Factors Affecting the Pharmacokinetic Characteristics of Rapacuronium

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Background: Rapacuronium is a new nondepolarizing muscle relaxant with rapid onset and offset. As part of a study to determine its neuromuscular effects, the authors sampled plasma sparsely to determine the influence of age, gender, and other covariates on its pharmacokinetic characteristics.

Methods: Of 181 patients receiving a single bolus dose of 0.5–2.5 mg/kg rapacuronium, 43 (aged 24–83 yr) had plasma sampled 3 or 4 times to determine plasma concentrations of rapacuronium and its metabolite, ORG9488. Pharmacokinetic analysis was performed using a population approach (mixed-effects modeling) to determine the influence of demographic characteristics and preoperative laboratory values on the pharmacokinetic parameters.

Results: Rapacuronium's weight-normalized plasma clearance was $7.03 \cdot (1 - 0.0507 \cdot (\text{HgB} - 13))$ ml $\cdot$ kg^{-1} $\cdot$ min^{-1}, where HgB is the patient's preoperative value for hemoglobin (g/100 ml); however, rapacuronium's blood clearance (11.4 ± 1.4 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}, mean $\pm$ SD) did not vary with hemoglobin. Rapacuronium's weight-normalized pharmacokinetic parameters were not influenced by age, gender, or other covariates examined. Plasma concentrations of ORG9488 were typically less than 14% those of rapacuronium during the initial 30 min after rapacuronium administration.

Conclusions: In this patient population, neither age nor gender influence elimination of rapacuronium. This finding contrasts to an age-related decrease in plasma clearance observed in a study of 10 healthy volunteers and in a pooled analysis of the pharmacokinetic data from 206 adults in multiple clinical studies. Even if ORG9488 has a potency similar to that of rapacuronium, its plasma concentrations after a single bolus dose of rapacuronium are sufficiently small to contribute minimally to neuromuscular blockade. (Key words: Modeling; muscle relaxants; ORG9487; population analysis.)

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RECENTLY, we reported that both the onset and recovery of rapacuronium bromide (ORG9487, Organon Inc., West Orange, NJ, and Organon Teknika, Boxtel, Netherlands) are rapid.[1] As part of that five-center study, plasma samples were collected from a subset of patients. These samples were used to determine the pharmacokinetic characteristics of rapacuronium; the potential effects of age, gender, and other demographic characteristics on the pharmacokinetics of rapacuronium; and the concentrations of ORG9488, the metabolite of rapacuronium. To study the largest number of patients while minimizing the number of samples obtained from each patient, a sparse sampling regimen (3 or 4 samples per patient) was used in conjunction with a population pharmacokinetic analysis. We now report the results of this pharmacokinetic analysis. The plasma samples in the present study were also used in a pooled analysis of samples from a number of clinical studies of rapacuronium. Results from the analysis of the samples for this five-center study were then compared with those from the larger pooled analysis.

Methods

After obtaining approval from each local institutional review board at the University of British Columbia,

Table 1. Demographic Data for 43 Subjects Given 0.5–2.5 mg/kg Rapacuronium

	Mean	Standard Deviation	Range
Age (yr)	56	17	24–83
Height (cm)	164	14	122–193
Weight (kg)	70	14	44–101
Gender (male/female)	15/28	—	—
Physical status			
1	11		
2	26		
3	6		

Northwestern University, the University of Miami, Stanford University, and Columbia University and informed consent from each subject, we studied 43 patients (table 1). These patients are a randomly selected subset of 181 patients in whom the neuromuscular effects and intubating conditions of rapacuronium were assessed.[1] Exclusion criteria included weight > 130% of ideal body weight (determined from height and gender), concomitant administration of other drugs known to influence the response to muscle relaxants, and the presence of significant neurologic, hepatic, or renal disease. Within each institution, the intent was to obtain pharmacokinetic data from five adults aged 18–65 yr and from four aged > 65 yr. Details of the clinical care and monitoring of patients were reported previously.[1] Briefly, patients were American Society of Anesthesiologists physical status I–III and were anesthetized with propofol (50–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$), fentanyl (50–300 μg), and nitrous oxide and were then maintained normothermic and normocarbic.

