Pharmacokinetics of Rapacuronium in Infants and Children with Intravenous and Intramuscular Administration

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Background: A nondepolarizing muscle relaxant with an onset and offset profile similar to succinylcholine is desirable for pediatric anesthesia. The onset and offset of rapacuronium are rapid in children. In the current study, the authors determined its pharmacokinetic characteristics in children. In addition to administering rapacuronium by the usual intravenous route, the authors also gave rapacuronium intramuscularly to determine uptake characteristics and bioavailability.

Methods: Forty unpremedicated patients aged 2 months to 3 yr were anesthetized with halothane, 0.82–1.0% end-tidal concentration. When anesthetic conditions were stable, rapacuronium was injected either into a peripheral vein (2 mg/kg for infants, 3 mg/kg for children) or a deltoid muscle (2.8 mg/kg for infants, 4.8 mg/kg for children). Four venous plasma samples were obtained from each subject 2–240 min after rapacuronium administration. A mixed-effects population pharmacokinetic analysis was applied to these values to determine bioavailability, absorption rate constant, and time to peak plasma concentration with intramuscular administration.

Results: Plasma clearance was 4.77 ml · kg^{-1} · min^{-1} + 8.48 ml/min. Intramuscular bioavailability averaged 56%. Absorption from the intramuscular depot had two rate constants: 0.0491 min^{-1} (72.4% of absorbed drug) and 0.0110 min^{-1} (27.6% of the absorbed drug). Simulation indicated that plasma concentration peaks 4.0 and 5.0 min after intramuscular rapacuronium in infants and children, respectively, and that, at 30 min, less than 25% of the administered dose remains to be absorbed from the intramuscular depot.

Conclusions: In infants and children, rapacuronium's clearance and steady state distribution volume are less than in adults. After intramuscular administration, bioavailability is 56%, and plasma rapacuronium concentrations peak within 4 or 5 min. (Key words: Intramuscular injections; mixed-effects modeling; ORG9487.)

RECENT trials in adults[1] and children[2] showed that the onset of intravenous rapacuronium is rapid, approaching that of succinylcholine. In addition, recovery from a bolus dose of rapacuronium is similar to that from mivacurium, currently the nondepolarizing muscle relaxant with the shortest duration of action.[3] These characteristics suggest that rapacuronium can be valuable for pediatric anesthesia. In the current study, we determined the pharmacokinetics of rapacuronium in infants and children. In addition, because a recent pilot study from the University of California, San Francisco[2] suggested that intramuscular administration of rapacuronium permits intubation within 2 or 3 min without a prolonged duration of paralysis, we also determined the pharmacokinetic characteristics of intramuscular rapacuronium.

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Methods

The study was conducted using Organon's Investigational New Drug Application, (West Orange, New Jersey) and the protocol was approved by the institutional review board of the University of California, San Francisco. After obtaining informed consent from parents, we studied 40 pediatric patients, American Society of Anesthesiologists physical status I or II, undergoing elective peripheral surgery with minimal blood loss and fluid requirements. Patients were stratified into two groups by age: infants (2–11 months, 7.7 ± 1.7 kg [mean ± SD], n = 20) and children (1–3 yr, 13.0 ± 2.6 kg, n = 20). No patient had a history of bleeding disorder, neuromuscu-

lar disease, or hepatic or renal insufficiency. Patients were excluded if they received anticonvulsants or aminoglycoside or polypeptide antibiotics perioperatively. Neuromuscular effects of rapacuronium in these patients have been described previously.[2]

Patients were unpremedicated, and anesthesia was induced with nitrous oxide and halothane. After loss of consciousness, nitrous oxide was discontinued and inspired halothane was adjusted to produce end-tidal concentrations of 1.0% in children younger than 2.5 yr and 0.82% in children older than 2.5 yr. After establishing intravenous access, the trachea was intubated and ventilation was controlled to maintain normocapnia. After tracheal intubation, 66% nitrous oxide was added to the inspired gas. Patients were randomized to receive rapacuronium as either an intramuscular (n = 20) or an intravenous (n = 20) injection. If end-tidal halothane concentrations were stable for more than 5 min, rapacuronium (20 mg/ml) was injected either as a rapid bolus into a peripheral venous catheter in an upper or lower extremity or *via* a 21-gauge needle 1 to 2 cm into a single deltoid muscle after negative aspiration for blood. The intravenous dose of rapacuronium was 2 mg/kg for infants and 3 mg/kg for children; the intramuscular dose was 2.8 mg/kg for infants and 4.8 mg/kg for children.

Five venous blood samples were obtained from each patient. The initial sample was taken after induction of anesthesia but before rapacuronium administration, the remaining four samples were taken 2–240 min after rapacuronium. For each patient, target times for blood sampling differed, determined by randomization. To prevent degradation of rapacuronium, blood samples were added immediately to vials prefilled with sodium dihydrogen phosphate buffer (0.8 M). Blood was centrifuged within 30 min of sampling, and plasma was stored at −20°C. Concentrations of rapacuronium and its primary metabolite ORG9488 were determined by Corning Hazelton Labs (Hazelton, WI) using a high-performance liquid chromatography–mass spectroscopy technique. The assay is linear for concentrations more than 2 ng/ml for rapacuronium and ORG9488 both and has a coefficient of variation of less than 11% for rapacuronium and less than 20% for ORG9488. The amount of ORG9488 in each vial of rapacuronium was less than 1% of the quantity of rapacuronium (oral communication, January 1999, Viquar Pervaaz, Organon).

Code for the NONMEM analysis can be obtained from Dr. Fisher.

