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Bioavailability of Intramuscular Rocuronium in Infants and Children

Lynne M. Reynolds, M.D., Marie Lau, B.S.,† Ronald Brown, B.S.,† Andrew Luks, B.A., M.A.,‡ Manohar Sharma, Ph.D.,§ Dennis M. Fisher, M.D. ‖*

Background: **Intramuscular rocuronium, in doses of 1,000 μg/kg in infants and 1,800 μg/kg in children, produces complete twitch depression in 5–6 min. To determine the rate and extent of absorption of rocuronium after intramuscular administration, blood was sampled at various intervals after rocuronium administration by both intramuscular and intravenous routes to determine plasma concentrations (Cp) of rocuronium.**

Methods: **Twenty-nine pediatric patients ages 3 months to 5 yr were anesthetized with N_2O and halothane. The trachea was intubated, ventilation was controlled, and adductor pollicis twitch tension was measured. When anesthetic conditions were stable, rocuronium (1,000 μg/kg for infants and 1,800 μg/kg for children) was injected either intramuscularly (in the deltoid muscle) or intravenously. Four venous plasma samples were obtained from each child 2–240 min after rocuronium administration. A mixed-effects population pharmacokinetic analysis was applied to these values to determine bioavailability, absorption rate constant, and time to peak Cp with intramuscular administration.**

Results: **With intramuscular administration, rocuronium's bioavailability averaged 82.6% and its absorption rate constant was 0.105 min^{-1}. Simulation indicated that Cp peaked 13 min after rocuronium was given intramuscularly, and that 30 min after intramuscular administration, less than 4% of the administered dose remained to be absorbed from the intramuscular depot.**

Conclusions: **After rocuronium is administered into the deltoid muscle, plasma concentrations peak at 13 min, and approximately 80% of the administered drug is absorbed systemically. (Key words: Anesthesia: pediatric; pharmacokinetics. Injection: intramuscular; intravenous. Muscle relaxants: rocuronium bromide. Pharmacokinetics: bioavailability; mixed-effects modeling; NONMEM.)**

UNTIL recently, succinylcholine was the only muscle relaxant that produced effective neuromuscular blockade with intramuscular administration. We recently showed that deltoid (in contrast to quadriceps) injection of rocuronium (1,000 μg/kg in infants and 1,800 μg/kg in children) produces complete paralysis in 5–6 min in infants and children anesthetized with nitrous oxide and halothane, and also that these doses of intramuscular rocuronium permitted tracheal intubation at 2.5–3.0 min in a few lightly anesthetized patients.[1] No information exists regarding the rate and extent of absorption of rocuronium from the intramuscular depot. Accordingly, we measured plasma concentrations of rocuronium after intramuscular and intravenous administration to determine bioavailability.

Methods

The study was conducted using Organon Inc.'s Investigational New Drug Application, and the protocol was approved by our institutional review board. After obtaining informed consent from parents, we studied 29 pediatric patients who were classified as American Society of Anesthesiologists physical status 1 or 2 and undergoing elective surgery. Patients were divided by age into two groups: infants (ages 3–11 months; 8.4 ± 1.8 kg [means ± SD]; n = 13) and children (1–5 yr; 15.5 ± 4 kg; n = 16). We intended to study 24 patients (12 infants and 12 children) but added five patients because of problems with the assay, which are described later. No patient had a history of bleeding disorder, neuromuscular disease, or hepatic or renal insufficiency. Pa-

* Assistant Professor of Anesthesia.

† Staff Research Associate.

‡ Research Fellow. Present address: Medical Student, University of California, San Diego.

§ Research Chemist.

‖ Professor of Anesthesia and Pediatrics.

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Address correspondence to Dr. Fisher: Department of Anesthesia, University of California, San Francisco, California 94143-0648. Reprints will not be available. Address electronic mail to: ⟨fisher@zachary.ucsf.edu⟩

tients were excluded if they received anticonvulsants or aminoglycoside or polypeptide antibiotics during the period of the operation.

Eight patients received midazolam orally or nasally before operation; the remaining 21 were not premedicated. Anesthesia was induced with N_2O and halothane. After establishing intravenous access, the trachea was intubated and ventilation was controlled to maintain normocapnia. The inspired halothane concentration was adjusted to produce end-tidal halothane concentrations of 0.8–1.0% in children younger than 2.5 yr and of 0.7–0.8% in children older than 2.5 yr. Patients were randomized to receive rocuronium as either an intramuscular (n = 14) or intravenous (n = 15) injection. When end-tidal halothane concentrations and baseline twitch recordings were stable for >5 min, rocuronium (10 mg/ml) was injected *via* a 21-gauge needle 1–2 cm into a single deltoid muscle after negative aspiration for blood or as a rapid bolus into a peripheral intravenous catheter in the upper or lower extremity. The rocuronium dose was 1,000 μg/kg for infants and 1,800 μg/kg for children.

