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Pharmacokinetic–Pharmacodynamic Model for the Reversal of Neuromuscular Blockade by Sugammadex

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Background: **Sugammadex selectively binds steroidal neuromuscular blocking drugs, leading to reversal of neuromuscular blockade. The authors developed a pharmacokinetic-pharmacodynamic model for reversal of neuromuscular blockade by sugammadex, assuming that reversal results from a decrease of free drug in plasma and/or neuromuscular junction. The model was applied for predicting the interaction between sugammadex and rocuronium or vecuronium.**

Methods: **Noninstantaneous equilibrium of rocuronium-sugammadex complex formation was assumed in the pharmacokinetic-pharmacodynamic interaction model. The pharmacokinetic parameters for the complex and sugammadex alone were assumed to be identical. After development of a pharmacokinetic-pharmacodynamic model for rocuronium alone, the interaction model was optimized using rocuronium and sugammadex concentration data after administration of 0.1–8 mg/kg sugammadex 3 min after administration of 0.6 mg/kg rocuronium. Subsequently, the predicted reversal of neuromuscular blockade by sugammadex was compared with data after administration of up to 8 mg/kg sugammadex at reappearance of second twitch of the train-of-four; or 3, 5, or 15 min after administration of 0.6 mg/kg rocuronium. Finally, the model was applied to predict reversal of vecuronium-induced neuromuscular blockade.**

Results: **Using the *in vitro* dissociation constants for the binding of rocuronium and vecuronium to sugammadex, the pharmacokinetic-pharmacodynamic interaction model adequately predicted the increase in total rocuronium and vecuronium plasma concentrations and the time-course of reversal of neuromuscular blockade.**

Conclusions: **Model-based evaluation supports the hypothesis that reversal of rocuronium- and vecuronium-induced neuromuscular blockade by sugammadex results from a decrease in the free rocuronium and vecuronium concentration in plasma and neuromuscular junction. The model is useful for prediction of reversal of rocuronium and vecuronium-induced neuromuscular blockade with sugammadex.**

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IDEALLY, neuromuscular blocking agents should have a rapid onset and offset of neuromuscular blockade (NMB).[1] Of the nondepolarizing neuromuscular blocking agents used in clinical practice, rocuronium shows the most rapid onset of NMB and has an intermediate to long duration of action. To decrease its duration of action, a cyclodextrin has been designed to specifically bind rocuronium, thereby reversing rocuronium-induced NMB. The effectiveness and safety of this cyclodextrin, sugammadex, for the reversal of rocuronium-induced NMB has been reported in several preclinical[2–3] and clinical studies[4–11]; these studies have investigated sugammadex administered at a variety of time points, including administration 3 min after a rocuronium dose and at reappearance of the second twitch (T_2) of train-of-four (TOF) stimulation.

Pharmacokinetic studies consistently show decreased rocuronium clearance and increased total rocuronium concentrations shortly after sugammadex administration. As discussed by others,[1,4,6] rocuronium bound by sugammadex is eliminated by renal excretion with a total clearance that is approximately one-third that of unbound rocuronium. As a result, higher total rocuronium concentrations are observed after sugammadex administration, as compared with administration of rocuronium alone.[4–6] However, it is hypothesized that the free rocuronium concentration decreases after sugammadex administration, resulting in decreased availability of rocuronium at the nicotinic receptors.[1,4,6] As a result, a more rapid reversal of NMB is observed. Although consensus exists about the proposed mechanism of action for the reversal of rocuronium-induced NMB after sugammadex administration, this hypothesis has not been confirmed by measuring the actual free rocuronium concentration. The absence of an analytical method to separate free rocuronium from sugammadex-bound rocuronium prevents testing of this hypothesis.[3] However, mechanism-based pharmacokinetic–pharmacodynamic (PK-PD) modeling and simulation can serve as an alternative method to evaluate the proposed mechanism of action of sugammadex. Mechanism-based PK-PD modeling involves the description of the processes in the causal path between drug administration and effect in a strictly quantitative manner.[12] Adequate prediction of the observed data using a mechanism-based PK-PD model based on the proposed pharmacology and (patho) physiology should support the underlying hypotheses. The validity and accuracy of the model and its underlying mechanism can be improved if the model is based on prior knowledge from different sources (*i.e.*, preclinical, *in vitro* bioassays) and is derived under different experimental circumstances.