** The hybrid approach uses conditional estimates of ηs for selected parameters and first-order estimates for the remaining ηs.

Pharmacokinetic analyses were performed using the NONMEM statistical package[4]# with the first-order or hybrid approaches.** Analyses were performed using two- and three-compartment models. Parameters of the two-compartment model were weight-normalized volume of the central compartment (V_1), volume of the second compartment (V_2), clearance (Cl), and distribution clearance $(Cl_{distribution})$. Additional parameters of the three-compartment model were weight-normalized volume of the third compartment (V_3) and slow-distribution clearance (Cl_{slow}); $Cl_{distribution}$ was renamed Cl_{rapid}. Volume of distribution at steady state (V_{ss}) equaled $V_1 + V_2$ or $V_1 + V_2 + V_3$. With intramuscular administration, we initially assumed that the absorption process was first-order; that is, the rate of absorption was proportional to the quantity of rapacuronium remaining in the intramuscular depot. This absorption process is described by the equation

Absorption rate = $F \cdot$ dose $\cdot k_{absorption} \cdot$ exp

$$(- k_{absorption} \cdot \text{time}), \quad (1)$$

in which F is the bioavailable fraction, $k_{absorption}$ is the absorption rate constant (estimated in the analysis), and time is the interval since drug administration. Additional absorption models were also evaluated. Absorption, distribution, and elimination half-lives were determined using standard formulas.

Intraindividual variability for Cl was assumed to be log-normally distributed, modeled as

$$\ln(Cl_i) = \ln(Cl) + \eta_i, \quad (2)$$

in which Cl_i is the estimate for Cl for the ith individual, Cl is the typical value for the population, and η_i is a random variable with mean 0.0 and variance Ω^2. Interindividual variability for each of the pharmacokinetic parameters was modeled in a similar manner. With three-compartment models, interindividual variability in Cl_{rapid} was assumed to have the same magnitude as that for Cl_{slow}; interindividual variability for V_2 was assumed to have the same magnitude as that for V_3. Residual variability between predicted and measured plasma concentrations of rapacuronium initially was assumed to have two components: one proportional to the predicted concentration ("constant coefficient of variation"), and one additive (homoscedastic error). Additional error models with a single component also were evaluated.

After the "typical" values were determined, we used the NONMEM *post hoc* step to determine values for the pharmacokinetic parameters for each individual. These

values were plotted against each of the covariates age and weight and evaluated for systematic trends (*e.g.*, a relation between Cl and age) using a smoother (lowess, a nonlinear regression function). If trends appeared, these covariates were incorporated into the pharmacokinetic model. Models with additional pharmacokinetic parameters (either additional compartments, additional parameters to allow for interindividual variability, or the influence of covariates on a particular pharmacokinetic parameter) were accepted if they improved the objective function ($P < 0.01$ necessitates a decrease of 6.6 units for one additional parameter or 9.2 units for two additional parameters) and either improved the pattern of residual differences between measured and predicted values for plasma concentration of rapacuronium or decreased the trend between a pharmacokinetic parameter and a covariate.

Because the time to peak plasma concentration with intramuscular administration is a function of all the pharmacokinetic parameters, its typical value and confidence limits cannot be determined using Student t values. Instead, we determined the time to peak plasma concentration using the NONMEM simulation mode. Using the typical values for the pharmacokinetic parameters and allowing for the interindividual variability determined in the pharmacokinetic analysis, we simulated the plasma concentration *versus* time course of 250 infants weighing 5 kg and 250 children weighing 15 kg who were administered intramuscular rapacuronium. Time to peak plasma concentration was determined for each of these simulated individuals, and the fifth, fiftieth (median), and ninety-fifth percentile values were determined. We also used the typical values for bioavailability and the absorption rate constants to simulate the typical time course of rapacuronium remaining to be absorbed from the intramuscular depot. Finally, we used log-linear interpolation of the *post hoc* estimates for plasma concentration of rapacuronium to estimate the plasma concentration in each subject 30 min and 60 min after administration of rapacuronium.

For ORG9488, the ratio of each plasma concentration to the corresponding plasma concentration of rapacuronium was determined and plotted against time. The influence of age and route of administration on these ratios was assessed visually.

Values are reported as the mean $\pm$ SD. Comparisons between infants and children and between intravenous and intramuscular administration were performed using the Student t test for unpaired data; $P < 0.05$ was considered statistically significant.

Results

One supplemental plasma sample was obtained from each of three patients: an infant (intravenous group) at 201 min and two children (intravenous group) at 4 and 211 min (fig. 1). The final plasma sample could not be obtained in two patients (one infant, intravenous group at 240 min; one child, intravenous group at 120 min) because of loss of venous access. A total of 161 plasma samples (excluding blank samples) were used in the analysis, 80 of these underwent intramuscular administration.

Pharmacokinetic Analysis

A three-compartment pharmacokinetic model fit the plasma concentration data better than did a two-compartment model. (The objective function decreased by 127.406 units and the residual differences between predicted and measured concentrations improved. [table 1]). Not permitting interindividual variability in Cl_{rapid}, Cl_{slow}, V_2, and V_3 increased the objective function by only 5.764 units (model 3 *vs.* model 2; $P > 0.5$ for the deletion of two parameters); therefore, subsequent models did not permit interindividual variability in these parameters. Because subsequent analyses necessitated the use of the NONMEM hybrid approach, model 3 was repeated using the hybrid approach (model 4).