Rapacuronium was administered over 5 s into a rapidly flowing intravenous line. Rapacuronium doses were 0.5 (N = 8), 1.0 (N = 9), 1.5 (N = 9), 2.0 (N = 9), and 2.5 (N = 8) mg/kg. Venous blood samples were obtained from each patient using a block design, *i.e.*, the first sample was obtained 2–5 min after drug administration, the second, 5–15 min after drug administration, the third, 45–240 min after drug administration, and if possible, a fourth sample, 240–360 min after drug administration. A "blank" sample was obtained before administration of rapacuronium. Investigators were not assigned specific times within the four time blocks to obtain samples. 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 an HPLC-MS technique. The assay is linear for concentrations > 2 ng/ml for both rapacuronium and ORG9488 and has a coefficient of variation of < 11% for rapacuronium and < 20% for ORG9488. The amount of ORG9488 in each vial was < 1% of the quantity of rapacuronium (personal communication, August 1998, Viquar Pervaaz, Organon Inc.).

The pharmacokinetic characteristics of rapacuronium were determined using a population approach, *i.e.*, values for all subjects were analyzed simultaneously to determine "typical" values for the pharmacokinetic parameters for the population and the influence of covariates (*e.g.*, demographic characteristics, preoperative laboratory values, weight-normalized dose, and site of the study) on these parameters. We also determined residual interindividual variability in these pharmacokinetic parameters not explained by the covariates, and standard errors for each parameter.

Two-compartment models had the parameters clearance (Cl), distributional clearance ($Cl_{distribution}$), and volumes of the central and peripheral compartments (V_1 and V_2, respectively). Three-compartment models had, in addition, a slow distributional clearance (Cl_{slow}) and a volume of the deep peripheral compartment (V_3); in addition, $Cl_{distribution}$ was renamed Cl_{rapid}. Interindividual variability was permitted for each of the pharmacokinetic parameters and was assumed to be log-normally distributed. For example, the estimate for clearance for the *ith* individual (Cl_i) was modeled as:

$$Cl_i = Cl \cdot \exp(eta_i) \qquad (1)$$

where Cl is the typical value for the population, and eta_i is a random variable with mean 0.0 and variance $omega^2$. In some models, interindividual variability was assumed to be the same for Cl_{rapid} as for Cl_{slow} and for V_2 as for V_3. Residual error between predicted and measured concentrations was initially assumed to have two components (*epsilons*): one proportional to the predicted plasma concentrations ("constant coefficient of variation") and the other additive. This model was chosen because most assays have a constant coefficient of variation when concentrations are significantly larger than the lower limit of quantification of the assay; however, as concentrations approach this limit, error of the assay becomes a larger percentage of the predicted concentration. Half-lives were determined using standard formulas.

All analyses were performed using a model-building approach. Details of a similar model-building approach

for rapacuronium in 20 young adults with normal or absent renal function in whom extensive sampling was performed were reported previously.[2] Briefly, we first determined whether a two- or three-compartment model was appropriate for rapacuronium, whether pharmacokinetic parameters should be weight-normalized, and whether the error model should contain both the constant coefficient of variation and additive components. For each analysis, both population parameters and *post hoc* (individual Bayesian) estimates were obtained. Then we examined the role of covariates, including the demographic characteristics age, weight, height, and gender; preoperative values for hematocrit, hemoglobin, serum concentrations of creatinine, bilirubin, AST, and ALT; and creatinine clearance, weight-normalized dose, and the institution at which the study was conducted. Creatinine clearance was determined for each subject using the Cockroft/Gault nomogram[3] based on weight, gender, age, and preoperative serum creatinine values. The potential role of covariates was determined by plotting the *post hoc* estimates of the parameters against the covariates; a smoother (lowess, a local nonlinear regression) was used to evaluate trends visually. If a covariate appeared to influence the parameter, its role in the model was tested (see Results section for an example); it was incorporated into the pharmacokinetic model if it improved the quality of the fit of the model to the data as judged by a decrease in NONMEM's objective function (for $P < 0.01$, 6.6 units for one additional parameter, 9.2 units for two).

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 on these ratios was assessed visually.