Five venous blood samples were obtained from each patient. The initial sample was obtained after induction of anesthesia but before rocuronium administration; the remaining four samples were obtained between 2 and 240 min after rocuronium administration. For each patient, target times for blood sampling differed, as determined by randomization (table 1). This "randomized block" approach provides maximal information for a population pharmacokinetic approach when "sparse sampling" is used.[2]

Supramaximal square-wave train-of-four stimuli were administered at 2 Hz every 12 s to the ulnar nerve *via* needle electrodes at the wrist. Evoked tension of the adductor pollicis was measured using a Grass FT-03 force transducer (Grass Instrument Company, Quincy, MA) while maintaining preload at 50–100 g. The force signal was amplified (DC bridge signal conditioner; Gould Electronics, Valley View, OH), digitized (NB-MIO-16, National Instruments, Austin, TX) on a Macintosh computer, and displayed (LabView; National Instruments). The ratio of the first component of the train-of-four (T1) to its control value was determined. Each train-of-four was recorded on a strip chart (TA240; Gould).

Respiratory gas was sampled at the y-connector to determine the partial pressure of carbon dioxide by infrared analysis (Capnomac Ultima; Datex, Helsinki, Finland). Arterial oxygen saturation was measured continuously (N200 Oximeter; Nellcor, Hayward, CA). Systolic blood pressure and heart rate (Dinamap; Critikon, Tampa, FL) were measured before and every minute for 5 min after rocuronium administration.

The injection site and the skin of the trunk and face were observed for erythema; signs consistent with histamine release were sought. At the end of surgery, 20 μg/kg atropine and 70 μg/kg neostigmine were administered to antagonize residual paralysis. In the postanesthetic recovery room, patients were examined for signs of weakness, such as inability to sustain leg lift[3]; the

Table 1. Age, Weight, and Target Sampling Regimen for Pediatric Patients Given Rocuronium Intravenously or Intramuscularly

Age Group	Route of Administration	Age (yr)	Weight (kg)	Target Sampling Times (min)
Infants	Intravenous	0.30	6.4	5, 12, 90, 190
		0.59	7.5	4, 18, 45, 190
		0.77	11.2	5,* 18,* 30, 120
		0.82†	9.8	5, 18, 30, 240
		0.84	9.3	2, 24, 90, 240
		0.97	8.6	4, 8, 45, 120
		0.97	10.5	3, 8, 60, 150
	Intramuscular	0.27	5.2	6, 20, 45, 190
		0.48	7.4	2, 10, 60, 120
		0.53	6.3	8, 10, 30, 120
		0.74	9.3	4, 25, 45, 240
		0.87	8.6	4, 25, 30, 240
		0.87	9.5	2, 15, 90, 150
Children	Intravenous	1.5	9.0	5, 18, 60, 120
		1.6	13.5	5,* 24,* 45, 240
		2.9	16.4	3,* 8,* 30,* 150
		3.1†	12.0	5, 24, 90, 150
		3.3	14.2	3, 24, 90, 240
		3.9†	16.7	3, 8, 30, 190
		4.0	16.8	4,* 18,* 60, 120
		4.7	16.7	2, 12, 45, 190
	Intramuscular	1.6	12.0	2, 20, 30, 190
		1.9	12.2	4, 25,* 30, 120
		1.9	12.9	6, 15, 60, 150
		3.3	11.4	2, 15,* 45, 240
		4.8	19.2	6, 25, 90, 150
		5.0†	19.5	8, 15, 90, 190
		5.3†	20.7	4, 25, 45, 120
		5.5	24.0	8, 10, 60, 240

* Concentration of rocuronium exceeded the upper limit of the standard curve for this assay. Consequently, this value was not used in the pharmacokinetic analysis.

† This patient was added to the analysis to supplement the plasma samples with concentrations exceeding the upper limit of the assay.

injection site was examined for signs of tissue inflammation or damage.

Blood samples were iced immediately, and, after centrifugation, plasma was buffered with 0.8 M NaH_2PO_4 and stored at −20°C until analysis using gas-liquid chromatography.[4] The lower limit of sensitivity of the assay is 10 ng/ml rocuronium, with a coefficient of variation <12% at that concentration.