Plots from model 4 showed that with both age groups, measured and population-predicted concentrations after 100 min were biased: The ratios were higher with intramuscular compared with intravenous administration. This could result from incorrect modeling of the absorption process, that is, not allowing for persistent absorption of rapacuronium from the intramuscular depot. To account for this, we tested a model in which the administered dose was absorbed from two separate compartments, each of which had its own rate constant. The sum of the amount absorbed from each of these absorption compartments equals the product of the bioavailability fraction and the administered dose. The fraction of the dose absorbed from each of the two absorption compartments was estimated in the analysis. The objective function for model 5 decreased by 70.429 units compared with model 4, bias was no longer evident in the plots, and the fit of the model to the data was good.

Plots of the *post hoc* estimates of Cl *versus* weight from model 5 suggested that Cl had both a weight-normalized and an additive component (Cl = slope · weight + intercept; ml/min). Permitting Cl to have weight-normalized and additive components improved
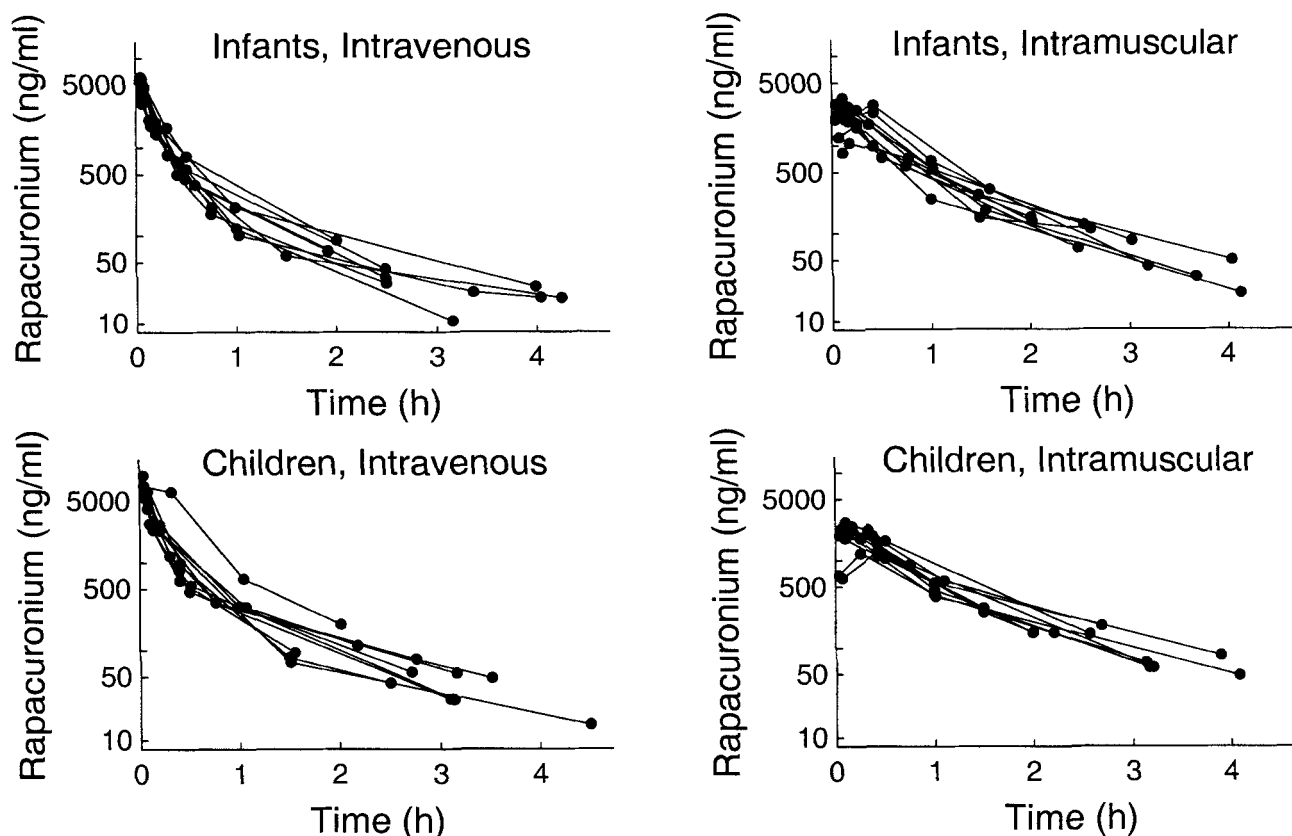
Fig. 1. Time course of rapacuronium plasma concentrations (normalized to a dose of 1 mg/kg) after intravenous or intramuscular administration. Circles indicate measured values; lines connect values for each patient. Values for some patients overlie those for others.

the objective function of model 6 by 11.873 units compared with model 5 ($P = 0.006$ for the addition of one parameter). Plots from model 5 also suggested an alternate explanation: weight-normalized Cl differed between infants and children. Permitting weight-normalized Cl to differ between infants and children (model 7) decreased the objective function by 14.593 units compared with model 5 ($P = 0.001$ for the addition of one parameter). However, the resulting population-predicted concentrations were biased (e.g., for infants, measured concentrations were consistently larger than predicted), suggesting that model 7 was not appropriate. Therefore, model 6 was used as the basis for further analyses.