Results

Plasma Concentrations of Rapacuronium

Rapacuronium and ORG9488 were detected in all samples obtained after administration of rapacuronium. Only 13 subjects had a sample obtained after 240 min (fig. 1). Values for three plasma rapacuronium samples are not included in the analysis. These samples were obtained before administration of rapacuronium, and the measured plasma concentrations ranged from 4.7 to 12.9 ng/ml. These concentrations are close to the limit of quantification of the assay (and markedly less than those concentrations observed after administration of rapacuronium) and were presumed to be artifacts. Plasma con-
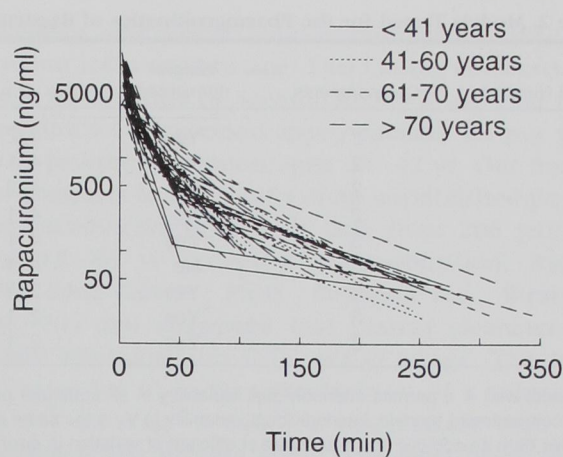

Fig. 1. Plasma concentrations of rapacuronium from 43 subjects given 0.5–2.5 mg/kg are normalized to a rapacuronium dose of 1 mg/kg. Values for each subject are connected; line styles indicate the age group.

centrations of rapacuronium decreased rapidly after its administration; there was no apparent relationship between plasma concentrations and age (fig. 1).

Model Building for Rapacuronium

An error model with only a constant coefficient of variation yielded a fit as good as one with both a constant coefficient of variation and an additive component (table 2, model #2 *vs.* model #1 and model #4 *vs.* model #3). With two-compartment models (model #1 *vs.* model #3 and model #2 *vs.* model #4) and three-compartment models (model #5 *vs.* model #6), weight-normalization improved the quality of the fit of the model to the plasma concentration data. Three-compartment models yielded better fits than corresponding two-compartment models (model #5 *vs.* model #2 and model #6 *vs.* model #4). Thus, all subsequent analyses used a three-compartment model in which pharmacokinetic parameters were weight-normalized and had a constant coefficient of variation error model.

With model #5, interindividual variability in both V_1 and Cl_{rapid}/Cl_{slow} was small; for example, interindividual variability in V_1 was $< 0.01\%$. Therefore, model #7 differed from model #5 by not permitting interindividual variability in either V_1 or C_{rapid}/Cl_{slow}. The objective function and quality of fit of this model was identical to that for model #5, suggesting that interindividual variability was not needed for V_1 or Cl_{rapid}/Cl_{slow}. Plots of the *post hoc* values of Cl *versus* covariates suggested that Cl had both an additive and weight-normalized component (figure not shown). However, model #8, in which Cl had both an additive and weight-normalized compo-

Table 2. Models Tested for the Pharmacokinetics of Rapacuronium

Model Number	Compartments	Weight-normalized	No. of η, ϵ*	Issue Tested	Objective Function
1	2	Yes	4, 2	Weight normalization, number of compartments, ϵ	1906.747
2	2	Yes	4, 1	Weight normalization, number of compartments, ϵ	1906.747
3	2	No	4, 2	Weight normalization, number of compartments, ϵ	1938.705
4	2	No	4, 1	Weight normalization, number of compartments, ϵ	1938.711
5	3	Yes	4, 1	Weight normalization, number of compartments, ϵ	1895.369
6	3	No	4, 1	Weight normalization, number of compartments, ϵ	1925.077
7	3	Yes	2, 1	Number of η	1895.369
8	3	Yes	2, 1	Model 7 plus Cl varies with weight	1894.176
9	3	Yes	2, 1	Model 7 plus Cl varies with hematocrit	1885.788

* A model with 4 η permits interindividual variability in all structural parameters. A model with 2 η permits interindividual variability in Cl and V_2/V_3. With three-compartment models, interindividual variability in V_3 is the same as for V_2; interindividual variability in Cl_{slow} is the same as for Cl_{rapid}. A model with 2 ϵ includes both an additive and a constant coefficient of variation in error between observed and predicted values. A model with 1 ϵ includes only the constant coefficient of variation in error between observed and predicted values.

nent, failed to fit better than model #7. Covariate plots for model #7 also suggested a relationship between Cl and each of preoperative hemoglobin (fig. 2) and hematocrit. Because hemoglobin and hematocrit correlate, only one of these could be incorporated into the model. Hemoglobin was selected because preoperative hematocrit was unavailable for one subject, whereas preoperative hemoglobin was available for all subjects.

