 800 µg/kg of rocuronium in the k_{eo} values. Each parameter exhibited a great intra-group variability, and ranges varied up to 300-fold. *Conclusions:* Individual PDMWOPC was successfully performed in children receiving different doses of rocuronium during isoflurane anesthesia. However, wide ranges of computed parameters, i.e., k_e, k_{eo}, γ and IR_{50} were obtained. We therefore propose to model these data using a population approach (*Rev Mex Anest* 1999;22:225-229).

Key words: Clinical pharmacology, inhalatory anesthesia, neuromuscular nondepolarizing agents, nonlinear dynamics.

RESUMEN

Modelaje farmacodinámico sin concentraciones plasmáticas del rocuronio administrado a niños bajo anestesia general con isofluorano. *Objetivo:* Obtener parámetros farmacodinámicos para entender el curso temporal del efecto del rocuronio en niños, mediante la utilización de modelaje farmacodinámico sin concentraciones plasmáticas de la respuesta neuromuscular a nivel del músculo aductor del pulgar, posterior a la administración de diferentes dosis de rocuronio. *Material y métodos:* Se estudiaron 45 niños de 2-14 años de edad (ASA 1), programados para cirugía electiva, que requerían de intubación endotraqueal. Se monitorizó a los pacientes por medio del TOF-Guard, y se registraron la relación entre la primera respuesta y la basal (T1:T0) y la relación entre la primera y la cuarta señal de tren de cuatro. La respuesta de T1:T0 se modeló en función del tiempo por medio del modelo farmacodinámico descrito por Bragg y cols. *Resultados:* El modelaje se realizó exitosamente en cada uno de los pacientes. Tres parámetros (k_e, γ, e IR_{50}) fueron semejantes con las tres dosis, mientras que los valores de keo fueron significativamente diferentes ($p<0.05$) entre las dosis de 400 y 600, y entre las dosis de 600 y 800 µg/kg de rocuronio. Los parámetros obtenidos mostraron una gran variabilidad intra-grupo, y la relación entre el valor superior y el inferior fue, en algunos casos, incluso más de 300. *Conclusiones:* El modelaje farmacodinámico sin farmacocinética de diferentes dosis de rocuronio administrado a pacientes pediátricos bajo anestesia general con isofluorano, fue realizado exitosamente en forma individual. Sin embargo, los valores de los parámetros obtenidos (k_e, k_{eo}, γ e IR_{50}) presentaron rangos muy amplios, por lo que proponemos la realización de modelaje poblacional a las respuestas de estos pacientes (*Rev Mex Anest* 1999;22:225-229).

Palabras clave: Agentes neuromusculares no depolarizantes, anestesia inhalatoria, dinámica no-lineal, farmacología clínica.

§The current study was not supported in any form by any Pharmaceutical company. *Research Fellow in Bio-Pharmacy, Unit of Medical Research in Pharmacology, Hospital de Especialidades, Centro Médico Nacional "Siglo XXI", Instituto Mexicano del Seguro Social. **Staff Research Associate, Unit of Medical Research in Pharmacology, Hospital de Especialidades, Centro Médico Nacional "Siglo XXI", Instituto Mexicano del Seguro Social, and Attending Researcher, Department of Anesthesia, Respiratory Therapy and Pain Clinic, Hospital Infantil de México "Federico Gómez". Correspondence to: Alejandro A. Nava-Ocampo, U.I.M-Farmacología C.M.N. "Siglo XXI", IMSS, AP 73032, Mexico City 03020, Mexico. EMail: alnavao@hotmail.com

ROCURONIUM is a non-depolarizing muscle relaxant with a short time to onset and of intermediate duration of action, clinically used in adult and children patient[1-4]. The pharmacodynamic modeling has been helpful to explain the time-course of the effect of neuromuscular relaxants. However, most models require plasma concentrations to model the pharmacodynamics of the neuromuscular relaxant[5-7].