The affinity of rocuronium and a variety of other compounds for sugammadex has been measured *in vitro* by isothermal microcalorimetry, providing a measure of the equilibrium dissociation constant (K_d).[13] Using the K_d, the free rocuronium concentration can be calculated on the basis of the total rocuronium and sugammadex concentration. Under the assumptions that only the free rocuronium concentration is cleared *via* the rocuronium clearance pathway (*i.e.*, excretion *via* urine and bile) and that the complex is cleared *via* the sugammadex pathway (most likely renal clearance, since the sugammadex clearance is close to the glomerular filtration rate[4]), the effect of sugammadex administration on the overall clearance of total rocuronium can be predicted. In addition, according to the free drug hypothesis, NMB is related to the free rocuronium concentration, and reversal of rocuronium-induced NMB is a measure of the change in free rocuronium concentration in the biophase. Consequently, if the underlying assumptions are valid, the observed reversal of NMB should be adequately predicted by a PK-PD model, linking the free rocuronium concentration to NMB.

In the current study, we tested the hypothesis that the *in vitro* K_d can be used to predict the observed change in the total rocuronium concentration after sugammadex administration to humans. The other model parameters were estimated using pharmacokinetic and pharmacodynamic data from healthy Caucasian volunteers and Japanese and Caucasian patients. PK-PD modeling implicitly requires making assumptions about the model structure. As it is not always possible to justify these assumptions *a priori*, (*e.g.*, is the *in vitro* K_d valid *in vivo*?), it is essential to validate these assumptions by evaluating the ability to predict data from other studies, which were performed under different circumstances (e.g., administration of sugammadex at reappearance of T_2) and were not used to estimate the model parameters.

A key element of mechanism-based PK-PD modeling is the explicit distinction between drug-specific and biologic system-specific properties.[12] Hence, if the system is adequately described, the model should allow predicting the effects of other drugs of the same class after adjusting the drug-specific parameters. We evaluated whether the PK-PD interaction model could be used to predict the pharmacokinetic and pharmacodynamic parameters of vecuronium, another steroidal neuromuscular blocking drug, which also binds specifically to sugammadex, albeit with a somewhat lower affinity than that of rocuronium.[9] For this purpose, we evaluated if the same model structure as applied for rocuronium, but with vecuronium-specific pharmacokinetic and pharmacodynamic model parameters, could also predict the observed changes in the pharmacokinetic and pharmacodynamic parameters of vecuronium (administered as a 0.1 mg/kg intubating dose) after administration of sugammadex at reappearance of T_2.[9]

Materials and Methods

In this study, a parsimonious (*i.e.*, the simplest model that could adequately describe the data) PK-PD interaction model was developed to describe data from different clinical trials exploring the pharmacokinetic and pharmacodynamic profile of rocuronium and sugammadex alone and in combination. Part of the data were used to estimate the model parameters; other data were used for external validation by fixing all model parameters and simulating the validation dataset. Resemblance between simulated and observed data were used to confirm the accuracy and validity of the model.

Study Data

Table 1 summarizes the studies used for model development (calibration) and validation. Calibration study 1 and validation studies 1, 2, and 3 (table 1) have been published previously and were conducted after institutional review board approval as described by Gijsenbergh *et al.*,[4] Sorgenfrei *et al.*,[7] Sparr *et al.*,[6] and Suy *et al.*[9], respectively. The protocol of calibration study 2 (table 1) was approved by the institutional review boards of the Surugadai Hospital (Tokyo, Japan), Keio University (Tokyo, Japan), Tokyo Women's Medical University (Tokyo, Japan), and Kyorin University (Tokyo, Japan). The institutional review board of the Columbia University (New York, New York) approved the protocol for calibration study 3 (table 1). All patients gave written informal consent according to the Declaration of Helsinki.

Data Analysis

The analysis was performed by means of nonlinear mixed-effects modeling using NONMEM version V, release 1.1 (University of California at San Francisco, San Francisco, CA).[14] The pharmacokinetic and pharmacodynamic data were analyzed sequentially. The first order conditional method with interaction was used for estimation.