The influence of hemoglobin on clearance was modeled as:

$$\text{TVCL} = \text{THETA}(1)$$
$$\cdot (1 + \text{HGFACTOR} \cdot [\text{HgB} - 13]) \quad (2)$$

where TVCL is the "typical value" of clearance for a subject with a given hemoglobin; THETA(1) is the mean value for clearance for all subjects and is estimated in the analysis; HGFACTOR is determined in the analysis; HgB is each subject's hemoglobin measured before surgery; and 13 is approximately the average value for hemoglobin (in mg/100 ml) in these patients.‡‡ The objective function for this model improved compared with model #7 ($P < 0.002$). Although Cl decreased with increasing hemoglobin, Cl(blood) (determined for the 42 subjects in whom preoperative values of hematocrit were available as Cl[plasma]/[1 - hematocrit], assuming that rapacuronium's distribution in blood is limited to plasma) was $11.4 \pm 1.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (mean $\pm$ SD) and did not vary with hemoglobin (fig. 3).

With model #9, a plot of *post hoc* values for Cl divided by the typical value of Cl against creatinine clearance

‡‡ The influence of hemoglobin on Cl is modeled in this way so that the value for THETA(1) applies to the "typical" patient, *i.e.*, the patient with a preoperative hemoglobin value of 13 g/dl.

(fig. 4) and against serum creatinine (not shown) suggested that subjects with creatinine clearance < 90 ml/min or serum creatinine > 1.0 mg/100 ml have a decreased Cl of rapacuronium; however, there are too few subjects in this study with creatinine clearance < 90 ml/min or serum creatinine > 1.0 mg/100 ml to demonstrate statistical significance. There was no apparent relationship between any of the remaining covariates measured and the pharmacokinetic parameters.

Thus, in the optimal three-compartment model (#9) for the pharmacokinetic parameters of rapacuronium, all parameters are weight-normalized, and Cl varies with hemoglobin (table 3, fig. 5). Cl decreased from 8.10 ml · kg^{-1} · min^{-1} with a hemoglobin of 10 g/100 ml to a value of 5.96 ml · kg^{-1} · min^{-1} with a hemoglobin of 16 g/100
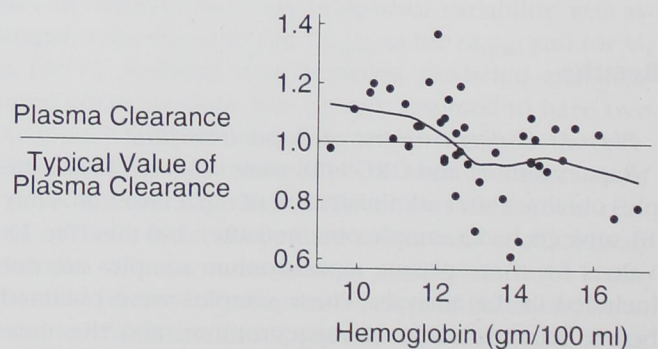

Fig. 2. Values for the *post hoc* estimates of Cl divided by the typical value of Cl of rapacuronium determined from model #7 using NONMEM's *post hoc* step are plotted against preoperative values for plasma hemoglobin. The line is a smoother (lowess, a local regression) that suggests that Cl decreases with increasing hemoglobin.
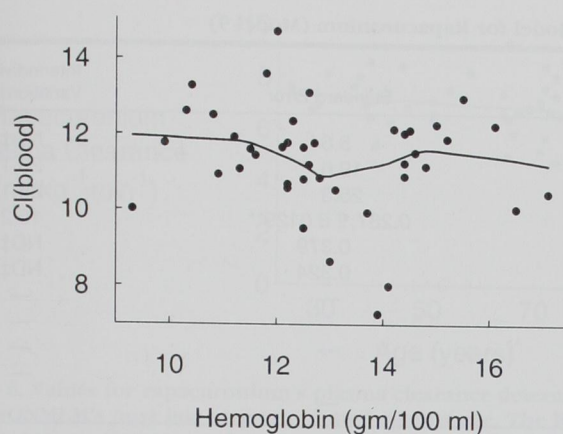
Fig. 3. Values for blood Cl of rapacuronium determined from model #9 using NONMEM's *post hoc* step are plotted against preoperative values for hemoglobin. Blood Cl was calculated from plasma Cl assuming that rapacuronium's distribution in blood is limited to plasma. The line is a smoother (lowess, a local regression) that suggests that there is no relationship between blood Cl of rapacuronium and hemoglobin.