Plots for model 6 suggested that V_1 differed as a function of gender. To evaluate this, model 8 permitted V_1 to differ between males and females. The objective function decreased by 0.433 units compared with model 6 ($P > 0.50$ for the addition of one parameter), indicating that V_1 did not differ between genders. Covariate plots

for model 6 also suggested that the fraction of the intramuscularly administered dose absorbed from the first absorption compartment (as opposed to the second absorption compartment) varied with patient weight or with the volume of drug administered (which was a function of weight and age group). The former was incorporated into model 9 as

$$FACT1 = THETA(12) \tag{3}$$

$$TVCMT1 = THETA(10) \tag{4}$$

$$INCMT1 = TVCMT1 \cdot (1 + FACT1 \cdot (WT - 10)) \tag{5}$$

$$LGTCMT = LOG(INCMT1/(1 - INCMT1)) + ETA(10) \tag{6}$$

$$FXCMT1 = EXP(LGTCMT)/(1 + EXP(LGTCMT)), \tag{7}$$

Table 1. Models Tested for the Pharmacokinetics of Rapacuronium

Model No.	Compartments	Method	No. of ηs*	No. of ϵs*	Issue Tested	Objective Function
1	2	First-order	6	2	No. of compartments	2328.453
2	3	First-order	6	2	No. of compartments	2201.047
3	3	First-order	4	2	No. of ηs	2206.811
4	3	Hybrid	4	2	Model No. 3 with hybrid approach	2274.997
5	3	Hybrid	6	2	Model No. 4 with new absorption model	2204.568
6	3	Hybrid	6	2	Model No. 5 + effect of weight on Cl	2192.695
7	3	Hybrid	6	2	Model No. 5 + effect of age group on Cl	2189.975
8	3	Hybrid	6	2	Model No. 6 + effect of gender on V_1	2192.262
9	3	Hybrid	6	2	Model No. 6 + effect of weight on FxCMT1	2184.789
10	3	Hybrid	6	2	Model No. 6 + effect of injectate volume on FxCMT1	2167.089
11	3	Hybrid	5	1	Model No. 9 + no η on FXCMT1 + error model	2184.789

* ηs permit interindividual variability; ϵs are the components of the error model.

Cl = clearance; V_1 = volume of distribution of the central compartment; FXCMT1 = inverse logit transform if LGTCMT (see text for explanation).

where FACT1 is estimated in the analysis, TVCMT1 is the typical value for the fraction of bioavailable drug absorbed from the first absorption compartment [*i.e.*, with rate constant $k_{absorption}(1)$], INCMT1 is the value for that fraction for an individual of weight (WT; in kilograms), 10 is approximately the median value for weight in this population, LGTCMT is a logit transformation to ensure that typical and individual values for the fraction of bioavailable drug absorbed from the first compartment are bounded by 0 and 1, and FXCMT1 is the inverse logit transform if LGTCMT. The objective function for model 9 decreased by 7.906 units compared with model 6 (P = 0.005). In model 10, we evaluated whether the volume of drug administered influenced the fraction of the drug administered dose absorbed from the first absorption compartment. Although the objective function for model 10 decreased by 25.606 units compared with model 6 (P = 0.005), the resulting population-predicted concentrations were biased (*e.g.*, nearly all initial measured values were markedly less than the corresponding predicted values). Thus, model 9 was used as the basis for further analyses.

The results of model 9 suggested that interindividual variability for the fraction of bioavailable drug absorbed from the first absorption compartment was trivial. In addition, the additive component of the error model was trivial. Therefore, model 11 differed from model 9 by deleting the η term in equation 6 and by having only the constant coefficient component in the error model. The resulting objective function was identical to that for model 9. Plots of pharmacokinetic parameters from model 11 *versus* covariates did not reveal any remaining

relation between the covariates and the pharmacokinetic parameters nor bias in the ratio of measured to predicted plasma concentrations (fig. 2).

Thus, the "optimal" pharmacokinetic model (model 11) had three compartments and permitted interindividual variability in Cl, V_1, bioavailability, and each of the absorption rate constants. The typical value for Cl was 4.77 ml · kg^{-1} · min^{-1} + 8.48 ml/min (fig. 3, table 2). Distributional clearances and volumes of distribution were all weight-normalized. Although Cl varied with weight, half-lives varied minimally (table 3). With intramuscular administration, the typical value for F was 56%. For a 10-kg child, approximately 28% (varying with weight) of bioavailable rapacuronium was absorbed with a rate constant of 0.011 min^{-1}; the remaining 72% was absorbed with the rate constant 0.0491 min^{-1}. The fraction of the bioavailable dose absorbed with a rate constant of 0.011 min^{-1} decreased with increasing weight.

Pharmacokinetic Simulations

For a simulated 5-kg infant, the median time after intramuscular administration for plasma concentration to peak was 4.0 min; the fifth and ninety-fifth percentiles were 2.5 and 6.3 min, respectively. For the 15-kg child, median time to peak plasma concentration was 5.0 min; the fifth and ninety-fifth percentiles were 3.0 and 7.5 min, respectively. The quantity of rapacuronium remaining in the intramuscular depot initially was larger in children than in infants (fig. 4); values converged approximately 45 min after intramuscular administration. At 30 min and 60 min after administration, mean plasma concentrations of rapacuronium were greater after intra-
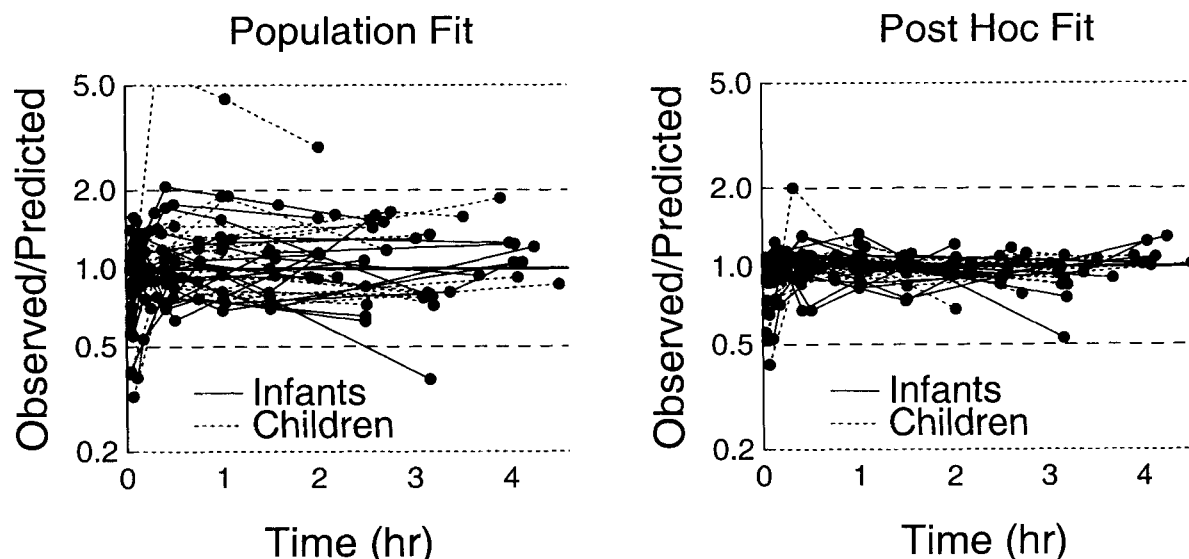
Population Fit