Pharmacokinetic analyses were performed using the NONMEM statistical package.# As in all bioavailability analyses, we assumed that all clearances and volumes of distribution were identical with the two different routes of administration (intravenous and intramuscular); in turn, any difference between routes of administration in the plasma concentration (Cp) *versus* time profile results from differences in bioavailability, rate of absorption, and dosing regimen (if present). Analyses were performed using one-, two-, and three-compartment models. In addition, we tested models in which pharmacokinetic parameters were weight normalized and those in which they were not. Parameters of these pharmacokinetic models included volume of the central compartment (V_1), volume of the second compartment (V_2), volume of the third compartment (V_3), clearance (Cl, elimination clearance equal to $V_1 \cdot k_{10}$), rapid and slow distribution clearance (Cl_{rapid}, equal to $V_1 \cdot k_{12}$; and Cl_{slow}, equal to $V_1 \cdot k_{13}$), and volume of distribution at steady state (Vss, equal to $V_1 + V_2 + V_3$). With intramuscular administration, we assumed first-order absorption with rate constant k_a from the intramuscular depot into the central compartment; bioavailability of intramuscular administration was designated F. Absorption half-life ($t_{1/2}$absorption) was determined as $\ln(2)/k_a$. For the two-compartment model, distribution and elimination half-lives ($t_{1/2}\alpha$ and $t_{1/2}\beta$, respectively) were determined using standard equations.[5] For the three-compartment model, rapid and slow distribution half-lives ($t_{1/2}\pi$ and $t_{1/2}\alpha$, respectively) and elimination half-life ($t_{1/2}\beta$) were determined iteratively.**

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

$$\ln(Cl_i) = \ln(Cl) + \eta i, \quad (1)$$

where Cl_i is the estimate for Cl for the i^{th} 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 V_1 was modeled in a similar manner. Some models permitted interindividual variability for Cl_{rapid}, Cl_{slow}, V_2, V_3, k_a, and/or F, modeled in a similar manner; however, interindividual variability in Cl_{rapid} was assumed to be the same as for Cl_{slow} and that for V_2 equal to that for V_3.

After the "typical" values were determined, we used NONMEM's *post-hoc* step to determine values for the pharmacokinetic parameters for each patient. Plots of the pharmacokinetic parameters for each patient were plotted against each of the covariates age and weight and examined 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 containing 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 ($P < 0.01$ requires a decrease of 6.6 units for one additional parameter or 9.2 units for two additional parameters), and they either improved the pattern of residual differences between measured and predicted values for Cp or decreased the trend between a pharmacokinetic parameter and a covariate.

Because time to peak Cp with intramuscular administration is a function of all the pharmacokinetic parameters, its typical value and confidence limits cannot be determined using Student's *t* values. Instead, we determined the time to peak Cp using NONMEM's simulation mode. Using the "typical" values for the pharmacokinetic parameters and allowing for the interindividual variability determined in the pharmacokinetic analysis, we simulated the Cp *vs.* time course of 250 individuals given rocuronium intramuscularly. Time to peak Cp was determined for each of these 250 individuals and the 5th, 50th (median), and 95th percentile values were determined. We also used the typical values for F and k_a to simulate the typical time course of rocuronium remaining to be absorbed from the intramuscular depot. Finally, we used NONMEM's *post-hoc* step to estimate the plasma rocuronium concentration in each patient 60 min after rocuronium administration. Mean values for intramuscular and intravenous administration were compared using Student's *t* test for unpaired data. Peak depression of twitch tension (expressed as a percentage decrease from the control value) and times to 10% (la-

Beal SL, Sheiner LB: NONMEM's User's Guide. San Francisco, University of California San Francisco, 1992.