ml. Half-lives also varied with hemoglobin, although minimally. Age (fig. 6), gender, weight, and other covariates did not influence the pharmacokinetic parameters, although there is a suggestion that Cl decreases with serum creatinine > 1.0 mg/100 ml or creatinine clearance < 90 ml/min.

Plasma Concentrations of ORG9488

Plasma concentrations of ORG9488 peaked early after administration of rapacuronium (fig. 7), then decreased slowly. During the 30 min after administration of rapacuronium, plasma concentrations of ORG9488 were < 14% of corresponding rapacuronium concentrations in 79 of 82 measurements (fig. 8). For the remaining three measurements, the ratio of ORG9488 to rapacuronium was 21–27%. In samples obtained > 30 min after rapacuronium administration, the ratio of concentrations of ORG9488 to those of rapacuronium increased progressively. There were no apparent age-related differences in either the plasma concentrations of ORG9488 or the ratio of these concentrations to rapacuronium.

Discussion

In this group of patients aged from 24 to 83 yr, we observed that rapacuronium's pharmacokinetic char-

§§ This is an unlikely explanation in that < 1% of the area under the plasma concentration *versus* time in Szenohradszky *et al.*'s study occurred after 4 h. In addition, a longer sampling period should result in a smaller value for Cl, in contrast to the larger value observed by Szenohradszky *et al.*

acteristics and plasma concentrations of ORG9488 were not influenced by age. This finding contrasts to a recent observation by Szenohradszky *et al.*[2] that rapacuronium's Cl decreased approximately 1% per yr of age in healthy volunteers aged 20–42 yr. Our finding also contrasts to the results of an unpublished pooled pharmacokinetic analysis of data from 206 patients aged 18–83 yr (personal communication, August 1998, Edna Gilvary, Ph.D., Organon Inc., West Orange, NJ) that suggested that plasma clearance decreases approximately 0.7% per yr of age. The "typical" value for Cl in Szenohradszky *et al.*'s volunteers was $9.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, a value larger than that reported in the present study. The most likely explanation for these differences between the two studies is the minimal overlap in age between studies— only one of Szenohradszky *et al.*'s volunteers was aged more than 33 yr, and only 9% of patients in the present study were aged less than 33 yr. However, Szenohradszky *et al.*'s estimate of Cl for a "typical" 45-yr-old subject is $8.1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, a value not markedly different from the value for Cl reported in the present study.

Several other differences between the two studies may also contribute to the different findings regarding the effect of age on Cl. First, Szenohradszky *et al.* studied healthy volunteers not undergoing surgery, whereas we studied patients undergoing surgery. Second, Szenohradszky *et al.* sampled plasma for 8 h and may have detected age-related changes in the slope of the plasma concentration *versus* time curve that occurred after sampling was completed in the present study.§§ Finally, Szeno-
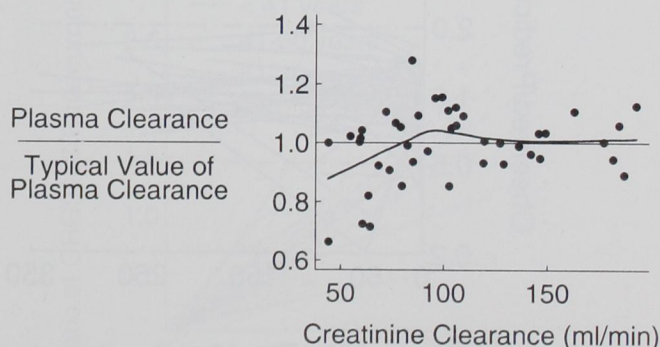

Fig. 4. Values for the *post hoc* estimates of Cl divided by the typical value of Cl of rapacuronium determined from model #9 using NONMEM's *post hoc* step are plotted against preoperative values of creatinine clearance (ml/min). The line is a smoother (lowess, a local regression) that suggests that creatinine clearance < 90 ml/min is associated with decreased plasma Cl of rapacuronium.