Post Hoc Fit

Fig. 2. Values for the measured concentrations of rapacuronium divided by concentrations predicted in the pharmacokinetic analysis (model 11) are plotted against time for each patient. (*Left*) Values from the population analysis. (*Right*) Values from the *post hoc* analysis. If the pharmacokinetic model fit the data perfectly, all lines would lie horizontally at 1.0. The improved fit with the *post hoc* model is expected because that approach permits interindividual variability.

muscular administration than after intravenous administration and greater in children than in infants (table 4).

Plasma Concentrations of ORG9488

After intravenous administration of rapacuronium, plasma concentrations of ORG9488 peaked early (fig. 5) and then decreased slowly. With intramuscular administration of rapacuronium, plasma concentrations of ORG9488 peaked 1–2 h after administration and then decreased slowly. During the 30 min after administration of rapacuronium, plasma concentrations of ORG9488
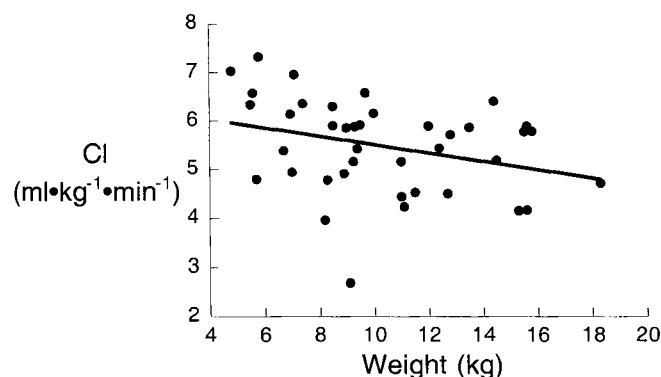

Fig. 3. Values for weight-normalized clearance estimated in the NONMEM *post hoc* pharmacokinetic analysis (model 11) are plotted against weight. The line, determined by linear regression, is consistent with weight-normalized clearance decreasing with weight.

were less than 10% of corresponding rapacuronium concentrations in 71 of 83 measurements. For the remaining measurements, the ratio of ORG9488 to rapacuronium was 10–22%. In samples obtained more than 30 min after rapacuronium administration, the ratio of concentrations of ORG9488 to those of rapacuronium increased progressively (fig. 6). There were no apparent age-related differences in plasma concentrations of ORG9488. However, with intravenous administration of rapacuronium, the ratios of plasma concentrations of ORG9488 to those of rapacuronium were generally greater in infants than in children (fig. 6).

Discussion

We determined the pharmacokinetic characteristics of rapacuronium with intravenous and intramuscular administration. Our analysis indicates that Cl is approximately $6.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for a 5-kg infant and $5.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for a 15-kg child. These values are slightly less than the Cl values for rapacuronium in adults, with intravenous administration recently reported in two other studies. Szenohrdazsky *et al.*[5] reported that Cl was $9.40 \cdot (1 - 0.00909 \cdot [\text{Age} - 30]) \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in anesthetized volunteers aged 20–42 yr. Fisher *et al.*[6] reported that Cl for rapacuronium was $7.03 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in adults aged 24–83 yr and did not vary with age.

Table 2. Parameter Estimates* of Three-compartment Pharmacokinetic Model for Rapacuronium (Model No. 11)

	Typical Value	Standard Error	Interindividual Variability† (%)
$k_{absorption}(1)$ (min^{-1})	0.0110	0.0030	33.0
$k_{absorption}(2)$ (min^{-1})	0.0491	0.00849	19.1
Bioavailability (%)	56.0	13.0	21.7
Fraction absorbed with $k_{absorption}(1)$	$0.276 \cdot (1 - 0.0918 \cdot (WT - 10))$	0.0736, 0.0236‡	ND#
V_1 (ml/kg)	9.92	2.39	34.8
V_2 (ml/kg)	22.8	11.9	ND#
V_3 (ml/kg)	66.4	26.4	ND#
Cl	$4.77 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} + 8.48 \text{ ml/min}$	0.966, 5.17§‖	25.2
Cl_{rapid} (ml $\cdot$ kg^{-1} $\cdot$ min^{-1})	2.78	1.88	ND#
Cl_{slow} (ml $\cdot$ kg^{-1} $\cdot$ min^{-1})	0.745	0.284	ND#
V_{SS} (ml/kg)	99.1	—	—

* Standard error and interindividual variation are reported only for those parameters estimated by NONMEM. For those structural parameters with more than one component (*i.e.*, Fraction absorbed with $k_{absorption}$ (1) and Cl), interindividual variability applies to the combination of components.