Visual Predictive Check

Model performance was validated using a visual predictive check, which evaluated whether the identified model was able to predict the observed variability in the pharmacokinetic and/or pharmacodynamic observations for 50% of the population.[15] As the number of observations[3–8] was small it was decided to use a smaller prediction interval, as compared with the generally applied interval of 90%.[15] The outcome of the trial was simulated by drawing random samples from the distributions for the interindividual and residual variability for 1,000 hypothetical patients. Resemblance between simulated (median, 25th and 75th percentiles) and original distributions indicated the accuracy of the model (*i.e.*, 50% of the observed data should fall within the predicted range for 50% of the variability).

Table 1. Overview of the Clinical Studies That Were Used for Model Calibration and Validation

Study Name	Study Description	Drug	Number of Subjects	Number of Samples			Ref.
				PK		PD*	
				V	A		
Calibration study 1 (part I)	Assessment of tolerability, safety, and PK of 0.1, 0.2, 0.5, 1, 2, 4, or 8 mg/kg sugammadex IV in male volunteers	Sugammadex alone	16	29	—	—	4
Calibration study 1 (part II)	Evaluation of efficacy of 0.1, 0.5, 1, 2, 4, or 8 mg/kg sugammadex on the reversal of 0.6 mg/kg rocuronium-induced NMB	Rocuronium alone	10	9	15	395 (TOF, T_2)	4
		Sugammadex with rocuronium	10	9	15	—	—
		Rocuronium with sugammadex	10	9	15	395 (TOF)	—
Calibration study 2	Comparison of the PK, PD, and safety of rocuronium after 0.3, 0.6, or 0.9 mg/kg IV in male and female Japanese patients undergoing routine operations using balanced anesthesia	Rocuronium	59		19	—	Data on file
Calibration study 3	Investigation of the PK, PD, and safety of an intubating dose of 0.6 mg/kg rocuronium in 22 young adult (18–< 60 yr) patients under balanced anesthesia	Rocuronium	22		22	—	Data on file
Validation study 1	Multicenter, randomized, assessor-blinded, placebo-controlled, parallel dose-finding trial in 27 male patients to assess the efficacy, safety, and PK of 0, 0.5, 1, 2, 4, or 6 mg/kg sugammadex administered after 0.6 mg/kg rocuronium at reappearance of T_2. Patients were scheduled for surgical procedures with an anticipated duration of anesthesia of at least 60 minutes, without further need for muscle relaxation other than for intubation	Rocuronium alone	27, (5/22)†	5/2	—	—	7
		Rocuronium with sugammadex	27	5	—	27 (time to recovery of TOF 0.9)	—
Validation study 2	Multicenter, randomized, assessor-blinded, placebo-controlled, parallel dose-finding trial in male patients to assess the efficacy, safety, and PK of 0, 1, 2, 4, 6, or 8 mg/kg of sugammadex IV administered 3, 5, or 15 min after administration of 0.6 mg/kg rocuronium. All patients were scheduled for surgical procedures with an anticipated duration of anesthesia of at least 75 minutes, without further need for muscle relaxation other than for intubation	Rocuronium alone	7	5	—	—	6
		Rocuronium with sugammadex	97	5	—	97 (time to recovery of TOF 0.9)	—
Validation study 3	Multicenter, randomized, assessor-blinded, dose-finding trial to explore the difference in dose-response relationship of sugammadex administered at reappearance of T_2 after 0.1 mg/kg vecuronium or 0.6 mg/kg rocuronium. Patients were scheduled for surgical procedures with an anticipated duration of anesthesia of at least 60 minutes, without further need for muscle relaxation other than for intubation	Vecuronium alone	9	7	—	315 (TOF)	9
		Vecuronium with sugammadex	9	14	—	34 (time to recovery of TOF 0.9)	—

* Neuromuscular function was monitored by acceleromyography using the TOF-Watch-SX® acceleromyograph (Organon Ireland, a part of Schering-Plough Corporation; Dublin, Ireland). † Placebo- or sugammadex-treated patients.

A = arterial PK sample; NMB = Neuromuscular blockade, PD = pharmacodynamics, PK = pharmacokinetics, T_2 = twitch height of second twitch after train-of-four stimulation, TOF = train-of-four ratio; V = venous PK sample.

PK-PD Interaction Model

The PK-PD interaction model was composed of several submodels, including the PK-PD model for rocuronium and the pharmacokinetic-interaction model. The former described the relationship between the plasma concentrations of rocuronium and NMB, and the latter described the plasma concentration of sugammadex and rocuronium after concomitant administration. The full PK-PD interaction model is shown in figure 1.