A pharmacodynamic model without plasma concentrations (PDMWOPC) analysis was described in 1994 for responses to vecuronium in adult patients[8]. One year later, another PDMWOPC method used to model the effect of atracurium was also described[9]. These two models were tested in adult patients.

On the other hand, the effects of three different doses of rocuronium (400, 600 and 800 μg/kg) in children under isoflurane anesthesia were recently evaluated[10]. Times to onset and duration of action were then computed by means of sigmoidal analysis of time-course of the effect. However, this classic dynamic analysis, at least applied to neuromuscular relaxants, need to divide the curve in the "onset" curve and the "recovery" curve. Whereas the PDMOWPC methods mentioned above[8,9], are performed by using the complete time-course of the effect, considering the onset, stabilization and recovery periods can be described by some parameters computed by the modeling method.

In order to obtain pharmacodynamic parameters that could be useful to understand the time-course of the effect of rocuronium in children, we performed the PDMWOPC of neuromuscular response of the *adductor pollicis* to different doses of rocuronium administrated to children from the study previously published elsewhere[10], by using the method described by Bragg et al[8].

MATERIAL AND METHODS

The data used for the PDMWOPC analysis were published previously by Villegas-Sánchez et al., in the form of onset and recovery times[10]. Clinical conditions and method to obtain the neuromuscular response were also described. Briefly, 45 children aged 2-14 yr. (ASA physical status 1), undergoing elective surgery requiring tracheal intubation were studied. Using the TOF-Guard (Biometer International A/S, Odense, Denmark) the ulnar nerve was stimulated supraximally with repetitive trains-of-four (2Hz for 2 s) at the wrist using surface electrodes. The ratio of the height of the first response to the control height (T1:T0) and the ratio of the fourth to the first response

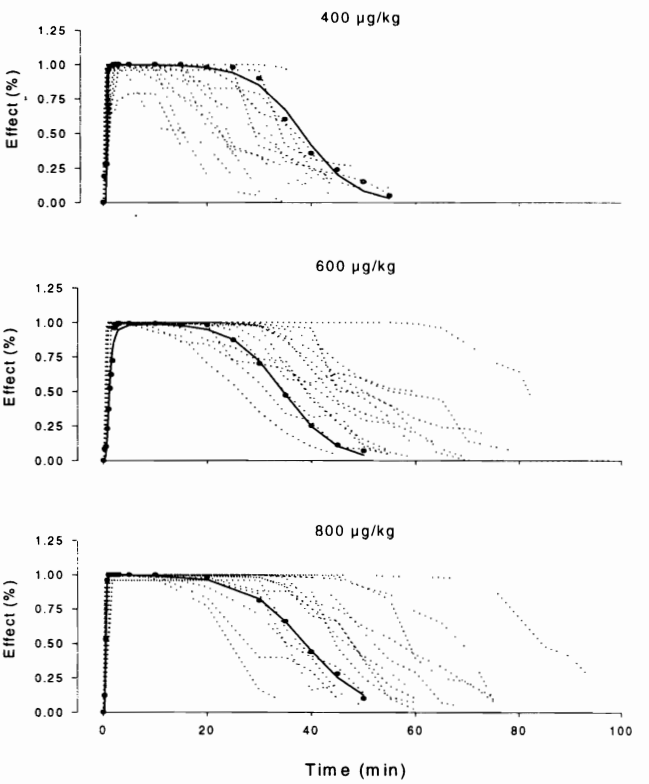

Figura 1. Responses of the adductor pollicis to different doses of rocuronium administrated to children during isoflurane anesthesia. Dashed lines display the data from each subject. The solid line represents the time-course of paralysis for one patient modeled, in every dose, by using the PDMWOPC method plotted simultaneously with the observed response (full circles).

were measured. The stimulus of the train-of-four were performed at the following times: every 15 s up to 180 s (3min), and thereafter every 5 min up to all patients reached a 100% recovery. The patients were randomly allocated to receive either intravenous dose of 400, 600 or 800 μg/kg of rocuronium.