† Computed as 100% $\cdot \sqrt{\Omega^2}$ where Ω^2 = variance (η); sixty-eight % of the population lies within this range of the typical value.

‡ The value 0.0736 applies to the value 0.276; the value 0.0236 applies to the value 0.0918.

§ The value 0.966 applies to the value 4.77; the value 5.17 applies to the value 8.57.

‖ Although the standard error of Cl_{rapid} and the non-weight-normalized component of Cl are large (suggesting that these values do not differ from zero), a likelihood profile shows justification for both the three-compartment model and the two components of Cl.

Not determined because interindividual variability was not justified statistically for this parameter.

$k_{absorption}$ (1) = rate constant for absorption from the first absorption compartment; $k_{absorption}$ (2) = rate constant for absorption from the second absorption compartment.

The finding that Cl for rapacuronium is smaller in children than in adults differs from that for other muscle relaxants. For example, the Cls of *d*-tubocurarine[7] and vecuronium[8] are similar in children and adults. Because the three studies involving rapacuronium used identical assays, and the pharmacokinetic analyses were performed by the same individual, it is unlikely that the findings of the current study result from experimental error. We are unable to explain why Cl for rapacuronium is smaller in infants and children than in adults. Although

infants and children have a smaller Cl compared with adults, the rate at which plasma concentrations decay after bolus doses is more rapid in infants and children (fig. 7). This results from a smaller steady state volume of distribution in infants and children than in young healthy adults (381 and 445 ml/kg in women and men, respectively).[5]

Initially, we modeled absorption from the intramuscular depot using a single first-order rate constant; that is,

Table 3. Estimates for Rapacuronium Half-lives and the Fraction Absorbed with Each Absorption Half-life as a Function of Weight (Model No. 11)

	Weight (kg)*			
	5	10	15	20
Fraction absorbed with $t_{1/2}$absorption(1)	0.402	0.276	0.149	0.023
$t_{1/2}$absorption(1) (min)	63.0	63.0	63.0	63.0
$t_{1/2}$absorption(2) (min)	14.1	14.1	14.1	14.1
$t_{1/2}\pi$ (min)	0.67	0.72	0.74	0.75
$t_{1/2}\alpha$ (min)	8.1	8.5	8.6	8.7
$t_{1/2}\beta$ (min)	69	71	71	71

Distribution and elimination half-lives apply to intravenous and intramuscular administration; absorption half-lives apply only to intramuscular administration.

* Values of 5–20 kg are reported because these are the approximate lower and upper limits in the sample.
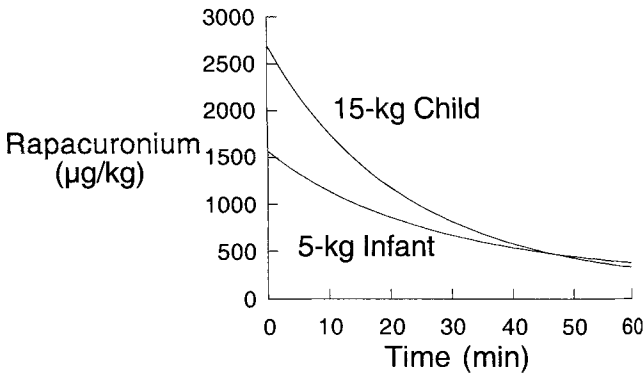

Fig. 4. Quantity of rapacuronium remaining to be absorbed from the intramuscular depot is plotted against time. Values were determined by simulation based on the parameters determined in the pharmacokinetic analysis (table 2). Values at time zero are the product of the dose administered and the "typical" value of bioavailability; these initial values are larger for children than for infants because of the larger dose administered.

Table 4. Values for Predicted Plasma Concentration of Rapacuronium (ng/ml) 30 min and 60 min After Administration by the Intravenous or Intramuscular Routes