Pharmacokinetic Model

The rocuronium and sugammadex concentration data were described by a three-compartment model with first-order elimination from the central compartment,

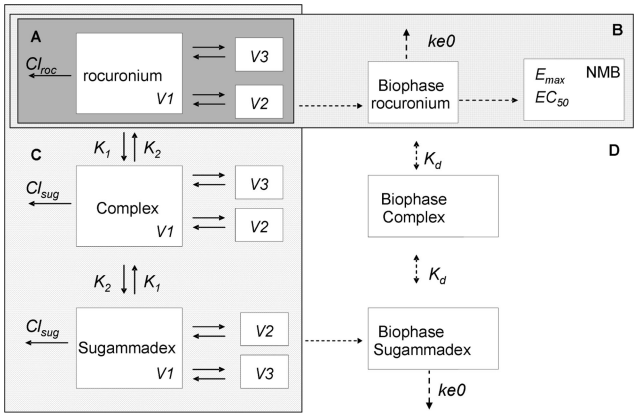

Fig. 1. Schematic representation of the pharmacokinetic–pharmacodynamic (PK-PD) interaction model for rocuronium and sugammadex. (*A*) PK model for rocuronium alone; (*B*) PK-PD model for rocuronium alone; (*C*) PK interaction model; (*D*) PK-PD interaction model; Cl_{roc} = rocuronium clearance; Cl_{sug} = sugammadex clearance; EC_{50} = concentration at 50% of maximum effect; E_{max} = maximum effect; K_1 = association rate constant; K_2 = dissociation rate constant; K_d = equilibrium dissociation constant; *ke0* = distribution rate constant between first peripheral and biophase (effect) compartment; NMB = neuromuscular blockade; *V1* = volume of central compartment; *V2* = volume of first peripheral compartment; *V3* = volume of second peripheral compartment.

parameterized in terms of volume of distribution of the central (*V1*), first (*V2*), and second peripheral compartment (*V3*), intercompartmental clearance from the central to the first (*Q2*) and from the central to the second (*Q3*) peripheral compartment, and clearance from the central compartment (*Cl*). Hysteresis between arterial and venous plasma sugammadex concentration was modeled by adding a compartment to the model for the venous concentration, with a first-order rate constant (k_{vo}) linking the venous concentration to the arterial concentration.

It was assumed that equilibrium of the interaction between rocuronium and sugammadex was not achieved instantaneously. Therefore, the kinetics of the complex formation were described by equation 1, in which [Roc_{free}] is the free concentration of rocuronium, [Sug_{free}] is the free concentration of sugammadex, [*Cplx*] is the concentration of the complex, K_1 is the association rate constant, and K_2 is the dissociation rate constant.

$$[Roc_{free}] \cdot [Sug_{free}] \underset{K_2}{\overset{K_1}{\rightleftarrows}} [Cplx] \tag{1}$$

The K_d is defined as the ratio between K_2 and K_1 (equation 2).

$$K_d = \frac{K_2}{K_1} = \frac{[Roc_{free}] \cdot [Sug_{free}]}{[Cplx]} \tag{2}$$

As only total rocuronium and sugammadex concentration data were available, the pharmacokinetics of the complex could not be determined independently. It was assumed that the pharmacokinetic profile of the complex was identical to that of free sugammadex. The model was simplified further by setting the volume of all compartments equal to *V1* of free sugammadex. Equation 3 describes the kinetics of the complex. CL_{cplx} is the clearance of the complex from the plasma, $V1_{cmplx}$ is the apparent volume of distribution of the central compartment, and k_{1x} and k_{x1} are the rate constants for distribution between the central and the two peripheral compartments. $C_{cplx,x}$ is the complex concentration in the compartments, and $C_{roc,1}$ and $C_{sug,1}$ are the free rocuronium and sugammadex concentration in the central compartment, respectively.