Pharmacodynamic modeling

The neuromuscular response T1:T0 was fitted to time by using the PDMWOPC method previously described by Bragg et al. (equation A7, reference 8), in order to estimate the following parameters: the apparent rate constant of elimination (k_e), the rate constant for equilibrium between plasma and the effect compartment (k_{e0}), the sigmoidicity factor of the relationship between concentrations in the effect compartment and the effect (γ) and the infusion rate that produces 50% effect at steady state (IR_{50}).

Rev. Mex. Anest 1999;22:225-229

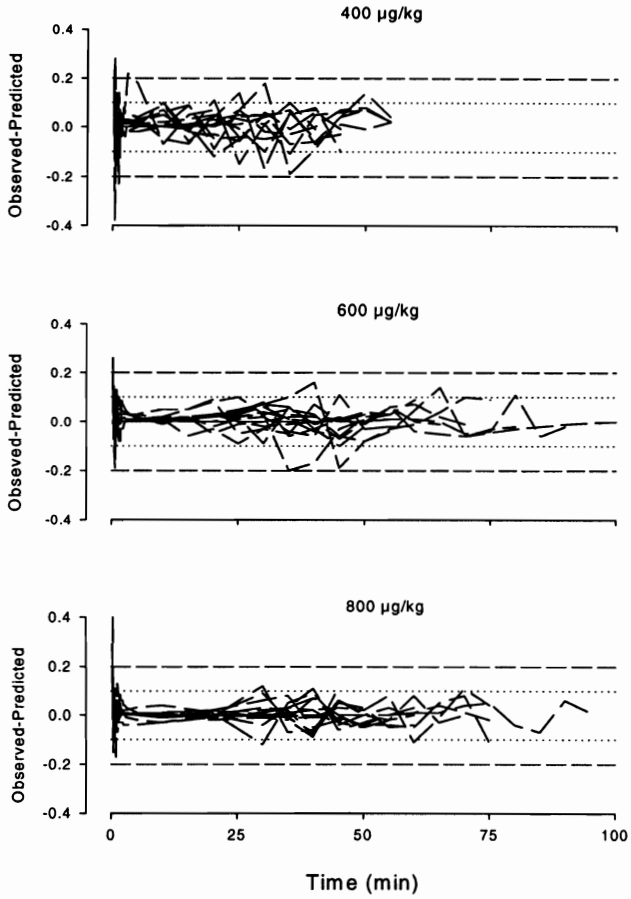

Figura 2. Unweighted residual error plots expressed as observed – predicted effect over time of the three doses of rocuronium administrated to children during isoflurane anesthesia.