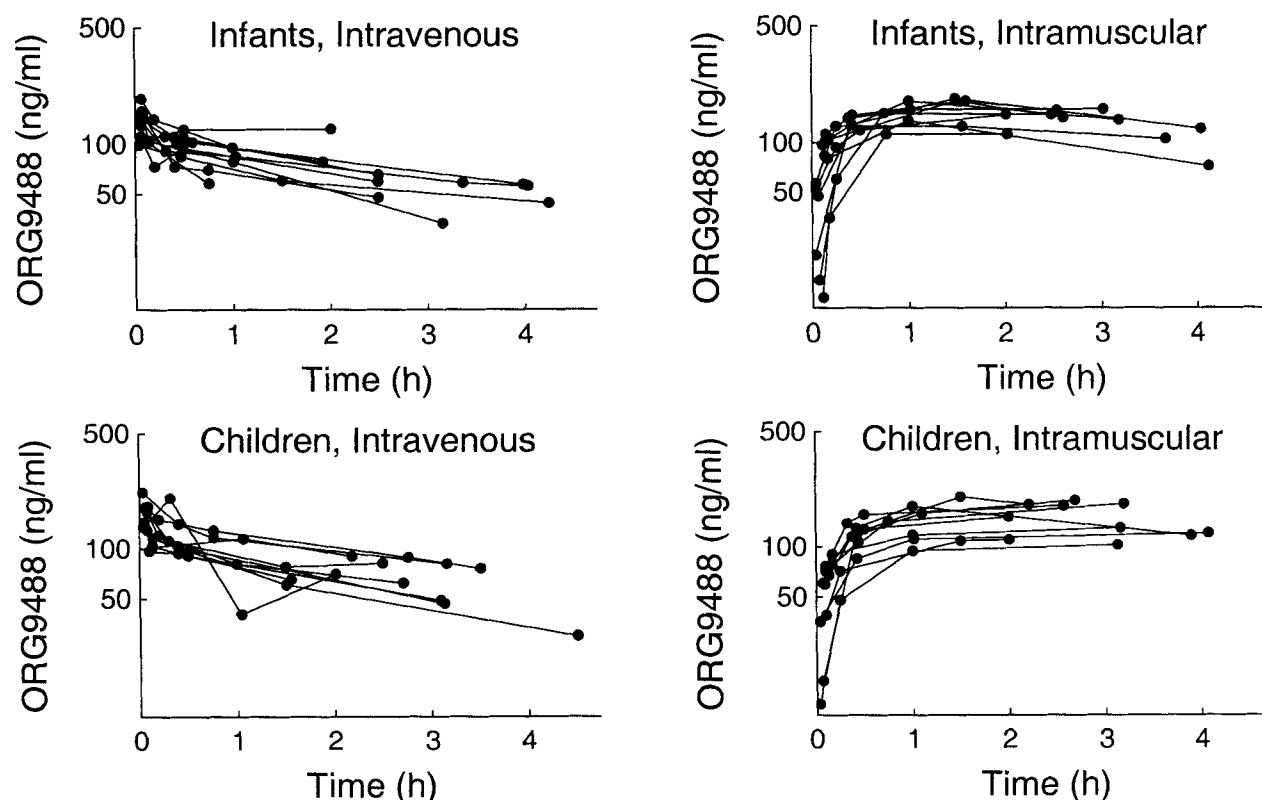|	Infants	Children
30 Min after administration of rapacuronium		
Intravenous	1160 ± 440*	2860 ± 1450*
Intramuscular	3510 ± 820*	5680 ± 1030*
60 Min after administration of rapacuronium		
Intravenous	410 ± 170*	970 ± 390*
Intramuscular	1490 ± 370*	2980 ± 650*

Values are mean ± SD.

* Different from other route of administration and from the other age group for the same time after administration of rapacuronium.

assuming that the rate of absorption of rapacuronium from muscle was proportional to the quantity remaining in the muscle. This model was biased, as evidenced by plots of the ratio of measured to predicted plasma concentrations *versus* time. To address this bias, we tested

an alternate absorption model in which bioavailable rapacuronium was absorbed from two different compartments, each of which had different absorption rate constants. The resulting fit of the model to the data improved markedly, suggesting that the more complicated absorption model was appropriate. The traditional model with a single first-order rate constant often is used because it has the correct mathematic form (integration of equation 1 yields the bioavailable dose). However, there is not necessarily a physiologic basis for this model. In addition, local characteristics, such as the proximity of administered drug to local capillaries and pressure increases resulting from tissue expansion, may influence the rate of absorption. Although our previous studies of intramuscular rocuronium[9] did not show the need for a complicated absorption model, our previous success in modeling absorption with a single first-order rate constant may result from a limited quantity or quality of data.

The fraction of rapacuronium absorbed with intramuscular administration was estimated as only 56%. This

Fig. 5. Time course of plasma concentrations of the rapacuronium metabolite ORG9488 (normalized to a rapacuronium dose of 1 mg/kg) after intravenous or intramuscular administration. Circles indicate measured values; lines connect values for each patient. Values for some patients overlie those for others.
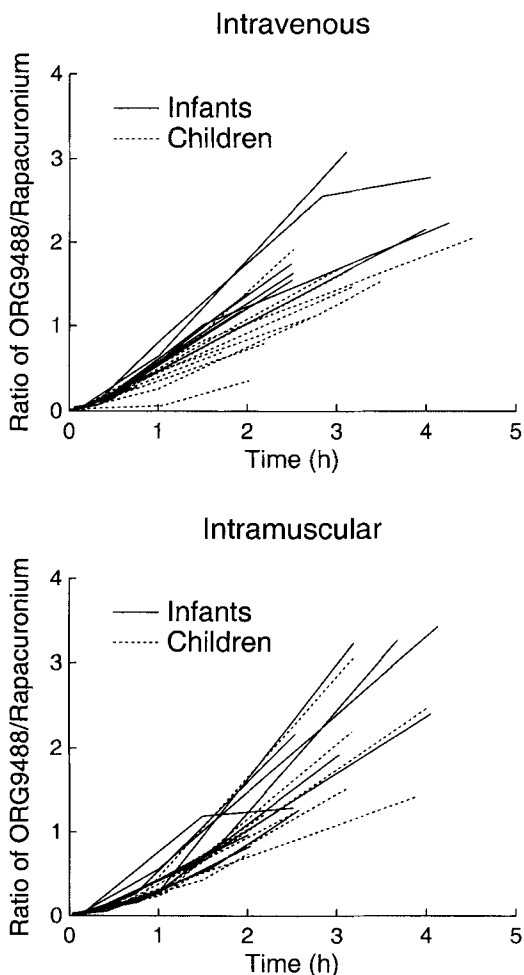
Intravenous

Intramuscular

Fig. 6. Ratio of the concentration of ORG9488 to the concentration of rapacuronium. Values for each subject are connected; line styles indicate the age group.

administration of rocuronium (13 min for both infants and children). This shorter time to peak plasma concentrations is consistent with the onset of intramuscular rapacuronium being faster than that of intramuscular rocuronium.[2,10]