$$\begin{cases} \dfrac{dC_{cplx,1}}{dt} = [C_{roc,1} \cdot C_{sug,1} \cdot K_1] \\ \quad - [C_{cplx,1} \cdot K_2] - \dfrac{C_{cplx,1} \cdot CL_{cplx}}{V1_{cmplx}} \\ \quad + k_{21} \cdot C_{cplx,2} - k_{12} \cdot C_{cplx,1} \\ \quad + k_{31} \cdot C_{cplx,3} - k_{13} \cdot C_{cplx,1} \\ \dfrac{dC_{cplx,2}}{dt} = k_{12} \cdot C_{cplx,1} - k_{21} \cdot C_{cplx,2} \\ \dfrac{dC_{cplx,2}}{dt} = k_{13} \cdot C_{cplx,1} - k_{31} \cdot C_{cplx,3} \end{cases} \tag{3}$$

The pharmacokinetics of rocuronium and sugammadex were described with equation 4, in which CL_{drug} is the clearance of rocuronium or sugammadex from plasma, $k_{1x,drug}$ and $k_{x1,drug}$ are the rate constants for distribution between the central and the two peripheral compartments for rocuronium and sugammadex, and $A_{drug,x}$ is the amount of rocuronium or sugammadex in one of the compartments.

$$\begin{cases} \dfrac{dA_{drug,1}}{dt} = -[C_{roc,1} \cdot C_{sug,1} \cdot K_1] \cdot V1_{cmplx} \\ \quad + [C_{cplx,1} \cdot K_2] \cdot V1_{cmplx} - CL_{drug} \cdot C_{drug,1} \\ \quad + k_{21,drug} \cdot A_{drug,2} - k_{12,drug} \cdot A_{drug,1} \\ \quad + k_{31,drug} \cdot A_{drug,3} - k_{13,drug} \cdot A_{drug,1} \\ \dfrac{dA_{drug,2}}{dt} = k_{12,drug} \cdot A_{drug,1} - k_{21,drug} \cdot A_{drug,2} \\ \dfrac{dA_{drug,3}}{dt} = k_{13,drug} \cdot A_{drug,1} - k_{31,drug} \cdot A_{drug,3} \end{cases} \tag{4}$$

The pharmacokinetic parameters for sugammadex were optimized to data from part I and II of calibration study 1 (table 1), whereas the pharmacokinetic parameters of rocuronium were fixed to the individual specific (*post hoc*) parameters of the pharmacokinetic model for rocuronium alone. The parameter K_2 was estimated, whereas K_1 was calculated using a K_d value of 0.1 μM, which was derived *in vitro* by isothermal microcalorimetry.[13]

In vitro binding studies showed that sugammadex does not bind to human plasma proteins (data on file, N.V. Organon; Oss, The Netherlands). In the absence of sugammadex, approximately 37% of rocuronium is bound to plasma proteins (data on file, N.V. Organon; Oss, The Netherlands). The extent of protein binding declines when

sugammadex is added until all rocuronium is captured by sugammadex and, consequently, no rocuronium is bound to plasma proteins. It was concluded that the binding affinity of rocuronium for sugammadex is much greater than that for plasma proteins. As a result, protein binding was ignored in the interaction model.

Pharmacodynamic Model

The relationship between the rocuronium plasma concentration and NMB was described by a hypothetical effect-compartment to link the rocuronium concentration in plasma or one of the peripheral compartments ($C_{roc,x}$) to the concentration at the effect site (Ce_{roc}) using a first-order rate constant (*ke0*)[16–18] (equation 5).

$$\frac{dCe_{roc}}{dt} = ke0 \cdot \left(C_{roc,x} - Ce_{roc}\right) \quad (5)$$

The concentration-effect relationship was described by equation 6 with parameters for the baseline TOF ratio (E_0), the maximum effect (E_{max}), the Ce_{roc} resulting in an effect of 50% of E_{max} (EC_{50}), and a sigmoidicity parameter (γ). Data from part II of calibration study 1 were used to estimate the pharmacodynamic parameters for rocuronium. The pharmacokinetic parameters were fixed to individual-specific estimates, which were obtained using the pharmacokinetic model for rocuronium alone.

$$E = E_0 - \left(\frac{E_{\max} \cdot Ce_{roc}^{\gamma}}{\left(EC_{50}^{\gamma} + Ce_{roc}^{\gamma}\right)}\right) \quad (6)$$