** Excel Solver. Microsoft, Redmond, Washington.

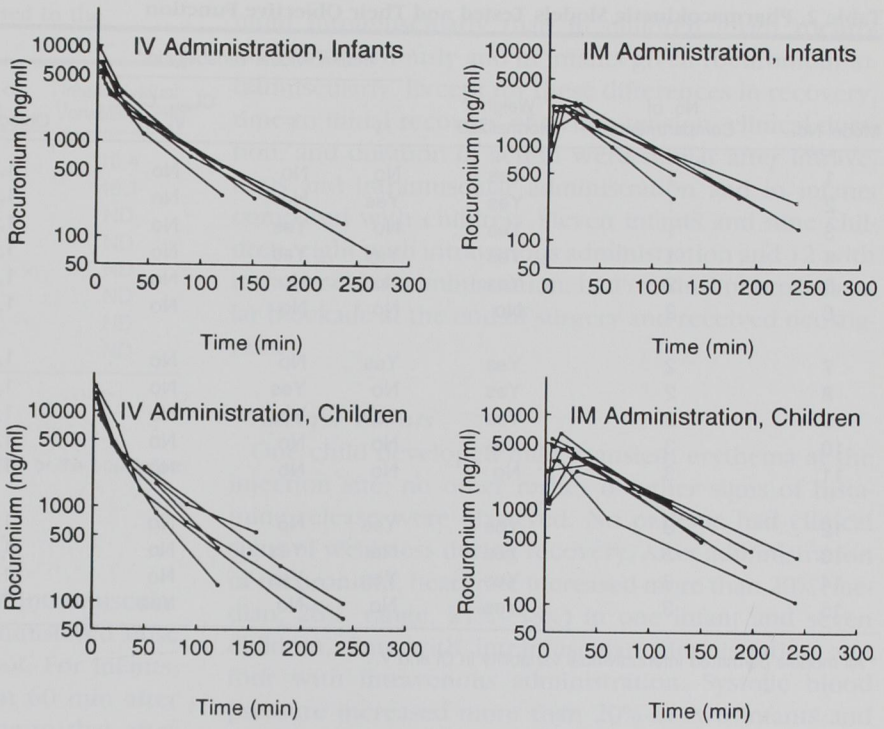

Fig. 1. Time course of rocuronium plasma concentrations after intravenous or intramuscular administration to infants (1,000 μg/kg) or children (1,800 μg/kg). Circles indicate measured values, and lines connect values for each patient. In one child (intravenous group), only a single plasma concentration value was used in the analysis (see table 1). Values for two infants, one with each route of administration, overlie those for others.

tency), 50%, and peak twitch depression (onset) and time to initial (>1%), 10%, 25% (clinical duration), and 90% recovery of twitch tension (duration of action) were determined. Values are reported as means ± SD. Comparisons between infants and children and between intravenous and intramuscular administration were performed using Student's *t* test for unpaired data; $P < 0.05$ (corrected, with the Bonferroni inequality, for multiple comparisons) was considered significant.

Results

Pharmacokinetic Analysis

In six patients (four with intravenous administration, two with intramuscular), values for one to three plasma samples exceeded the upper limit of the standard curve for the rocuronium assay (table 1). These 11 Cp values exceeding the upper limit of the standard curve for the assay were not used in the pharmacokinetic analysis; however, the standard curve was altered so that no subsequent samples exceeded the upper limit. To compensate for the missing Cp data, we studied an additional five patients, assigned to the same groups as the patients whose data were excluded. Four other patients had one supplemental plasma sample each: the infant (intramuscular group) at 2 min, and the children at 6 min and 27 min (intramuscular group) and at 180 min (intravenous group). In one child (intravenous group), the 190-min sample could not be obtained because venous access was lost. A total of 108 plasma samples (excluding blank samples) were used in the analysis, 57 of them from the intramuscular group (fig. 1).

A two-compartment pharmacokinetic model fit the Cp data better than a one-compartment model (as indicated by an improvement in the objective function of 68 points, and by visual assessment of the residual differences between predicted and observed concentrations; table 2). Adding a third compartment further improved the quality of the fit (fig. 2). For both the two- and three-compartment models, weight normalization of the pharmacokinetic parameters improved the quality of the fit (model 5 *vs.* model 6 and model 10 *vs.* model 11). Permitting interindividual variability in Cl_{rapid}, Cl_{slow}, V_2, V_3, k_a or F or both did not further improve the quality of the fit. Plots of values for Cl and V_1 for each patient (determined using NONMEM's *post-hoc* step) *versus* covariates age and weight did not reveal a sys-

Table 2. Pharmacokinetic Models Tested and Their Objective Function

Model No.	No. of Compartments	Weight Normalized	Interindividual Variability in:*			Objective Function	Statistical Significance
			k_a	F	Cl_{rapid}, Cl_{slow}, V_2, V_3		
1	1	Yes	No	No	No	1,504.162	—
2	1	Yes	Yes	No	No	1,504.162	Not different from model 1
3	1	Yes	No	Yes	No	1,504.162	Not different from model 1
4	1	Yes	Yes	Yes	No	1,504.162	Not different from model 1
5	2	Yes	No	No	No	1,436.430	$P < 0.01$ *versus* model 1
6	2	No	No	No	No	1,507.960	Objective function worse than model 5
7	2	Yes	Yes	No	No	1,436.389	Not different from model 5
8	2	Yes	No	Yes	No	1,436.203	Not different from model 5
9	2	Yes	Yes	Yes	No	1,436.127	Not different from model 5
10	3	Yes	No	No	No	1,423.997	$P < 0.01$ *versus* model 5
11	3	No	No	No	No	1,498.403	Objective function worse than model 10
12	3	Yes	Yes	No	No	1,423.997	Not different from model 10
13	3	Yes	No	Yes	No	1,423.783	Not different from model 10
14	3	Yes	Yes	Yes	No	1,423.783	Not different from model 10
15	3	Yes	No	No	Yes	1,423.746	Not different from model 10

* All models permitted interindividual variability in Cl and V_1.

tematic influence of the covariates on the pharmacokinetic parameters.