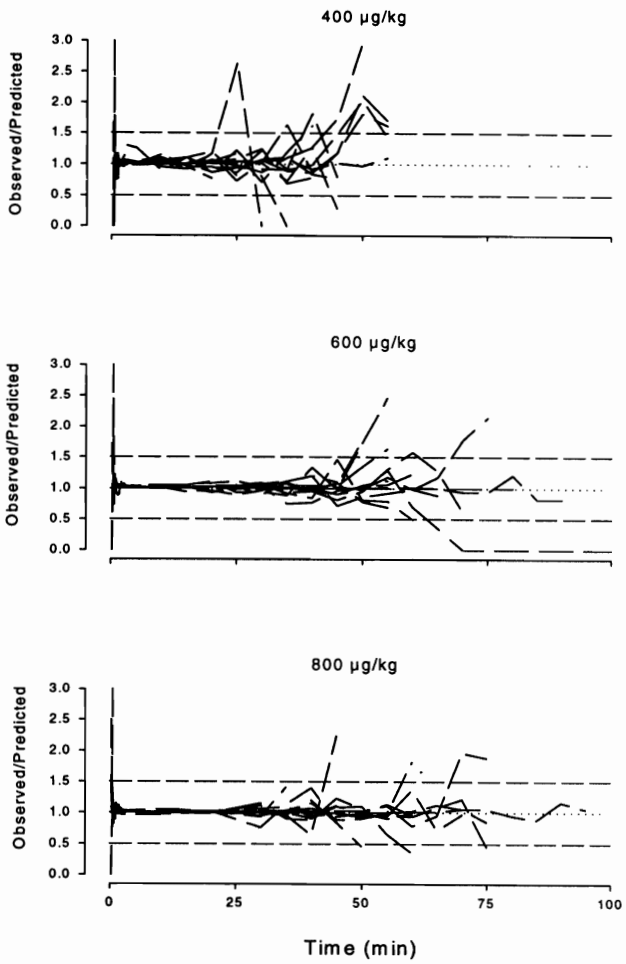

Figura 3. Ratios of observed to predicted effect over time of the three doses of rocuronium administrated to children during isoflurane anesthesia.

The PDMWOPC was computed by means of the SigmaPlot 4.01 (SPSS México, Mexico City, Mexico) for Windows™ 95. The SigmaPlot curve fitter uses the Marquad-Levenberg algorithm to find the parameters of the independent variable that give the best fit between the equation and the data. Every parameter was estimated for each child and results were grouped by dose of rocuronium.

The performance measures of the model were realized using the method described by Zomorodi et al[11]. The quality of fit of the pharmacodynamic model to the data was also judged by the correlation coefficient automatically computed by SigmaPlot, and by visual examination of both plots of the ratio of observed to predicted effect and plots of unweighted residuals error (observed effect – predicted effect), both related to time.

Statistical Analysis

All results were summarized by means of descriptive statistics including mean ± SD, median and ranges. In order to identify differences of individual fitting among the three doses, comparisons were performed non-parametrically by using the Kruskal-Wallis test followed by Wilcoxon rank sum test. Two-tailed probabilities of $p<0.05$ were considered significant. The 95% confidence intervals for non-parametric data were calculated as previously described[12].

RESULTS

In Figure 1, we plotted the observed time-course of the effects of each dose of rocuronium in every patient. We also plotted an "example" patient

Table 1. The k_e, k_{eo}, γ and IR_{50} from children receiving either dose of 400, 600 and 800 μg/kg of rocuronium during isoflurane anesthesia, obtained with PDMWOPC of the time course of the effect.

	DOSE (μg/kg)		
	400	**600**	**800**
k_e (min^{-1})			
Mean ± SD	1.59 ± 1.46	2.39 ± 1.96	1.52 ± 1.37
Median (ranges)	1.52 (0.20 - 4.68)	2.51 (0.23 - 6.3)	1.62 (0.064 - 4.69)
95% Confidence Intervals	0.44 - 2.37	0.49 - 3.79	0.11 - 2.62
k_{eo} (min^{-1})			
Mean ± SD	0.054 ± 0.053	0.020 ± 0.02	0.037 ± 0.035
Median (ranges)	0.03 (0.003 - 0.2)	0.01* (0.003 - 0.07)	0.03** (0.01 - 0.12)
95% Confidence Intervals	0.019 to 0.088	0.004 to 0.03	0.01 to 0.05
γ			
Mean ± SD	10.22 ± 12.5	15.15 ± 9.32	9.51 ± 6.53
Median (ranges)	15.1 (1.71 - 49.72)	15.99 (2.53 - 34.14)	7.02 (2.64 - 23.52)
95% Confidence Intervals	2.29 to 10.78	5.36 to 21.98	3.42 to 14.68
IR_{50} ($\mu g.kg^{-1}.min^{-1}$)			
Mean ± SD	10.36 ± 17.6	5.58 ± 8.30	12.06 ± 15.63
Median (ranges)	34.24 (0.21 - 71.25)	1.42 (0.23 - 29.38)	3.55 (1.51 - 55.59)
95% Confidence Intervals	1.60 to 12.10	0.53 to 8.71	2.00 to 20.88
Performance measures			
MDWR (%)	1.00	0.00	0.00
MDAWR (%)	3.00	2.00	1.00