We evaluated whether the observed change in NMB can be described by linking the concentration in the effect compartment to the free rocuronium concentration. In addition, we evaluated the hypothesis that both rocuronium and sugammadex distribute to the neuromuscular junction where both compounds instantly form a complex. As a result, rocuronium-induced NMB decreases because of a reduction in the free and pharmacologically active fraction. As the neuromuscular junction was represented by the effect compartment in the PK-PD model, the free rocuronium concentration (Ce_{free}) in the effect compartment was calculated from the total concentration of rocuronium and sugammadex in the effect compartment using equation 7, in which $Ce_{roc,tot}$ and $Ce_{sug,tot}$ are the total concentrations of rocuronium and sugammadex, respectively. As there was no information on the rate of distribution of sugammadex to the effect compartment, the same *ke0* value was assumed for rocuronium and sugammadex.

$$Ce_{free} = Ce_{roc,tot} \cdot \left(\frac{2 \cdot K_d}{(Ce_{sug,tot} - Ce_{roc,tot} - K_d) + \sqrt{(Ce_{sug,tot} - Ce_{roc,tot} - K_d)^2 + 4 \cdot K_d \cdot Ce_{sug,tot}} + 2 \cdot K_d}\right) \quad (7)$$

PK-PD Interaction Model for Vecuronium

For external validation of the PK-PD interaction model, it was determined whether the effect of sugammadex administration on vecuronium pharmacokinetics and pharmacodynamics could be predicted also with the same model structure, but with vecuronium-specific pharmacokinetic and pharmacodynamic parameter values. By assuming the K_1 parameter representing the probability that two molecules meet to form a complex, this parameter is considered compound-independent. Hence, by assuming the same K_1 for vecuronium and rocuronium, the K_2 was derived from equation 2 using a vecuronium-specific K_d of 0.175 μM (data on file, N.V. Organon; Oss, The Netherlands). The remaining vecuronium pharmacokinetic and pharmacodynamic parameters were identified by fitting the model to the data. The pharmacokinetic profile of vecuronium was described by a two-compartment model with first-order elimination.[19]

Statistical Model

The interindividual variability in most model parameters was modeled using equation 8, where θ_i is the individual specific parameter value for the subject, *i*, θ_{mean} is the population mean, and η_i is the difference of the logarithm between the individual value of the subject *i* and the population mean. η_i is normally distributed with a mean of zero and a variance ω^2.

$$\theta_i = \theta_{mean} \cdot e^{\eta_i} \quad (8)$$

The residual variability was described by the general equation 9, in which Y_{ij} is the jth observation of individual i, $PRED_{ij}$ is the jth model prediction for individual *i*, and $\varepsilon_{prop,ij}$ and $\varepsilon_{add,ij}$ are the proportional and additive residual errors for the jth prediction of individual *i*. $\varepsilon_{prop,ij}$ and $\varepsilon_{add,ij}$ are normally distributed with mean 0 and a variance σ^2.

$$Y_{ij} = PRED_{ij} \cdot \left(1 + \varepsilon_{prop,ij}\right) + \varepsilon_{add,ij} \quad (9)$$

In the pharmacokinetic model for rocuronium, both $\varepsilon_{prop,ij}$ and $\varepsilon_{add,ij}$ were identified, whereas for the sugammadex pharmacokinetic model only $\varepsilon_{prop,ij}$ was identified. The residual error in the PK-PD models was described by $\varepsilon_{add,ij}$ only.

Results

Model Development

The pharmacokinetics of rocuronium administered alone to Japanese and Caucasian patients could be described by the three-compartment model (fig. 2). *Cl, V1, Q2, V3,* and *Q3* values for rocuronium differed between Japanese and Caucasian patients (table 2). This difference could not be explained by observed differences in body weight, height, and age between the Japanese and Caucasian subpopulation. In addi-