Thus the "optimal" pharmacokinetic model had three compartments and permitted interindividual variability in Cl and V_1. The typical value for Cl was 4.03 $ml \cdot kg^{-1} \cdot min^{-1}$ (table 3) and did not vary with age or weight (fig. 3); the typical value for V_1 was 105 ml/kg and did not vary with age or weight (fig. 4). With intramuscular administration, the typical value for F was 82.6% and did not vary with age or weight. The typical value of k_a was 0.105 min^{-1} (resulting in an absorption half-life of 6.6 min) and did not vary with age or weight. Volume of distribution at steady state was 325 ml/kg (table 4). Rapid and slow distribution half-lives were 2.5 and 27 min, respectively; elimination half-life was 127 min. These values did not differ between infants and children.

Simulations based on the pharmacokinetic parameters indicated that the median time after intramuscular administration when Cp peaked was 13 min; the 5th and 95th percentiles were 9 and 19.8 min, respectively. Fifteen minutes after intramuscular administration, the quantity of rocuronium simulated to remain in the intramuscular depot was 171 μg/kg in infants and 308 μg/kg in children (fig. 5); the value is greater in children than in infants because of the larger dose administered.

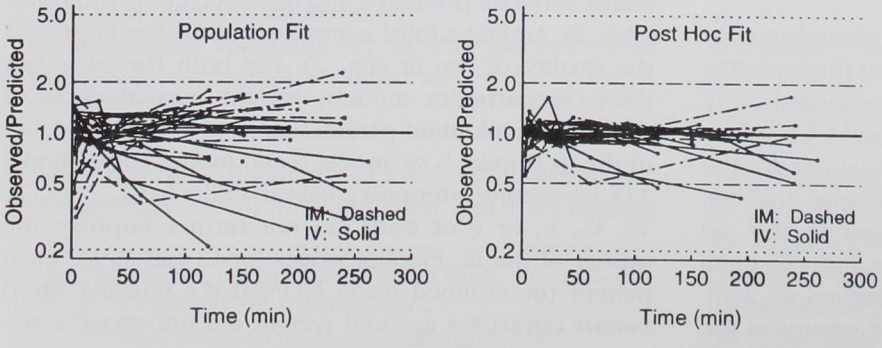

Fig. 2. Values for the observed concentrations of rocuronium divided by concentrations predicted in the pharmacokinetic analysis (expressed as a percentage) are plotted against time for each patient. The left panel presents values from the population analysis, and the right panel shows values from the *post-hoc* analysis. If the pharmacokinetic model fit the data perfectly, all lines would lie horizontally at 1.0.

Table 3. Parameters for Rocuronium Estimated in the Population Pharmacokinetic Analysis

	Typical Value	Standard Error of Estimate* (%)	Interindividual Variability† (%)
Cl	4.03 ml · kg^{-1} · min^{-1}	8.2	16.4
V_1	105 ml/kg	16.3	48.1
Cl_{rapid}	11.8 ml · kg^{-1} · min^{-1}	18.1	ND
V_2	85.7 ml/kg	16.9	ND
Cl_{slow}	0.975 ml · kg^{-1} · min^{-1}	22.5	ND
V_3	134 ml/kg	84.3	ND
F	82.6%	7.5	ND
k_a	0.105 min^{-1}	15.4	ND

ND = not determined in this model.

* Expressed as a percentage of the typical value.

† Computed as 100% · $\sqrt{\Omega^2}$ where Ω^2 = variance (η); 68% of the population lies within this range of the typical value.

Simulations indicated that 30 min after intramuscular administration, less than 4% of the administered dose remained to be absorbed from the depot. For infants, mean plasma rocuronium concentration 60 min after intramuscular administration was similar to that after intravenous administration (table 5); however, for children, mean rocuronium concentration was larger after intramuscular administration.

Twitch Tension

All patients developed complete twitch depression. With both intramuscular and intravenous administration, times to 10% and 90% twitch depression were similar in infants and children (table 6); however, time to twitch depression was more rapid with intravenous, compared with intramuscular, administration. Time to initial recovery was longer in children given rocuronium intramuscularly than in children given rocuronium intravenously and in infants given rocuronium intramuscularly. Except for these differences in recovery, time to initial recovery of twitch tension, clinical duration, and duration of action were similar after intravenous and intramuscular administration and in infants compared with children. Eleven infants and nine children, eight with intravenous administration and 12 with intramuscular administration, had residual neuromuscular blockade at the end of surgery and received neostigmine.