Thirty to 60 min after intramuscular administration, the simulated percentage of an administered dose that remained to be absorbed from the intramuscular depot was larger with rapacuronium than in our previous study with rocuronium.[9] Despite a significant percentage of the bioavailable dose of rapacuronium remaining in the depot, and therefore slowly absorbed, we saw no evidence for residual weakness with intramuscular rapacuronium. It is possible that the differences in the simulated quantities of rapacuronium and rocuronium in the intramuscular depot are artifacts of the analysis, particularly the use of two absorption compartments for rapacuronium and only one for rocuronium. Alternatively, the larger weight-normalized volume of intramuscular rapacuronium compared with that of intramuscular rocuronium may affect the absorption profile. The absence of observations of the quantity of drug remaining in the depot limits our ability to quantify this amount.

Plasma concentrations of the rapacuronium metabolite are less than those of rapacuronium during the first hour after bolus administration of rapacuronium, but exceed the concentration of rapacuronium after approximately 2 h. Because the effects of a bolus dose of rapacuronium dissipate within 15–30 min, and those of an intramuscular dose within 30–60 min, the 2-h concentrations of both the parent compound and the metabolite are not clinically important, despite the metabolite having a potency (defined by the plasma concentration that pro-

value is smaller than (although possibly not statistically different than) the bioavailable fraction of 82% estimated for intramuscular administration of rocuronium.[9] It is likely that some of the administered dose is lost through the puncture site of the injection; however, this was not quantified. Because weight-normalized volumes of rapacuronium (0.14 ml/kg in infants and 0.24 ml/kg in children) were larger than those for rocuronium (0.1 ml/kg for infants and 0.18 ml/kg for children), it is possible that the quantity of cutaneous loss is larger with a larger administered volume.

Time to peak plasma concentration with intramuscular administration was 4.0 min in a typical infant and 5.0 min in a typical child. These times are shorter than the time to peak plasma concentration with intramuscular
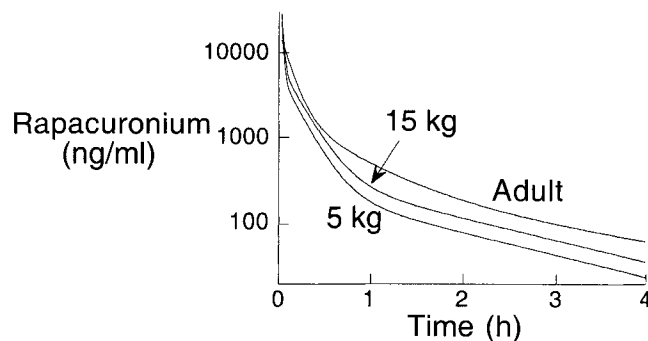

Fig. 7. Plasma concentrations of rapacuronium were simulated after a bolus intravenous dose of 1.5 mg/kg in an infant weighing 5 kg, a child weighing 15 kg, and an adult. Pharmacokinetic parameters for infants and children are those of the current study; values for adults are obtained from Szenohradszky *et al.*[5]

duces 50% twitch depression) of 50-100% more than that of rapacuronium.[11] However, with repeated administration, the concentration of the rapacuronium metabolite increases progressively, presumably leading to a cumulative effect, as has been shown for other nondepolarizing muscle relaxants that have a potent metabolite.[12,13]

Several aspects of our study design warrant comment. We obtained only four samples per patient. In addition, we estimated bioavailability without using the traditional crossover design in which each subject is observed on two or more occasions: once with intravenous administration and another with an alternate route of administration. Recently, Wright and Fisher[14] demonstrated that bioavailability could be estimated accurately using mixed-effects modeling (as in the current study) with as few as four samples per patient and a noncrossover design. Similarly, four samples were sufficient to estimate pharmacodynamic parameters accurately in simulations reported by Hashimoto and Sheiner.[15] In addition, we used an absorption model that differed from the usual first-order absorption model. Although we have no specific evidence to support this (or the simpler) model, our model with two absorption rate constants fits the data better than does the simpler model.

A second issue regards accuracy of certain of our pharmacokinetic parameters. Because we obtained venous, rather than arterial, samples to determine plasma concentrations of rapacuronium, and relatively few samples were obtained during the early distribution phase, it is possible that estimates for the rapid distribution half-life may be flawed. In addition, use of venous samples probably leads to an inaccurate estimate of V_1.

A third issue regards the estimate for V_{ss}: 99.1 ml/kg. This value is smaller than the value for extracellular fluid (approximately 20-25% of body weight),[16] the body compartment into which muscle relaxants are believed to be distributed. However, the estimate of the V_{ss} of rapacuronium is not markedly different than that for atracurium in children (129 ml/kg).[17]

Finally, we analyzed data for intramuscular and intravenous administration simultaneously. It is possible that the pharmacokinetic model that we use to explain intramuscular absorption is grossly incorrect. If so, the simultaneous analysis of intramuscular and intravenous plasma concentration data may "contaminate" the results that would be obtained if the intravenous data were analyzed separately.

In summary, Cl for rapacuronium is smaller in infants and children than in adults, but maturational changes in volume of distribution result in a more rapid decay in infants than in children and in children compared with adults. With intramuscular administration, 56% of the administered dose is bioavailable. Rapacuronium is absorbed at two different rates, with approximately 28% having an absorption half-life of 63 min and the remainder absorbed with a half-life of 14 min. Plasma concentrations of rapacuronium's potent metabolite are less than those of the parent compound during the initial 60 min after bolus rapacuronium administration.

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