Anesthesiology 2001; 94:47–55

Recirculatory Pharmacokinetics and Pharmacodynamics of Rocuronium in Patients

The Influence of Cardiac Output

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Background: **Recirculatory models are capable of accurately describing first-pass pharmacokinetics and the influence of cardiac output (CO), which is important for drugs with a fast onset of effect. The influence of CO on pharmacokinetic and pharmacodynamic parameters of rocuronium in patients was evaluated using a recirculatory pharmacokinetic model.**

Methods: **Fifteen patients were included to study rocuronium pharmacokinetics and pharmacodynamics. Bolus doses of rocuronium (0.35 mg/kg) and indocyanine green (25 mg) were injected simultaneously *via* a peripheral intravenous catheter. Blood samples were taken for 240 min from the radial artery. The force of contraction of the adductor pollicis after a train-of-four at 2 Hz every 12 s was measured. Arterial concentration–time curves of rocuronium and indocyanine green were analyzed using a recirculatory model. Pharmacodynamics were described using a sigmoid maximum effect (E_{max}) model.**

Results: **The CO of the patients varied from 2.43 to 5.59 l/min. Total distribution volume of rocuronium was 17.3 ± 4.8 l (mean ± SD). The CO showed a correlation with the fast tissue clearance (Cl_{T_f}; $r^2 = 0.51$), with the slow tissue clearance (Cl_{T_s}; $r^2 = 0.31$) and with the mean transit times of rocuronium except for the mean transit time of the slow tissue compartment. The blood–effect site equilibration constant (k_{e0}) was strongly correlated with CO ($r^2 = 0.70$).**

Conclusions: **Cardiac output influences the pharmacokinetics, including k_{e0}, for rocuronium in patients. For drugs with a fast onset of effect, a recirculatory model, which includes CO, can give a good description of the relation between concentration and effect, in contrast to a conventional compartmental pharmacokinetic model.**

THE effect of anesthetic drugs is generally assumed to depend on the drug concentration–time profile at the site of action. After an intravenous bolus injection or rapid intravenous infusion, the initial drug effects are likely to depend highly on blood flow, which is the major determinant of the initial distribution.[1] With muscle relaxants, this could result in differences in the onset of action. In the setting of a rapid sequence induction, this could result in differences in the time to reach reliable intubation conditions.

Because it is impossible to measure drug concentrations at the site of action, drug effects are commonly related to blood or plasma concentrations using a hypothetical effect site compartment. Theoretical effect site concentrations are linked to blood concentrations by the parameter k_{e0}, the blood–effect site equilibration rate constant.[2,3] When concentrations at the sites of action are dependent on tissue perfusion, k_{e0} would also be expected to depend on blood flow. However, in conventional pharmacokinetic–pharmacodynamic modeling blood flow is not accounted for.[4,5] In contrast to conventional pharmacokinetic models, recently developed recirculatory pharmacokinetic models incorporate cardiac output (CO).[6] Furthermore, in contrast to conventional compartmental models, which assume the drug concentration to peak at time zero and then decrease monotonically, recirculatory models do not assume instantaneous mixing of administered drug and blood and as such provide a much better description of the concentration–time profile during the initial mixing phase. This in itself may affect the estimation of k_{e0}, in particular when drug input is rapid and the onset of action is fast.[7] The importance of adequate description of the initial part of the concentration–time curve in pharmacokinetic–pharmacodynamic modeling has been demonstrated previously.[8,9] In these studies, semiparametric approaches were used. These do not account for blood flow but are capable of solving some of the shortcomings of compartmental models.

In this study we examined the pharmacokinetics and pharmacodynamics of rocuronium using a recirculatory pharmacokinetic model and compared the results with those obtained with conventional modeling. In addition we examined the relation between CO and the k_{e0}, as well as the other pharmacokinetic and pharmacodynamic parameters. Rocuronium was selected as a model drug because its onset of action is fast, its effects can be quantified easily and reliably, and because muscle blood flow is likely to be linked to CO.

Materials and Methods

Experimental Protocol

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center. The study comprised 15 female patients who were scheduled for eye surgery with general anesthesia. Informed consent was obtained from each patient. Exclusion criteria were as follows: (1) obesity (Quetelet index > 28);

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Received from the Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands. Submitted for publication November 29, 1999. Accepted for publication July 25, 2000. Support was provided solely from institutional and/or departmental sources.

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(2) history of cardiovascular disease, *i.e.*, hypertension, heart failure, recent myocardial infarction (< 6 months) or the use of cardiovascular medication; (3) diabetes mellitus; (4) immobility, because this may artificially decrease CO; and (5) participation in other studies.

Patients were premedicated with midazolam, 7.5 mg orally, 60 min before administration of anesthesia. In the operating room, electrocardiogram electrodes were placed, and a peripheral intravenous infusion was established. A pulse oximeter was connected for the measurement of arterial oxygen saturation. During local anesthesia with lidocaine 1%, a catheter was placed in a radial artery.