Adverse Events

One child developed mild, transient erythema at the injection site; no other rashes or other signs of histamine release were observed. No patients had clinical signs of weakness during recovery. After administration of rocuronium, heart rate increased more than 20% (median, 26%, range, 21%–58%) in one infant and seven children, four with intramuscular administration and four with intravenous administration. Systolic blood pressure increased more than 20% in two infants and three children (median, 26%; range, 22%–40%), one with intramuscular administration and four with intravenous administration. No patient had more than a 20% decrease in heart rate or systolic blood pressure.

Discussion

We recently reported that deltoid injection of rocuronium (1,000 μg/kg in infants and 1,800 μg/kg in children) produces complete paralysis and permits tracheal intubation at 2.5–3.0 min during light halothane anesthesia.[1] Time to 10% recovery of twitch tension with

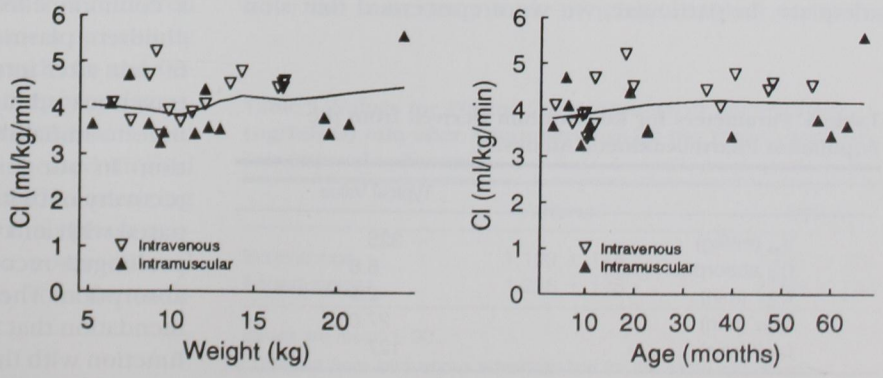

Fig. 3. Values for clearance (Cl) estimated in NONMEM's *post-hoc* pharmacokinetic analysis are plotted against weight and age. The line, determined using a smoother (lowess), suggests that there is no relation between Cl and either weight or age.

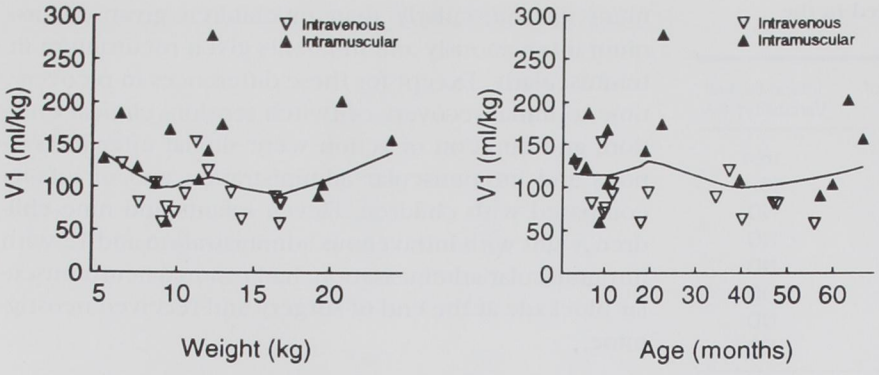

Fig. 4. Values for V_1 estimated in NONMEM's *post-hoc* pharmacokinetic analysis are plotted against weight and age. The line, determined using a smoother (lowess), suggests that there is no relation between V_1 and either weight or age.

these doses was 72 ± 13 min in infants and 86 ± 27 min in children. These values are larger than reported for clinical doses of rocuronium given intravenously in pediatric patients. For example, Woelfel et al.[6] reported that time to 25% recovery was 41.9 ± 13.6 min in infants and 26.7 ± 6.6 min in children[7] given 600 μg/kg rocuronium; time to 10% recovery was not reported in these studies. Two explanations are possible for rocuronium's prolonged duration of paralysis with intramuscular administration. First, doses of rocuronium administered in our study were larger than those typically given intravenously to infants and children (although the extent to which the large dose is bioavailable after intramuscular administration was unknown), and no data exist regarding duration of intravenous rocuronium doses >800 μg/kg in pediatric patients. Second, duration of paralysis might be increased if absorption from the intramuscular depot were delayed. Although all patients in the initial studies had adequate return of neuromuscular function (as demonstrated by recovery of train-of-four ratio and sustained leg lift[3]), the lengthy surgical procedures in some of these patients prevented us from assessing the earliest time at which recovery would be adequate. In particular, we were concerned that slow absorption from the intramuscular depot might sustain plasma concentrations of rocuronium and thereby place patients at risk for residual weakness. Thus the goal of the present study was to determine the extent and rate of absorption of rocuronium from the intramuscular depot.