Table 3. Parameter Estimates* of Three-compartment Pharmacokinetic Model for Rapacuronium (Model 9)

	Typical Value	Standard Error	Interindividual Variation† (%)
V_1 (ml/kg)	81.6	5.64	ND‡
V_2 (ml/kg)	65.6	19.6	28.1
V_3 (ml/kg)	169	25.3	28.1
Cl (ml·kg^{-1} · min^{-1})	$7.03 \cdot [1 - 0.0507 \cdot (HgB§ - 13)]$	0.287,¶ 0.0129**	16.2
Cl$_{rapid}$ (ml·kg^{-1} · min^{-1})	2.67	0.379	ND‡
Cl$_{slow}$ (ml·kg^{-1} · min^{-1})	1.37	0.324	ND‡
Vss (ml/kg)	316	—	—
$t_{1/2}\pi$ (min)	4.3–5.0	—	—
$t_{1/2}\alpha$ (min)	23.1–25.4	—	—
$t_{1/2}\beta$ (min)	102–105	—	—

* Standard error and interindividual variation are reported only for those parameters estimated by NONMEM.

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

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

§ HgB is preoperative hemoglobin in g/100 ml.

‖ Applies to value of 7.03.

** Applies to value of 0.0507.

hradszky *et al.* sampled intensively from all subjects (18 plasma samples from each of 10 subjects) in contrast to the small number of samples from each of the 43 patients in the present study. Regardless, the lack of age-related changes in Cl in the present study is reflected in minimal age-related changes in the recovery profile of rapacuronium.[1] The lack of age-related changes in Cl of rapacuronium differs from the finding for vecuronium (for which there is a 30%[4] to 50%[5] decrease in Cl in

elderly, compared with young adult, patients) and for rocuronium[6] (for which there is a 27% decrease in Cl in elderly, compared with young adult, patients). Combining the results of three analyses suggests that most of the age-related decrease in rapacuronium's Cl occurs in young adults.

One unexpected finding of the present study was that rapacuronium's plasma clearance varied with hematocrit or hemoglobin. Because rapacuronium does not pene-
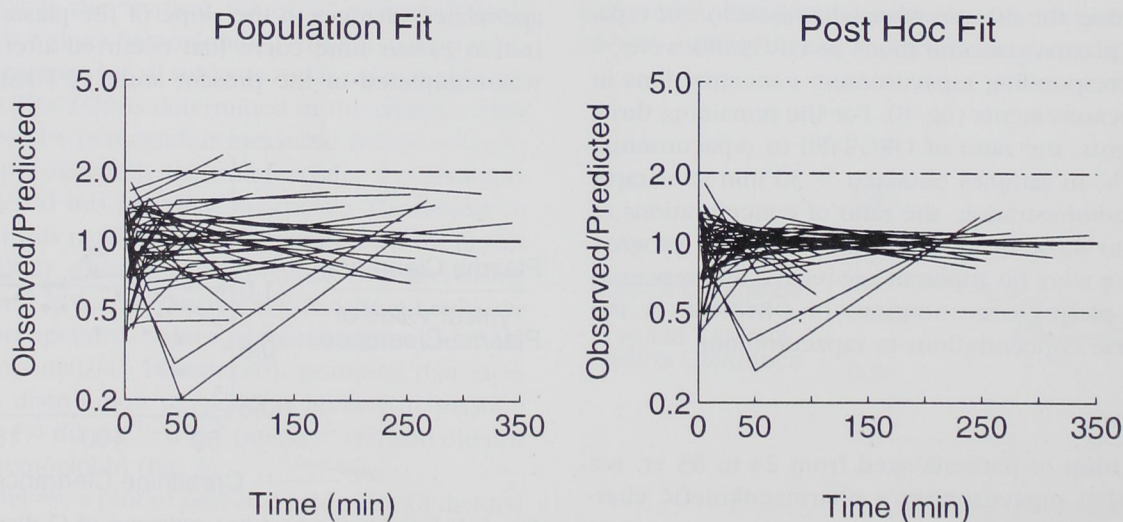
Population Fit