Anesthesia was induced and maintained with a target-controlled infusion of propofol and remifentanil. The target propofol concentration was set at 4 mg/ml. The remifentanil target concentration was adjusted according to the surgical requirement. After loss of consciousness, rocuronium 0.35 mg/kg was injected intravenously for muscle relaxation. To allow adequate measurement of muscle relaxation and CO in the period between induction of anesthesia and intubation of the trachea, intubation was delayed until 2 min after the administration of rocuronium. If the train-of-four ratio during the experiment recovered to more than 80%, vecuronium bromide was given as required to maintain adequate muscle relaxation for surgery. Vecuronium bromide does not interfere with the rocuronium assay.[10]

Rocuronium was given as a mixture with indocyanine green (ICG) and autologous blood. The mixture was prepared by adding 0.0385 ml/kg rocuronium (10 mg/ml; 0.3 mg/kg is ED_{95}[11]) to ICG, 25 mg in 2.5 ml of its solvent, and autologous blood to make a total volume of 10 ml. One milliliter of the mixture was stored for later measurement of the injectate concentrations, and the other 9 ml was put in a 10-ml syringe. The syringes were weighed before and after the experiment to allow calculation of the injected volume.

Sampling was performed from the radial artery catheter. Before the experiments, a 20-ml blood sample was drawn for construction of the calibration curves of ICG (5 ml) and rocuronium (15 ml). During the first 10 min of the experiment, sampling was performed with the aid of a specially constructed computer-controlled syringe pump and a fraction collector. Thereafter, samples were taken manually. The sample size was initially 1.5 ml (0.3 ml for ICG measurement and 1.2 ml for rocuronium measurement). After 10 min, the sample size was 3 ml (for rocuronium measurement only). Sampling started 3 s before injection of the drugs (blank sample) and continued for 240 min. The first minute's sampling was performed once every 3 s, the second minute's once every 10 s, and thereafter samples were taken at 2.5, 3, 4, 7, 10, 15, 30, 60, 120, 180, and 240 min. When the sampling device was used, *i.e.*, during the first 10 min of sampling, waste samples were taken to clear the system between the samples. Sampling volume was equal to the sum of the dead space volumes in the catheter and the extension lines to the sampling device.

Neuromuscular block was measured by applying a supramaximal stimulus to the ulnar nerve at the wrist and monitoring the response of the adductor pollicis (thumb adduction), using a force transducer (UC3, Gould Intrument Systems, Valley View, OH) connected to an amplifier (Datascope 2000A, Datascope Corporation, Paramus, NJ). The arm and the hand were immobilized. The nerve was stimulated with a train-of-four: four stimuli at 2.0 Hz were applied every 12 s. The ratios between the T1 and the baseline value of T1 before rocuronium administration were determined to describe the effect. Patients reaching less then 80% twitch depression were excluded from the study. Twitch depression measurements were performed according to predefined guidelines.[12,13]

The amplifier of the force transducer and the sampling machine were connected to a data acquisition computer (3T model PS1600, Twente Technology Transfer, Enschede, The Netherlands) for the registration of the events during the experiment.

Analytical Methods

The concentration of both the ICG and rocuronium were measured in all samples collected during the first 10 min; in samples collected after 10 min, only rocuronium concentrations were measured. Blood ICG concentrations were measured spectrophotometrically at 805 nm. For each experiment, a reference line was constructed from whole blank blood from the patient and known amounts of ICG. The absorption at 805 nm caused by ICG was considered to be the measured absorption minus the absorption measured in the blank sample collected before the experiment.

Whole-blood rocuronium concentrations were measured by high-performance liquid chromatography with a fluorescence detector, according to the method described by Kleef *et al.*[10] These measurements were performed at the Research Laboratory of the Research Group for Experimental Anesthesiology and Clinical Pharmacology, University Hospital Groningen, The Netherlands.

Data Analysis

For the pharmacokinetic analysis, a recirculatory model described by Krejcie *et al.*[6] (fig. 1), was used. In this model, the central assumption is that ICG is confined to the intravascular space and thereby defines the intravascular kinetics of other simultaneously injected drugs, in this case rocuronium.

The central intravascular part of the model, representing blood flow through the heart and the lungs, was described by two combined parallel pathways, a fast and a slow central pathway.[14] The shape of the first-pass concentration–time curve of ICG (*i.e.*, data before evidence of ICG recirculation) was described by the sum of

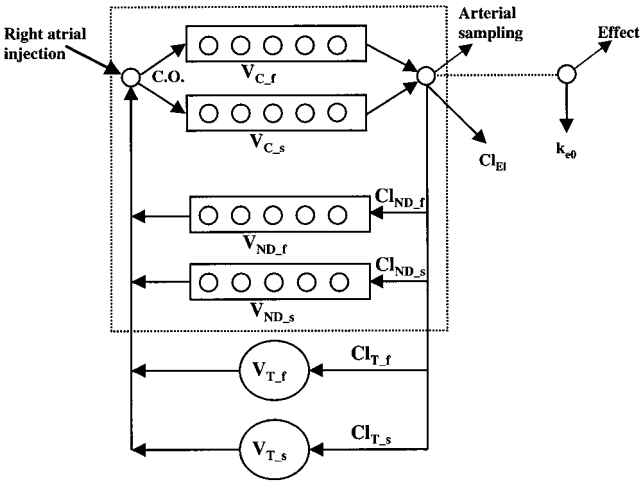

Fig. 1. The recirculatory model used to analyze indocyanine green and rocuronium pharmacokinetics and the rocuronium pharmacodynamics. The parts in the dashed box represent the model for indocyanine green. The complete model is used to describe rocuronium kinetics and dynamics. Cl_{EI} = elimination clearance; Cl_{ND_f} = fast nondistributive clearance; Cl_{ND_s} = slow nondistributive clearance; Cl_{T_f} = fast tissue clearance; Cl_{T_s} = slow tissue clearance; CO = cardiac output; k_{e0} = blood–effect site equilibration rate constant; V_{C_f} = fast central volume; V_{C_s} = slow central volume; V_{ND_f} = fast peripheral nondistributive volume; V_{ND_s} = slow peripheral nondistributive volume; V_{T_f} = fast peripheral tissue volume; V_{T_s} = slow peripheral tissue volume.