Table 4. Parameters for Rocuronium Derived from the Population Pharmacokinetic Analysis

	Typical Value
V_{ss} (ml/kg)	325
$t_{1/2}$ absorption (min)	6.6
$t_{1/2\pi}$ (min)	2.5
$t_{1/2\alpha}$ (min)	27.0
$t_{1/2\beta}$ (min)	127

The present study shows that bioavailability of intramuscular rocuronium is 82.6% and the half-life for absorption from the depot is 6.6 min. Based on "typical" values for bioavailability and absorption rate determined in the pharmacokinetic analysis, the quantity of rocuronium remaining to be absorbed from the intramuscular depot 30 min after rocuronium administration is 35 μg/kg in infants and 64 μg/kg in children (the larger residual dose in children is a function of the larger dose required in those patients). This residual quantity of rocuronium is <11% of the usual clinical dose (600 μg/kg). For infants, plasma rocuronium concentrations are similar 60 min after intramuscular and intravenous administration (table 5), consistent with the fact that recovery indices are similar for the two routes of administration (table 6). Thus persistent absorption of rocuronium from the intramuscular depot is not likely to be a common clinical problem in infants. However, for children, plasma rocuronium concentrations are larger 60 min after intramuscular administration than with intravenous administration, consistent with the longer time to initial recovery with intramuscular administration. In our initial study,[1] the longest time to initial recovery of twitch tension was 121 min in a child (compared with an average value of 70 min in children); this prolonged recovery may have resulted from delayed absorption. These findings reinforce our earlier recommendation that time to 10% recovery of neuromuscular function with these large doses of intramuscular rocuro-

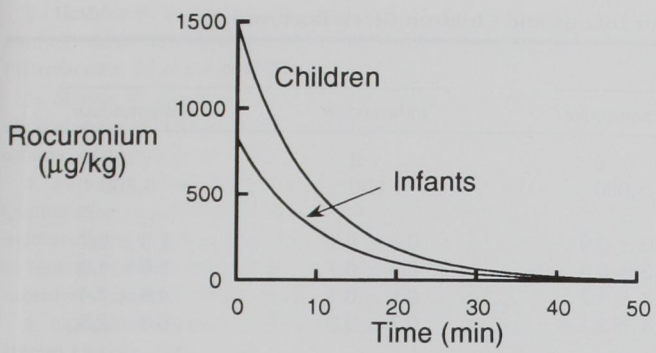

Fig. 5. Quantity of rocuronium remaining to be absorbed from the intramuscular depot is plotted against time. Values were determined by simulation based on the parameters determined in the pharmacokinetic analysis (table 3). Values are larger for children than for infants because of the larger dose administered (1,800 μg/kg *vs.* 1,000 μg/kg). Values at time zero are the product of the dose administered and the "typical" value of bioavailability.

nium is at least 1 h and that we do not recommend its use in procedures of briefer duration.

Pharmacokinetic simulations also indicate that the median time to peak Cp after intramuscular administration is 13 min but ranges from 9.0–19.8 min. This time to peak Cp explains why onset is delayed with intramuscular, compared with intravenous, administration, and suggests that the factor limiting onset of intramuscular rocuronium is the rate of absorption from the intramuscular depot.

The traditional approach to determine bioavailability is to study each patient twice, once with intravenous administration and once with the alternate route. In addition, most studies obtain many plasma samples from each patient. Our approach differs in that we used an unpaired design with sparse sampling; that is, we studied different patients in the intramuscular and intravenous groups and obtained a small number of samples from each patient. Obtaining paired data from children would require us either to study volunteers or to study those children who require repeated anesthesia and surgery. Neither of these choices seemed appropriate—studying pediatric volunteers raises ethical issues, and studying only those children requiring repeated surgical procedures might preselect children with underlying medical or surgical problems that alter their pharmacologic response. Thus we considered a nontraditional unpaired design. The second deviation from the traditional approach is our use of a sparse sampling regimen. Traditionally, pharmacokinetic studies required >10–15 samples per patient. In addition, data from each patient were analyzed separately. However, population pharmacokinetic tools such as nonlinear mixed-effects modeling and naive pooled data analysis permit reliable determination of pharmacokinetic characteristics when only a few samples are obtained from each person.

Recently, Wright and Fisher†† simulated whether a sparse sampling unpaired design yielded accurate estimates for bioavailability. Pharmacokinetic data for cisatracurium[8] were used to simulate data sets of ten persons in a paired study design (*i.e.*, each was given an intravenous and intramuscular dose of the muscle relaxant) or 20 persons in an unpaired study design (in which ten are given an intravenous dose and ten an intramuscular dose). Wright and Fisher permitted interindividual variability in the pharmacokinetic parameters and residual error in the "measured" values for plasma concentration. The magnitude of interindividual variability and residual error was permitted to vary, and the number of samples per patient was either 15 (rich sampling) or three to five (sparse sampling). Despite permitting large amounts of interindividual variability, increasing residual error, a small number of samples, and model misspecification (*e.g.*, using a one-compartment pharmacokinetic model to analyze data simulated from a two-compartment model), the value for bioavailability was estimated accurately. Thus it appears that our nontraditional approach yields reliable estimates for bioavailability.