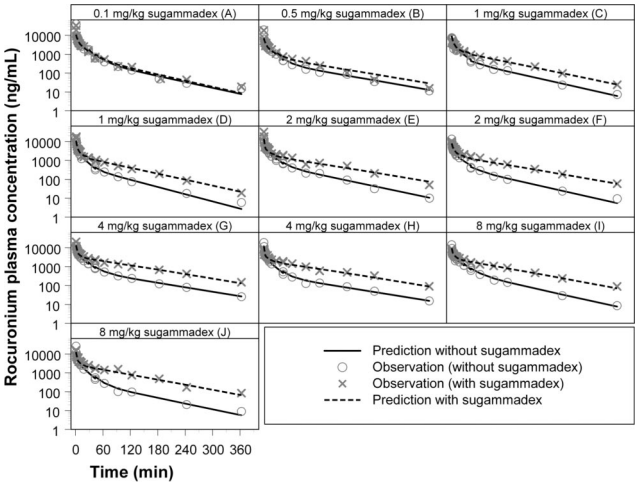

Fig. 2. Observed and predicted rocuronium plasma concentration profiles after administration of rocuronium 0.6 mg/kg alone or followed by sugammadex administration at 3 min at the following doses: (*A*) 0.1 mg/kg, (*B*) 0.5 mg/kg, (*C* and *D*) 1 mg/kg, (*E* and *F*) 2 mg/kg, (*G* and *H*) 4 mg/kg, or (*I* and *J*) 8 mg/kg. The *open circles* and *cross symbols* represent the observed rocuronium plasma concentration in calibration study 1 without and with sugammadex, respectively. The *solid* and *dashed lines* represent the population-predicted rocuronium plasma concentration without and with sugammadex, respectively.

tion, at the lowest rocuronium dose, tested only in Japanese patients (0.3 mg/kg), a different value for *V1* was identified (table 2).

The pharmacokinetics of sugammadex differed according to whether sugammadex was administered with anesthesia and rocuronium or without anesthesia, with higher *Q3* and *V3* values and lower *V2* and *Q2* values reported with sugammadex plus rocuronium, as compared with sugammadex alone (table 2).

With a K_2 of 0.00216 min^{-1} (dissociation half-life = 5.3 h) and a K_d value fixed to 0.1 μM, the pharmacokinetic interaction model adequately predicted the observed increase in total rocuronium concentration after sugammadex administration (fig. 2).

As E_0 and E_{max} could not be distinguished using the available NMB data, E_{max} was set to the individual estimate of E_0 . The fit of the observed rocuronium-induced NMB considerably improved by linking the concentration in the effect compartment to the first peripheral compartment (data not shown). Using this assumption, the population PK-PD model adequately described the time course of response after administration of 0.6 mg/kg rocuronium alone (table 2; fig. 3, dashed line). After fixing all individual specific pharmacokinetic and pharmacodynamic parameters for rocuronium, the PK-PD interaction model could not predict the observed rapid reversal of NMB (fig. 3, short-dashed line). However, assuming that sugammadex also distributes to the effect compartment, thereby lowering the free rocuronium concentration, resulted in an adequate prediction of the observed rapid reversal of NMB after sugammadex administration (fig. 3, solid line).

Model Validation

The observed recovery time (time from sugammadex administration to recovery of the TOF ratio to 90%) after sugammadex administration at 3, 5, or 15 min after administration of 0.6 mg/kg rocuronium closely resembled the predictions by the PK-PD interaction model (fig. 4). The predicted recovery time closely resembled the observed data for most scenarios, since the predicted median was within the 95% CI of the (bootstrapped) observed median (fig. 4, A and C). However, the observed reversal time after 1 and 2 mg/kg sugammadex administered 5 min after rocuronium was underpredicted (fig. 4B). When 1 mg/kg was administered 3 min after rocuronium, 0.1% of the 1,000 simulated patients showed a rebound in NMB, such as actually observed by Eleveld *et al.*[20], with a temporary increase in NMB after recovery to a TOF ratio of 90%. The maximum rebound was a decrease to a TOF ratio of 20%. However, none of the simulated patients showed rebound after 2 mg/kg. Also, the probability for rebound decreased to 0.04% when 1 mg/kg was administered 5 min after rocuronium.

The model could also adequately predict the observed recovery times from rocuronium and vecuronium-induced blockade after sugammadex administration at reappearance of T_2 (fig. 5). The time to reappearance of T_2 (*i.e.*, T_2 twitch height $\geq$ 1%) was simulated using a PK-PD model for the effect of rocuronium on the T_2 twitch height (fig. 5A). The parameter values were estimated using T_2 data from calibration study 1 (parameters not shown). Subsequently, the effect of sugammadex administration, at the simulated time of reappearance of T_2, on the TOF ratio was simulated for the same patients. Although the observed 95% CI did not include the predicted median after administration of 2 mg/kg, this observation seems to be inconsistent, since the model adequately predicted the observed recovery time for a 1 mg/kg lower and higher dose (fig. 5A).