two Erlang distribution functions, each representing the convolution of n 1-compartment models connected in series[15]:

$$C(t) = A_1 \cdot \frac{k_1^{n_1} t^{n_1-1}}{(n_1-1)!} e^{-k_1 t} + A_2 \cdot \frac{k_2^{n_2} t^{n_2-1}}{(n_2-1)!} e^{-k_2 t}$$

where n_1 and n_2 are the number of compartments in series in the central delay elements, k_1 and k_2 are the rate constants between the compartments in series, n_1/k_1 and n_2/k_2 are the mean transit times of the central delay elements, and A_1 and A_2 the areas under the first-pass concentration–time curves. The CO was determined by dividing the dose of ICG by the area under the first-pass ICG concentration–time curve ($A_1 + A_2$). The two Erlang functions were fitted to the data using the solver function in Quattro Pro (Borland, Scotts Valley, CA). The data were weighted uniformly during the first-pass fitting.

The parameters obtained from the Erlang functions were used as fixed parameters in a complete recirculatory model for ICG, including parallel fast and slow peripheral nondistributive circuits (each characterized by a volume and clearance: V_{ND_f} and Cl_{ND_f}, and V_{ND_s} and Cl_{ND_s}, respectively) and elimination clearance (Cl_{EI}). The sum of the clearances through the parallel fast and slow peripheral nondistributive circuits for ICG (for which clearances equal blood flows) equals the CO.[6] Estimates of the model parameters were obtained by an iterative fitting procedure using the SAAM II program (SAAM Institute, Seattle, WA). In this analysis, the data were iteratively reweighted over the predicted values.

The intravascular pharmacokinetic parameters of ICG were used to evaluate the arterial rocuronium data by adding to the central intravascular model a fast and a slow distributive peripheral tissue compartment (characterized by V_{T_f} and Cl_{T_f}, and V_{T_s} and Cl_{T_s}, respectively). For rocuronium, the ratio between fast and slow peripheral nondistributive clearances was set equal to that for ICG, but absolute values were not the same as for ICG.

The mean transit time (MTT) determines whether a nondistributive pathway is either a fast or slow pathway and similarly whether a distributive pathway represents a rapidly or slowly equilibrating tissue compartment. The MTTs equal the (blood) volumes of the compartments or compartments in series divided by the (blood) flow through the compartments. The total peripheral tissue MTT (MTT_T) is taken as the average of the fast peripheral MTT (MTT_{T_f}) and the slow peripheral MTT (MTT_{T_s}), weighted for the percentage of total blood flow through the fast and the slow peripheral distributive pathways. The fast nondistributive MTT (MTT_{ND_f}) and the slow nondistributive MTT (MTT_{ND_s}) are the same for ICG and rocuronium.

The relation between the measured arterial concentrations and the percentage neuromuscular block was described by connecting an effect compartment to the pharmacokinetic model (fig. 1) with a link parameter. The relation between effect-compartment concentration and effect was described with a sigmoid maximum effect (E_{max}) function with the baseline fixed at 0 % and the E_{max} fixed at 100 %, using the SAAM II program. Data with twitch height exceeding the control twitch height were not included in the analysis.

For the pharmacokinetic analysis, we also used a conventional compartmental model to be able to compare these parameters with the recirculatory parameters. Both three- and two-compartmental models were fitted. The optimal model was selected on the basis of the Akaike criterion.[16] The concentrations at 1, 2, 3, 4, 7, 10, 15, 30, 60, 120, 180, and 240 min were used for the compartmental analysis. The pharmacokinetic parameters obtained with this model were also used for a pharmacokinetic-pharmacodynamic analysis as described by Sheiner *et al.*[4] This analysis was also performed in SAAM II, with iteratively reweighting over the predicted concentrations.[17]

Statistics

Patient characteristics and pharmacokinetic and pharmacodynamic parameters are presented as mean ± SD. The correlations between CO and the pharmacokinetic and pharmacodynamic parameters and k_{e0}, were evaluated using linear regression. The pharmacodynamic parameters, derived with the recirculatory and compartmental models, were compared with the paired *t* test.

Table 1. Patient Characteristics

Parameter	Mean ± SD	Range
Age (yr)	38 ± 21	18–74
Weight (kg)	68 ± 11	46–86
Length (cm)	165 ± 8	151–177
CO (l/min)	3.86 ± 0.97	2.43–5.59

CO = cardiac output.

The criterion to reject the null hypotheses was P less than 0.05.