In our pharmacokinetic analysis, permitting interinvidual variability for k_a and F did not improve the quality of the fit. Although there is likely to be interindividual variability in both the rate and extent of absorption from the intramuscular depot, figure 1 shows that the Cp *versus* time curves for intramuscular administration have the same magnitude of interindividual variability

Table 5. Values for Plasma Concentration of Rocuronium (ng/ml) 60 min after Administration by the Intravenous or Intramuscular Routes

	Infants	Children
Intravenous	1,169 ± 124	1,627 ± 266
Intramuscular	1,258 ± 128	2,204 ± 284*

Values are mean ± SD.

* Different from intravenous administration for the same age group.

†† Wright PMC, Fisher DM: Unpublished data.

Table 6. Onset and Spontaneous Recovery of Twitch Depression for Infants and Children Given Rocuronium

	Infants		Children	
	Intravenous	Intramuscular	Intravenous	Intramuscular
N	7	6	8	8
Dose (μg/kg)	1,000	1,000	1,800	1,800
Onset (min)				
10% twitch depression*	0.3 ± 0.1	2.0 ± 0.9	0.3 ± 0.1	2.6 ± 0.7
50% twitch depression*	0.4 ± 0.1	3.2 ± 0.9	0.4 ± 0.1	3.5 ± 1.0
90% twitch depression*	0.5 ± 0.2	4.7 ± 1.2	0.5 ± 0.1	4.9 ± 1.4
100% twitch depression*	0.7 ± 0.3	7.4 ± 2.1	0.7 ± 0.2	6.3 ± 2.3
Spontaneous recovery (min)				
Initial recovery	54 ± 10†	55 ± 8‡	56 ± 11‡	68 ± 6
10% recovery	68 ± 14†	66 ± 9	65 ± 13	81 ± 15
25% recovery	77 ± 17†	74 ± 12	72 ± 15	87 ± 20§
90% recovery	110 ± 17¶	98 ± 24**	106 ± 24§	128 ± 29†

Values are mean ± SD. Statistical comparisons were made between infants and children and between intramuscular and intravenous routes.

* Intramuscular differs from intravenous for both age groups ($P < 0.05$).

† N = 6.

‡ Differs from intramuscular administration in children ($P < 0.05$).

§ N = 7.

¶ N = 4.

** N = 5.

as those for intravenous administration. This suggests that interindividual variability in both k_a and F is small.

The present study provides pharmacokinetic parameters for rocuronium for pediatric patients ages 3 months to 5 yr; these values can be compared with values reported previously by Vuksanaj and Fisher[9] for children ages 4–11 yr. The value for Cl in the present study, 4.03 $ml \cdot kg^{-1} \cdot min^{-1}$, is less than the value for the "typical" (50% percentile) 20-kg, 6-yr-old child reported in the earlier study (7.10 $ml \cdot kg^{-1} \cdot min^{-1}$). The minimal age overlap in the two studies (only 3 of 20 patients in the previous study and 2 of 15 patients in the intravenous group in the present study were ages 4 or 5 yr) limits comparison of the two studies. However, findings from these two studies suggest that Cl varies minimally during the first few years of life, peaks at 4–6 yr, and then gradually decreases to the value of 2.89 $ml \cdot kg^{-1} \cdot min^{-1}$ reported in adults.[10]

The present study provides additional insight into the potential clinical role of intramuscular administration of rocuronium. First, our analysis suggested that variability in bioavailability and rate of absorption were minimal or absent. Therefore, variability in the time course of intramuscularly administered rocuronium does not result from variability in absorption characteristics. Second, the bioavailability of 82.6% with intramuscular administration partially explains the magnitude of the dose required by this route. Whether intramuscular administration of rocuronium is widely adopted into clinical practice to replace elective intramuscular administration of succinylcholine remains to be determined.

In summary, when rocuronium is administered intramuscularly in the deltoid muscle, the absorption half-life is approximately 6.6 min, plasma concentrations peak at 13 min, and bioavailability exceeds 80%. These findings are consistent with initial neuromuscular recovery from these doses of intramuscular rocuronium occurring at 1–1.5 h, and they reinforce our recommendations that rocuronium should not be administered intramuscularly if duration of surgery is expected to be less than 60–90 min.

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