Post Hoc Fit

Fig. 5. Quality of fit of the pharmacokinetic model to the values for plasma concentration of rapacuronium. The *x* axis is time (min) after administration of rapacuronium. The *y* axis is the ratio of the measured concentration of rapacuronium to the value predicted by the population pharmacokinetic model (*left panel*) or the *post hoc* fit (*right panel*). Each line connects values from a single subject. If the model fit the data perfectly, all lines would lie horizontally at 1.0. The improved quality of fit of the *post hoc* values compared with those from the population model is expected because the *post hoc* model permits interindividual variability, whereas the population model does not.
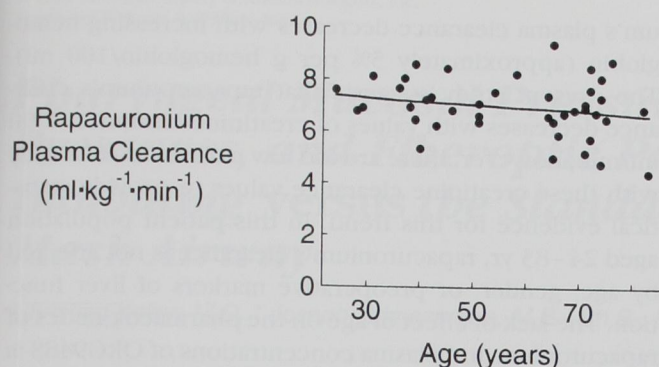
Fig. 6. Values for rapacuronium's plasma clearance determined in NONMEM's *post hoc* step are plotted against age. The line is a smoother (lowess, a local regression) that suggests that weight-normalized clearance does not change with age.

trate erythrocyte membranes,|||| we determined that rapacuronium's blood clearance did not vary with hematocrit. The effect of hematocrit or hemoglobin on rapacuronium's Cl may result from anemia increasing cardiac output and, in turn, blood flow to the liver and kidney. However, in the absence of measurements of organ blood flow in our patients, we can only speculate as to an explanation.

Our modeling suggested that rapacuronium's pharmacokinetics were described better by weight-normalized than non–weight-normalized parameters. This finding contrasts with the observation that weight-normalization worsens the quality of the pharmacokinetic fit for some other muscle relaxants.[7] Most likely our results can be explained by the small range of weights and lack of obese subjects in the present study. Therefore, results of the present study should not extrapolated for use with obese subjects.

Clearance of rapacuronium is larger than that of other nondepolarizing muscle relaxants, with the exception of mivacurium. This larger clearance presumably contributes, although minimally, to rapacuronium's rapid onset of action.[8] However, another feature, the rapid equilibration between plasma concentration and effect[8] (presumably a function of rapacuronium's low potency[9]), probably explains rapacuronium's rapid onset. The larger clearance of rapacuronium also presumably contributes to its brief duration of action. Distributional characteristics of rapacuronium are similar to those of other nondepolarizing muscle relaxants—its volume of

|||| When a bolus dose of ^{14}C-labeled rapacuronium was given to volunteers, radioactivity associated with erythrocytes appeared to be negligible for up to 6 h (unpublished data, September 1998, Bio-Pharma S.A., Belgium).
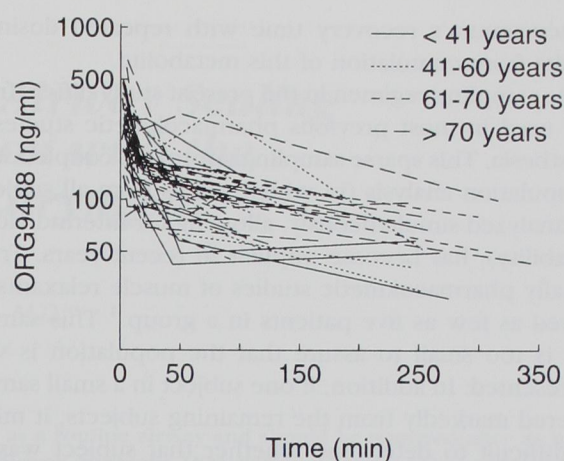
Fig. 7. Plasma concentrations of ORG9488 from 43 subjects given 0.5–2.5 mg/kg rapacuronium are normalized to a rapacuronium dose of 1 mg/kg. Values for each subject are connected; line styles indicate the age group.

distribution is small, presumably because its distribution is limited to the extracellular fluid space.