Results

The characteristics of the patients are presented in table 1. In 13 of the 15 patients, the complete pharmacokinetic–pharmacodynamic relation was investigated. In two patients, muscle relaxation could not be measured because of inadequate fixation of the arm during the experiment. These two patients were only included in the pharmacokinetic analysis. The CO ranged from 2.43 to 5.59 l/min (mean, 3.86 ± 0.97 l/min)

The first-pass concentration–time curves of ICG and rocuronium had the same shape and coincided when corrected for dose, indicating that no pulmonary uptake occurred. Peak concentrations were obtained after 0.49 ± 0.10 min with ICG and 0.50 ± 0.09 min with rocuronium, which was statistically not different. All patients reached more than 80% twitch depression. The raw pharmacokinetic and pharmacodynamic rocuronium data of all patients are shown in figure 2. First-pass rocuronium pharmacokinetics varied with CO; the first-pass concentration–time curves of rocuronium of all patients are shown in figure 3. The recirculatory pharmacokinetic parameters of ICG and rocuronium are presented in tables 2–4, together with the relations of the parameters with CO. The V_C of ICG and rocuronium and the V_{SS} of ICG were correlated with CO (table 2). The Cl_{El}, Cl_{ND_f} and Cl_{ND_s} of ICG and the Cl_{T_f} and Cl_{T_s} of rocuronium were also correlated with CO (table 3). All MTTs of ICG and rocuronium were correlated with CO except the central MTT (MTT_C) for ICG and the MTT_C and the MTT_{T_s} for rocuronium (table 4).

According to the Akaike criterion, the two-compartmental model was selected for the compartmental analysis. The two-compartmental pharmacokinetic parameters of rocuronium are presented in table 5. Figure 4 shows the measured concentration–time and the effect–time relations of one patient, as well as the fit obtained with the recirculatory model. Figure 5 shows the measured concentration–time curve and the recirculatory and compartmental fit for the first 4 min and for the whole experiment. Table 6 shows the pharmacodynamic parameters and the k_{e0}, estimated with both the recirculatory model and the compartmental model, as well as the relations with CO. The k_{e0} for the recirculatory model was strongly correlated with CO. The k_{e0} estimated with the two-compartmental was also correlated with CO. The relations between CO and k_{e0} are shown in figure 6. The values of k_{e0} and CE_{50} obtained with the compartmental pharmacokinetic model were significantly different from the values obtained with the recirculatory model. Age and CO ($r^2 = 0.39$; $P = 0.013$)

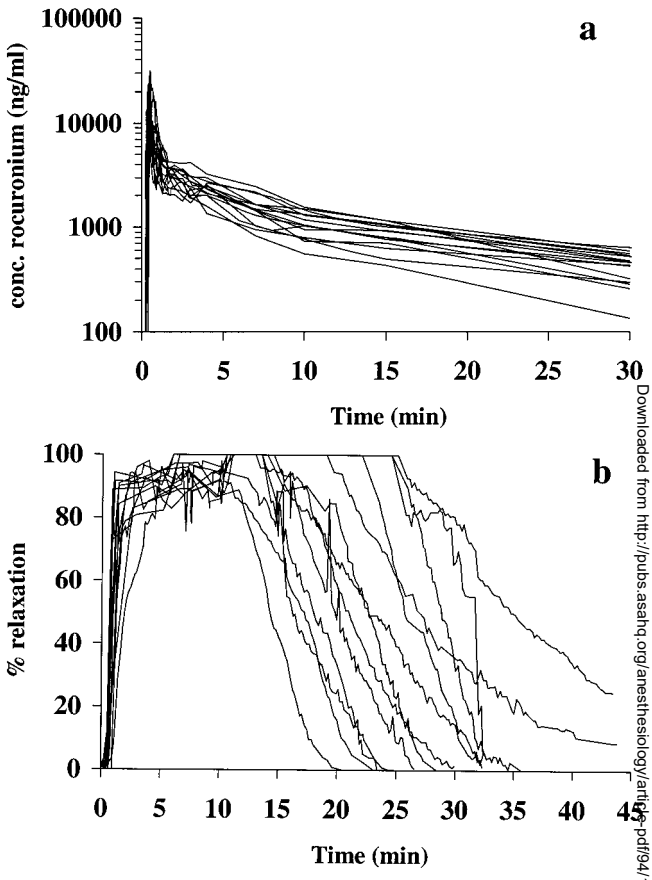

Fig. 2. (*A*) The rocuronium concentration–time profiles of 15 patients for the first 30 min of the experiment. (*B*) The rocuronium effect–time relation of 13 patients.

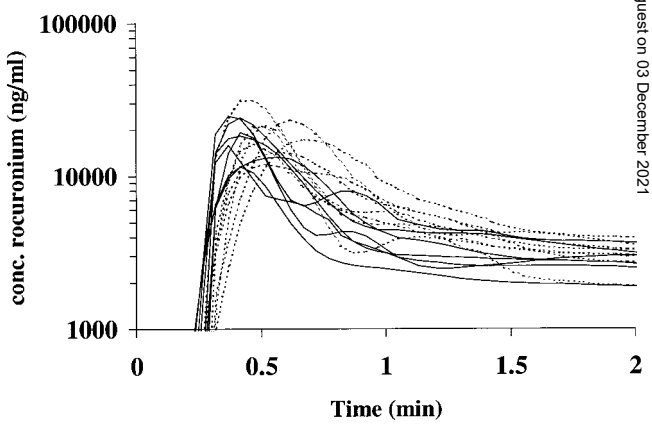

Fig. 3. Fits of the individual patients obtained with a recirculatory model showing the first 2 min. Straight line = patients with a cardiac output higher than the mean cardiac output; dotted line = patients with a cardiac output lower than the mean cardiac output.