SD = standard deviation, MDWR = median weighted residual, MDAWR = median absolute weighted residual.
*$p < 0.05$, dose of 400 vs. 600. **$p < 0.05$, dose of 600 vs. 800

whose observed values were simultaneously presented by those computed with the model, for every dose.

All patients were successfully modeled. The corresponding unweighted residual error plots for each three doses were shown in Figure 2. If the PDMWOPC fit the data perfectly, lines would lie horizontally at 0. As can be observed in the graph, there were differences among observed and predicted values during the evaluation period. However, the fit tends to be good since lines approach the "0-line". Additionally, the ratios of observed to predicted effect, plotted in Figure 3, also tended to be good. In this latter case, a perfect fit would lie horizontally at 1.0. Finally, the performance measures (showed in Table 1), quantitative expressions of the goodness of fit, also demonstrated a high quality fit with the PDMOWPC of data from patients in every dose.

The parameters computed for every dose of rocuronium were summarized in Table 1. Each parameter exhibited a great intra-group variability, and ranges reported in the table vary up to 300-fold. Results among the three doses were similar in three (k_e, γ and IR_{50}) of the four parameters, and significant differences ($p<0.05$) were observed between the doses of 400 and 600 and between 600 and 800 μg/kg of rocuronium in the k_{eo} values.

DISCUSSION

Traditionally, pharmacodynamic modeling of muscle relaxants has required that plasma concentrations of the muscle relaxant be quantified[5-7]. This is costly and complicates the study design, adds risks to the pediatric patient (associated with blood sampling), expense of measuring plasma concentrations of drugs, and potential delays in drug development if sensitive or specific assays are not available. Therefore, it has been suggested a potential role for modeling pharmacodynamic without plasma concentration data[8-9].

In the past, pharmacokinetics studies have focused on the individual, and thereafter determination of population pharmacokinetics parameters becomes an interesting point. However, some clinical inferences sustained in pharmacokinetic parameters can be wrongly performed[13]. Therefore, pharmacodynamics

Rev. Mex. Anest 1999;22:225-229

gained popularity both with and without plasma concentrations. More recently, PDMWOPC becomes an interesting option because does not need plasma concentrations. And population approach, i.e., parameters that define the typical pharmacodynamics behavior of a drug in a large group of subjects, can also be performed. During the population approach, covariates can also be incorporated into the PDMWOPC model.

In the present study, we successfully modeled the time-course of rocuronium by using a PDMWOPC method that does not require any plasma concentration. However, despite a good fit between observed and predicted effect was obtained in every case, a great variability in all the four parameters computed by the PDMWOPC method was present. These variations did not allow us to elaborate any conclusion in relation to similarities or differences among groups. In addition, these variations strongly suggest the application of a population approach, and to incorporated gender, age and weigh as potential covariates into the model. These potential covariates were previously significant related to times to spontaneous recovery of neuromuscular function[10].

Bragg et al., originally describing the PDMWOPC used herein, proposed that the k_e and k_{eo} were equivalent to same parameters but using plasma concentrations. In fact, their computed parameters for vecuronium were similar to those published previously using classical Pk/Pd modeling. In our, study we also lacked of plasma concentrations, however, comparison with those published elsewhere for rocuronium in children while using classical Pk/Pd[6,13], cannot be yet done until we have parameters obtained with population approach. In fact, performing the population approach of these data we could also test the predictability of new cases with population parameters obtained by us, and therefore validate the model.