Plasma concentrations of rapacuronium's metabolite, ORG9488, were markedly less than those of rapacuronium during the 30 min after rapacuronium's administration. However, concentrations of ORG9488 decreased less rapidly than those of rapacuronium (fig. 7), suggesting that ORG4988 would cumulate with repeated administration of rapacuronium. Despite preliminary data suggesting that ORG9488 is more potent than rapacuronium,[10] it is likely that concentrations of ORG9488 observed in the present study have minimal neuromuscular effect. However, it is possible that the increase in
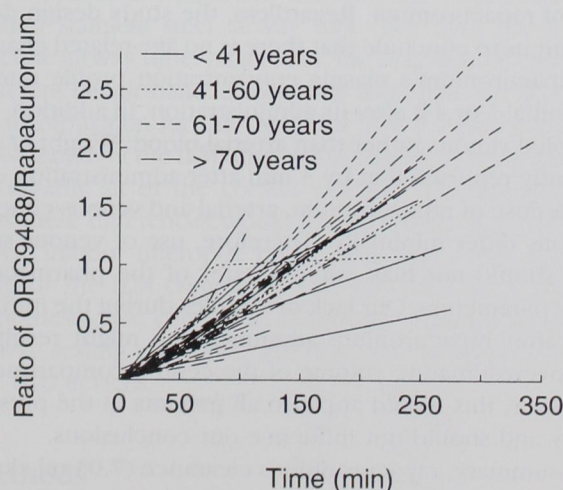

Fig. 8. Ratio of the concentration of ORG9488 to the concentration of rapacuronium is displayed. Values for each subject are connected; line styles indicate the age group.

rapacuronium's recovery time with repeated dosing[11] results from cumulation of this metabolite.

The sampling regimen in the present study differs from that used in most previous pharmacokinetic studies in anesthesia. This sparse sampling approach, coupled with a population analysis (in which values from all subjects are analyzed simultaneously, allowing for interindividual variability), has become popular in recent years. Traditionally pharmacokinetic studies of muscle relaxants involved as few as five patients in a group.[4] This sample size is too small to assure that the population is well represented. In addition, if one subject in a small sample differed markedly from the remaining subjects, it might be difficult to determine whether that subject was an outlier or represented the expected variability. For example, plasma clearance of aifentanil varies more than 10-fold in the population, presumably a result of the similarly large variability in activity of the enzyme responsible for its elimination, cytochrome P450 3A4.[12] By sampling from a larger number of subjects (43 in the present study), we are likely to obtain a better cross-section of the population. However, to minimize cost of the experiment, a smaller number of samples are obtained from each subject, necessitating the use of population pharmacokinetic techniques (mixed-effects modeling).

One limitation of the present study is that relatively few samples were obtained > 4 h after rapacuronium was given. This might limit our ability to estimate the elimination half-life—and consequently, plasma clearance—accurately and thereby limit our ability to detect age-related changes in the pharmacokinetic characteristics of rapacuronium. Regardless, the study design does permit us to conclude that there is no age-related change in rapacuronium's plasma concentration profile during the initial 3 or 4 h after its administration. In addition, we sampled venous rather than arterial blood. Wright *et al.*[8] recently reported that by 3 min after administration of a bolus dose of rapacuronium, arterial and venous concentrations differ minimally. Therefore, use of venous samples should not bias our estimates of the pharmacokinetic parameters. Our lack of samples during the initial 2 min after rapacuronium administration might result in our overestimating volume of the central compartment; however, this would apply to all patients in the present study and should not influence our conclusions.

In summary, rapacuronium's clearance (7.03 ml · kg^{-1} · min^{-1} for a patient with a hemoglobin of 13 g/100 ml) is larger than that of other nondepolarizing muscle relaxants, with the exception of mivacurium. Rapacuroni-

um's plasma clearance decreases with increasing hemoglobin (approximately 5% per g hemoglobin/100 ml). The present study suggests that rapacuronium's clearance decreases with values of creatinine clearance < 90 ml/min; however, there are too few patients in this study with these creatinine clearance values to provide statistical evidence for this trend. In this patient population aged 24–83 yr, rapacuronium's clearance is not affected by age, gender, or preoperative markers of liver function. The lack of effect of age on the pharmacokinetics of rapacuronium and plasma concentrations of ORG9488 is consistent with the similar duration of neuromuscular effect in young and elderly adults.

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