Table 2. Volumes (l) for Recirculatory ICG and Rocuronium Pharmacokinetics and Their Relation with CO

		V_C	V_{ND_f}	V_{ND_s}	V_{T_f}	V_{T_s}	V_T	V_{SS}
ICG	Mean	1.52	0.34	1.48				3.35
	SD	0.40	0.24	0.37				0.63
	Slope	0.34	0.0033	0.069				0.412
	Intercept	0.21	0.33	1.214				1.76
	r^2	0.68*	0.00	0.03				0.40*
Rocuronium	Mean	1.52	0.18	0.82	4.92	9.85	14.77	17.29
	SD	0.40	0.17	0.46	3.86	4.47	4.85	4.82
	Slope	0.34	−0.053	−0.083	−0.03	1.68	1.64	1.85
	Intercept	0.21	0.383	1.14	5.04	3.39	8.42	10.16
	r^2	0.68*	0.09	0.03	0.001	0.13	0.11	0.14

* $P < 0.05$. Note that values of V_C were estimated from ICG concentration–time data and included as fixed parameters in the full recirculatory model for rocuronium (see Methods).

ICG = indocyanine green; CO = cardiac output; V_C = central volume; V_{ND_f} = fast peripheral nondistributive volume; V_{ND_s} = slow peripheral nondistributive volume; V_{T_f} = fast peripheral tissue volume; V_{T_s} = slow peripheral tissue volume; V_T = peripheral tissue volume; V_{SS} = total distribution volume.

and age and k_{e0} of the recirculatory model ($r^2 = 0.36$; $P = 0.029$) were found to be correlated. No correlation between age and k_{e0} of the compartmental model was found.

Discussion

Until now, recirculatory models, the models described in this study, have not been used in pharmacokinetic–pharmacodynamic modeling in patients. In this study we demonstrated that the recirculatory pharmacokinetic model adequately describes the first-pass pharmacokinetics of rocuronium in patients. We also demonstrated that the recirculatory model can be used for pharmacokinetic–pharmacodynamic modeling and is capable of revealing that the k_{e0} of rocuronium, a drug with a fast onset of action, is strongly dependent on CO. The results of this study indicate that there is a significant difference between k_{e0} and CE_{50}, estimated with the aid of a recirculatory model *versus* a compartmental pharmacokinetic model after a bolus injection of rocuronium.

The importance of the pharmacokinetics and pharmacodynamics during the first minutes after a bolus injection, especially for drugs with a fast onset of effect, has been emphasized.[18] The inability of conventional compartmental models to describe the initial mixing of drugs was described by Chiou in 1979.[19] Since then, recirculatory models have been used as an alternative to describe the pharmacokinetics of various drugs in animals.[20,21] Minimal recirculatory models[22] and a precursor model of the more extensive recirculatory models have been used to describe pharmacokinetics in patients. However, to our knowledge, these specific recirculatory models with their ability to account for the influence of blood flow have not previously been used for integrated pharmacokinetic–pharmacodynamic modeling in patients.

The k_{e0} and CE_{50} of the recirculatory model differ significantly from the values found with a compartmental model (see table 6). This is undoubtedly related to the inability of compartmental models to characterize the concentration–time relation during the first few minutes after a bolus injection, *e.g.*, the front-end kinetics. A compartmental model misspecifies the early time course of drug concentration because it assumes the body to be homogeneous rather than a complicated system of tissues and organs in series and parallel.[23] Depending on the model, *i.e.*, two- or three-compartmental, initial drug concentrations may be either seriously underestimated

Table 3. Clearances (l/min) for Recirculatory ICG and Rocuronium Pharmacokinetics and Their Relation with CO

		Cl_{El}	Cl_{ND_f}	Cl_{ND_s}	Cl_{T_f}	Cl_{T_s}	Cl_T	ΣCl
ICG	Mean	0.69	1.87	1.29				3.86
	SD	0.19	0.64	0.44				0.97
	Slope	0.13	0.58	0.28				
	Intercept	0.19	−0.35	0.20				
	r^2	0.43*	0.76*	0.40*				
Rocuronium	Mean	0.45	1.02	0.68	1.47	0.23	1.70	3.86
	SD	0.11	0.57	0.38	0.94	0.20	1.13	0.97
	Slope	−0.006	0.13	0.081	0.70	0.11	0.81	
	Intercept	0.47	0.50	0.36	−1.23	−0.20	−1.43	
	r^2	0.003	0.051	0.04	0.51*	0.31*	0.49*	

* $P < 0.05$.

ICG = indocyanine green; CO = cardiac output; Cl_{El} = elimination clearance; Cl_{ND_f} = fast nondistributive clearance; Cl_{ND_s} = slow nondistributive clearance; Cl_{T_f} = fast tissue clearance; Cl_{T_s} = slow tissue clearance; Cl_T = peripheral tissue clearance; ΣCl = sum of the elimination clearance, fast and slow nondistributive clearances, and, when applicable, fast and slow tissue clearances.

Table 4. Mean Transit Times (min) for Recirculatory ICG and Rocuronium Pharmacokinetics and Their Relation with CO

		MTT_C	MTT_{ND_f}	MTT_{ND_s}	MTT_{T_f}	MTT_{T_s}	MTT_T
ICG	Mean	0.40	0.20	1.22			
	SD	0.07	0.13	0.36			
	Slope	−0.012	−0.075	−0.22			
	Intercept	0.45	0.49	2.06			
	r^2	0.031	0.31*	0.33*			
Rocuronium	Mean	0.40	0.20	1.22	4.84	54.94	11.47
	SD	0.07	0.13	0.36	3.05	22.27	6.47
	Slope	−0.012	−0.075	−0.22	−2.26	−9.09	−4.49
	Intercept	0.45	0.49	2.06	13.55	90.02	28.79
	r^2	0.031	0.31*	0.33*	0.51*	0.16	0.45*

* $P < 0.05$.