Finally, the neuromuscular function was monitored at the ulnar nerve using the TOF - Guard neuromuscular transmission monitor. Monitoring with simple nerve stimulators has been shown to be unreliable even in experienced hands. The use the TOF - Guard has previously been validated and showed a good correlation to more accurate method. However, it is not considered the gold standard and can generate "noise" in the measurement of the effect[14].

In conclusion, individual PDMWOPC was successfully performed in children receiving different doses of rocuronium during isoflurane anesthesia. However, wide ranges of computed parameters, i.e., k_e, k_{eo}, γ and IR_{50} were obtained. We therefore propose to model these data using a population approach and thereafter to test the predictability of population parameters in a new set of pediatric patients.

Aknowledgment

The authors are indebted with Dr. Diana Moyao-García, Head of the Department of Anesthesia, Respiratory Therapy and Clinic of Pain at the Hospital Infantil de México "Federico Gómez", SSa, Mexico City, for providing us data for the current study.

REFERENCES

1. Taylor P. Agents acting at the neuromuscular junction and autonomic ganglia. In: Molinoff PB, Ruddon RW, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 9th ed. International Edition; 1996:177-97.
2. Bikhazi GB, Marin F, Mouhanna J, Halliday NJ, Foldes FF. The dose response of ORG 9426 in children anesthetized with halothane (abstract). *Anesthesiology* 1991;75:A1067.
3. Woelfel SK, Brandom BW, Cook DR, Sarner JB. Effects of bolus administration of ORG-9426 in children during nitrous oxide-halothane anesthesia. *Anesthesiology* 1992;59:939-42.
4. Woelfel SK, Brandom BW, McGowan FX, Gronert BJ, Cook DR. Neuromuscular effects of 600 $\mu g.kg^{-1}$ of rocuronium in infants during nitrous oxide-halothane anaesthesia. *Paed Anaesth* 1994;4:173-7.
5. Schwinghammer TL, Kroboth PD. Basic concepts in pharmacodynamic modeling. *J Clin Pharmacol.* 1988;28:388-94.
6. Wierda JMKH, Meretoja OA, Taivainen T, Proost JH. Pharmacokinetics and pharmacokinetic-dynamic modelling of rocuronium in infants and children. *Br J Anaesth* 1997;78:690-5.
7. Fisher DM, Wright PMC. Are plasma concentration values necessary for pharmacodynamic modeling of muscle relaxants? *Anesthesiology* 1997;86:567-75.
8. Bragg P, Fisher DM, Shi J, Donati F, Meistelman C, Lau M, Sheiner LB. Comparison of twitch depression of the adductor pollicis and the respiratory muscles: pharmacodynamic modeling without plasma concentrations. *Anesthesiology* 1994;80:310-9.
9. Warwick NR, Graham GG, Torda TA. Pharmacokinetic analysis of the time course of effect of atracurium. *Clin Pharmacol Ther* 1995;57:390-7.
10. Villegas-Sanchez F, Charles-Torres JD, Moyao-Garcia D, Nava-Ocampo AA, Velázquez-Armenta EY. Rocuronium in children during isoflurane anesthesia: neuromuscular effect. *Arch Med Res* 1999;30:307-14.
11. Zomorodi K, Donner A, Somma J, Barr J, Sladen R, Ramsay J, Geller E, Shafer SL. Population pharmacokinetics of midazolam administered by target controlled infusion for sedation following coronary artery bypass grafting. *Anesthesiology* 1998;89:1418-29.
12. Campbell MJ, Gardner MJ. Calculating confidence intervals for some non-parametric analyses. *Br Med J* 1988;296:1454-6.
13. Minto Ch, Schnider T. Expanding clinical applications of population pharmacodynamic modelling. *Br J Clin Pharmacol* 1998;46:321-33.
14. Loan PB, Paxton LD, Mirakhur RK, Connolly FM, McCoy EP. The TOF-Guard neuromuscular transmission monitor. *Anaesthesia* 1995;50:699-702.