ICG = indocyanine green; CO = cardiac output; MTT_C = central mean transit time; MTT_{ND_f} = fast nondistributive mean transit time; MTT_{ND_s} = slow nondistributive mean transit time; MTT_{T_f} = fast peripheral mean transit time; MTT_{T_s} = slow peripheral mean transit time; MTT_T = total peripheral tissue mean transit time.

or overestimated. In contrast, recirculatory models are capable of accurately describing the front-end kinetics.[7] Obviously, inadequate characterization of the plasma concentration–time relation also has consequences for the pharmacodynamic analysis. When initial plasma concentrations are either underestimated or overestimated, the plasma concentration–effect relation will be distorted. This does not only affect the estimation of k_{e0}, but also the estimated pharmacodynamic parameters, as has been demonstrated by Ducharme *et al.*[9] and Fisher *et al.*[8] These investigators examined the pharmacodynamics of vecuronium using nonparametric and semiparametric models, respectively, and demonstrated that estimation of k_{e0} and pharmacodynamic parameters depends on adequate characterization of the plasma concentration–time curve, including the initial mixing phase. In this study, the k_{e0} estimated with a compartmental model was nearly twofold larger than that estimated with a recirculatory model, and the CE_{50} was approximately 22% lower. A recent study by Beaufort *et al.*[24] showed that including early blood samples in the pharmacokinetic–pharmacodynamic analysis of rocuronium and other muscle relaxants in pigs resulted in a significantly higher CE_{50} and a significantly smaller k_{e0} compared with the results obtained with a conventional sampling schedule.

This study showed a significant correlation between CO and k_{e0} for both the recirculatory and the compartmental model. However, the correlation between CO and k_{e0} was much stronger with the recirculatory model ($r^2 = 0.70$; fig. 6). When CO was corrected for body weight (CI), the relation between CI and k_{e0} still showed a very strong correlation for the recirculatory model ($r^2 = 0.60$, $P = 0.002$), whereas the relation for the compartmental model was no longer significant ($P > 0.05$). This indicates that the relation is probably not weight-dependent. CO is known to play an important role in the pharmacokinetics and the time course of action of muscle relaxants, including the onset of action during the initial distribution phase.[25] This is especially important for muscle relaxants that are used for rapid sequence induction, because the time to intubation must be as short as possible. The onset time of paralysis after intravenous bolus administration of a neuromuscular blocking drug depends mainly on the speed at which the relaxant reaches the postsynaptic acetylcholine receptors. Because muscle blood flow is related to CO, the high correlation between CO and k_{e0} strongly suggests a crucial role of muscle blood flow, *i.e.*, that the distribution to the site of action is perfusion-limited. This in al

Table 5. The Pharmacokinetic Parameters for Rocuronium Obtained with a Two-compartmental Model

Parameters	Two-compartmental (n = 15)
V_1 (l)	6.76 ± 1.69
V_2 (l)	3.73 ± 1.98
V_{SS} (l)	10.50 ± 3.54
Cl_{El} (l/min)	0.50 ± 0.14
Cl_{12} (l/min)	0.43 ± 0.20

V_{SS} = total distribution volume; Cl_{El} = elimination clearance.

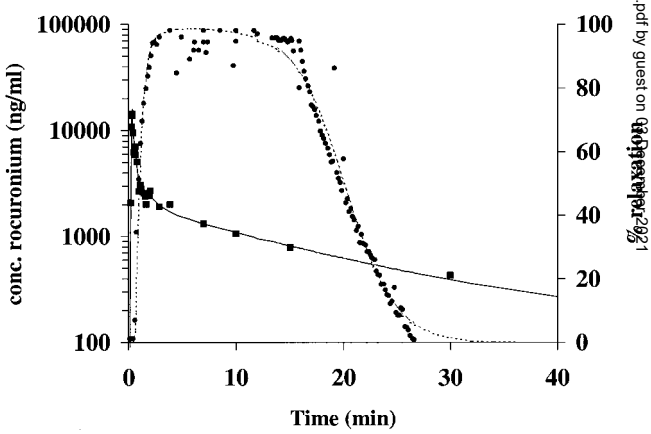

Fig. 4. The concentration–time and effect-time relations of an individual patient during the first 40 min after the bolus injection. The straight line describes the fit of the recirculatory model, and the dashed line describes the accompanying pharmacodynamic fit. The squares represent the measured rocuronium concentrations, and the dots the measured muscle relaxation.

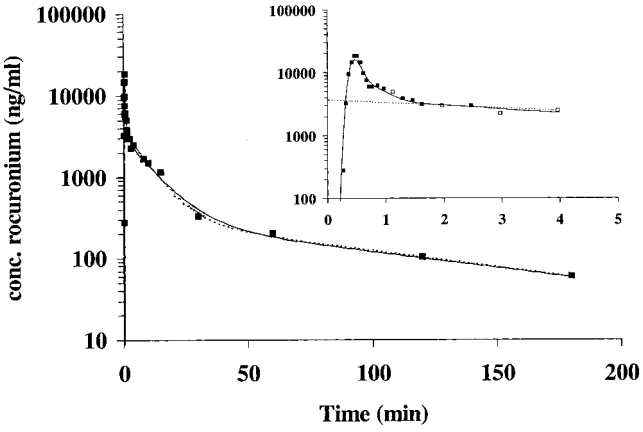

Fig. 5. The concentration–time relation of rocuronium for one individual patient for the whole experiment. The straight line represents the fit with the recirculatory model, and the dashed line represents the fit with the two-compartmental model. (*Inset*) The concentration–time relation is shown for the same patient for the first 4 min after bolus injection, and the measured concentrations that were used for the compartmental fit are left open. Note that samples collected during the first 20 s contained no or very small (< 10 ng/ml) concentrations of rocuronium and are therefore not shown.

likelihood constitutes the physiological basis of k_{e0} for drugs that have no diffusion limitation in their transfer to the effect sites.

In the present study, k_{e0} and pharmacodynamic parameters were derived after a bolus injection of rocuronium. It is conceivable that if these parameters were studied during and after a short infusion, the values derived by compartmental analysis would approach those derived by recirculatory analysis, because they would depend much less on the initial concentration–time data. On the other hand, the parameters thus derived may have a limited predictive value when the drug is administered as a bolus injection. Plaud *et al.*[26] studied rocuronium pharmacokinetics and their relation with pharmacodynamics after a 5-min infusion. The parameters they found (k_{e0} = 0.168 min−1; CE_{50} = 823 μg/ml) are comparable with the parameters obtained with the recirculatory pharmacokinetic model in the present study (k_{e0} = 0.129 min−1; CE_{50} = 876 μg/ml).

Table 6. Pharmacodynamic Parameters Obtained with Recirculatory and Compartmental Pharmacokinetic Modeling and Their Relation with CO

Parameter		Recirculatory	Two-compartmental
k_{e0} (min^{-1})	Mean ± SD	0.129 ± 0.036	0.239 ± 0.104*
	Slope	0.033	0.071
	Intercept	0.0042	−0.028
	r^2	0.70†	0.38‡
γ	Mean ± SD	8.75 ± 2.31	8.96 ± 9.22
	Slope	0.392	1.767
	Intercept	7.28	2.33
	r^2	0.024	0.030
CE_{50} (μg/l)	Mean ± SD	876 ± 118	684 ± 97*
	Slope	44.26	46.83
	Intercept	710	508
	r^2	0.12	0.19

* $P < 0.001$ *versus* recirculatory model. † $P < 0.001$. ‡ $P = 0.025$.

CO = cardiac output; k_{e0} = blood–effect-site equilibration constant; CE_{50} = effect compartment concentration at 50% of the maximum effect.

Our results showed a significant correlation between age and CO (r^2 = 0.39; P = 0.013) and between age and k_{e0} of the recirculatory model, whereas k_{e0} of the compartmental model was not age-dependent. Previous studies showed a relation between the k_{e0} and age for propofol[27,28] and for remifentanil,[5] both drugs with a fast onset of effect. Schnider *et al.*[28] also showed a relation between the time to peak effect of propofol and age, in which the time to peak effect was longer in the elderly. In our opinion, these observations may be, among others, reasons, a result of age-related changes in CO. Propofol and remifentanil are fast-acting drugs, and therefore the onset is likely to be flow-dependent. When blood–effect-site concentration equilibration is rapid, it is more likely to be flow-dependent, and therefore this could also be caused by age-dependent changes in CO.

The initial concentrations predicted (fitted) by the compartmental models depend heavily on the timing of first sampling and the number of compartments. The dependence on the number of compartments is illustrated in figure 7. The first concentration included in the compartmental fits was the 1-min sample, as this is the first sample included in most compartmental analyses. As illustrated, the three-compartmental model fitted the first data point much better than the two-compartmental model. However, based on an objective criterion (Akaike) and in view of the uncertainty in, and high correlation between, some of the model parameters, inclusion of a third compartment was not warranted.

These recirculatory pharmacokinetic models have been previously used only for analysis of animal data.[6,29] A difference with the use in patients lies in the fact that the venous injection site and the arterial sampling site were much more peripherally located in patients than in the animal studies. As a result, the central part of the recirculatory model represents more than just the heart and lungs. In our patients, the total central blood volume (V_C) was 1.52 l, representing 45% of the total blood volume, whereas in previous animal studies, V_C represented a smaller fraction of the total blood volume: 31%,[29] 34%,[6] and 32%.[30] Another implication of the peripheral bolus injection is the lack of correlation between MTT_c and CO.

The pharmacokinetic parameters found by Plaud *et al.*,[26] who used a two-compartmental pharmacokinetic model, can be compared with our results of the compartmental parameters but also with some recirculatory parameters. They found a total distribution volume (V_{ss}) of 14.8 l, which is in the same order as the value we found for the compartmental model (V_{ss} = 10.5 l) and with the recirculatory model (V_{ss} = 17.3 l). The elimination clearance of the two different models found in

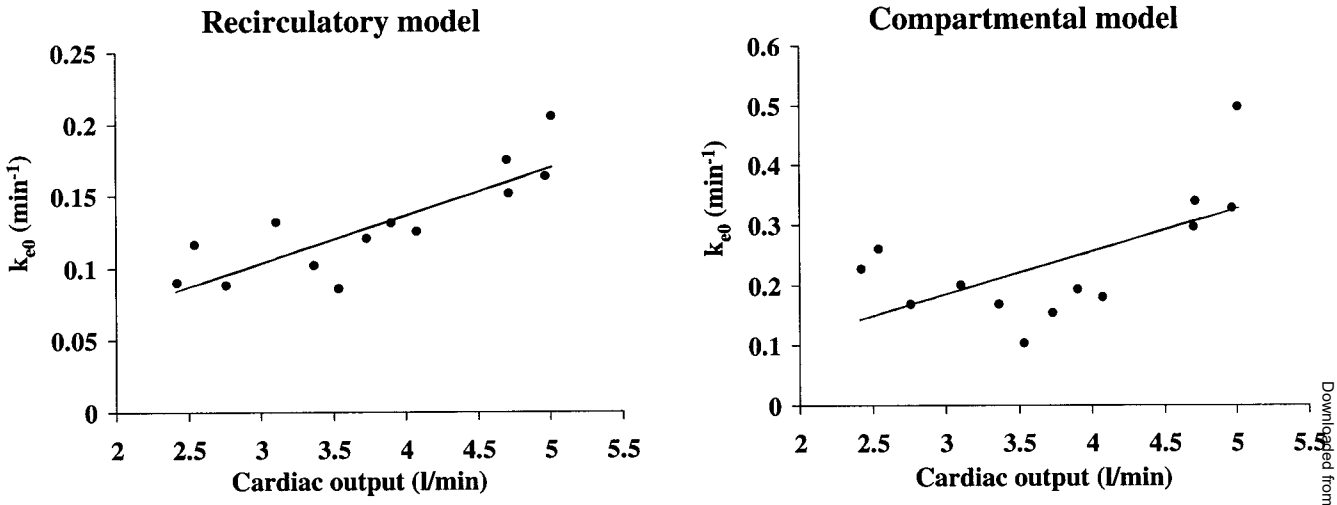

Fig. 6. Relation between the cardiac output and the blood–effect site equilibration rate constant (k_{e0}) for the recirculatory model and the compartmental model. The lines represent the linear relation.

this study (0.45 l/min and 0.50 l/min) are also comparable to the value of 0.58 l/min reported by Plaud *et al.*[26]

Some of the pharmacokinetic parameters were correlated to CO (tables 2–4). The influence of increasing CO on the tissue clearance or distribution rate is obvious, at least when tissue uptake is perfusion limited, as is the case with rocuronium. The influence on total distribution volumes is less obvious but has been reported previously.[29] The elimination clearance of rocuronium was not correlated with CO because rocuronium has a relatively low hepatic extraction ratio, and elimination clearance is probably more dependent on protein binding and hepatic enzyme activity (intrinsic clearance).[31]

Our observations have some clinical implications. As expected from the smaller k_{e0} in patients with a lower CO, these patients generally required a longer time before a twitch depression of more than 90% was obtained. For example, in the patient with the lowest CO (2.4 l/min) 90% twitch depression was obtained after 2.5 min, whereas in the patient with the highest CO (5.0 l/min), who was included in the pharmacodynamic evaluation, this was obtained after 1.5 min. In the context of a rapid-sequence induction, this indicates that not only the selection and the dose of the muscle relaxant are important, but the physiologic condition of the patient should also be taken into account.

In conclusion, this study demonstrated that recirculatory pharmacokinetic modeling adequately characterizes the plasma concentration–time relation of rocuronium, including the initial mixing phase, after a bolus dose. In addition, the study illustrated the role of the CO with respect to the pharmacokinetics, including the blood–effect site equilibration rate. Furthermore, it was shown that inadequate characterization of the initial concentrations using conventional pharmacokinetic models affects the estimated k_{e0} and CE_{50}. Adequate characterization of the initial phase using recirculatory modeling results in a more realistic, physiologically based estimation of these parameters.

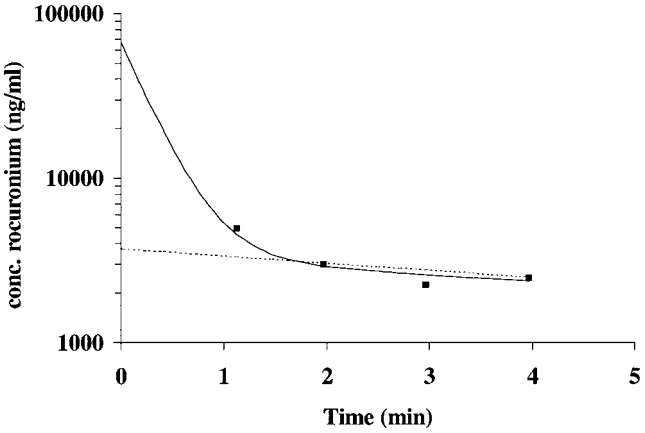

Fig. 7. The concentration–time relation of one individual patient for the first 4 min after bolus injection. The straight line represents the fit with a three-compartmental model, and the dashed line represents the fit with a two-compartmental model.

The authors thank Dr. J. Swen, M.D., Ph.D. (Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands), for help with the muscle relaxation measurements, M. J. Geerts, B.Sc. (Department of Anesthesiology, Leiden University Medical Center), for assistance during the experiments, and U. W. Kleef, B.Sc., and J. Roggeveld (Research Group for Experimental Anesthesiology and Clinical Pharmacology, University Hospital Groningen, Groningen, The Netherlands) for the determination of the rocuronium concentrations.

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