Vecuronium pharmacokinetics without sugammadex was adequately described by a two-compartment model (fig. 6). The time course of response was described with the same model structure as applied for rocuronium, but with vecuronium-specific pharmacokinetic and pharmacodynamic model parameters. As with rocuronium, the concentration in the effect compartment was linked to the vecuronium concentration in the first peripheral compartment. After replacing the rocuronium pharmacokinetic and pharmacodynamic parameters for those of vecuronium (table 3) and using a K_d value of 0.175 μM, while fixing the K_1 value to the value of the rocuronium model, the PK-PD interaction model described the pharmacokinetics (fig. 6) and pharmacodynamics (fig. 5B) of vecuronium after sugammadex administration at reappearance of T_2. However, the model appeared to underpredict the observed reversal time after administration of 0.5 mg/kg sugammadex, since all observations were greater than the predicted median.

Table 2. Pharmacokinetic and Pharmacodynamic Parameters of the Pharmacokinetic-Pharmacodynamic Interaction Model for Rocuronium and Sugammadex

Parameter		Value (CV%)	IIV [%;(CV%)]
PK parameters rocuronium alone (Japanese)			
Clearance	Cl (l/min)	0.252 (3.0)	23 (16)
Central volume of distribution	V1 (l)	2.56 (5.5)	38 (18)
Central volume of distribution (0.3 mg/kg)	V1 (l)	1.92 (39)	n.a. (n.a.)
Intercompartmental clearance 1–2	Q2 (l/min)	0.354 (4.9)	18 (41)
First peripheral volume of distribution	V2 (l)	3.26 (4.0)	25 (23)
Intercompartmental clearance 1–3	Q3 (l/min)	0.0584 (8.3)	32 (27)
Second peripheral volume of distribution	V3 (l)	4.42 (7.4)	22 (35)
PK parameters rocuronium alone (Caucasians)			
Clearance	Cl (l/min)	0.353 (17)	23 (16)
Central volume of distribution	V1 (l)	3.58 (17)	38 (18)
Intercompartmental clearance 1–2	Q2 (l/min)	0.565 (19)	18 (41)
First peripheral volume of distribution	V2 (l)	3.26 (4.0)	25 (23)
Intercompartmental clearance 1–3	Q3 (l/min)	0.134 (6.0)	32 (27)
Second peripheral volume of distribution	V3 (l)	7.64 (23)	22 (35)
PK parameters sugammadex alone			
Clearance	Cl (l/min)	0.109 (4.3)	21 (28)
Central volume of distribution	V1 (l)	3.47 (10)	36 (36)
Intercompartmental clearance 1–2	Q2 (l/min)	0.879 (14)	n.a. (n.a.)
First peripheral volume of distribution	V2 (l)	4.75 (14)	24 (38)
Intercompartmental clearance 1–3	Q3 (l/min)	0.0876 (12)	n.a. (n.a.)
Second peripheral volume of distribution	V3 (l)	5.86 (9.5)	n.a. (n.a.)
PK parameters sugammadex with rocuronium			
Clearance	Cl (l/min)	0.109 (4.3)	21 (28)
Central volume of distribution	V1 (l)	3.47 (10)	36 (36)
Intercompartmental clearance 1–2	Q2 (l/min)	0.427 (17)	n.a. (n.a.)
First peripheral volume of distribution	V2 (l)	2.3 (17)	24 (38)
Intercompartmental clearance 1–3	Q3 (l/min)	0.21 (25)	n.a. (n.a.)
Second peripheral volume of distribution	V3 (l)	8.93 (32)	n.a. (n.a.)
Distribution rate constant between arterial and venous plasma	$K_{v0,Org}$ (1/min)	0.531 (18)	n.a. (n.a.)
PK parameters interaction model			
Equilibrium dissociation constant	K_d (μM)	0.1 (—)	n.a. (n.a.)
Dissociation rate constant	K_2 (1/min)	0.00216 (16)	n.a. (n.a.)
PD parameters rocuronium			
Baseline TOF ratio = maximum effect	$E_0 = E_{max}$ (%)	106 (3.1)	9.90 (42)
Concentration at 50% of maximum effect	EC_{50} (ng/mL)	720 (5.6)	18 (42)
Distribution rate constant between first-peripheral and effect compartment	Ke0 (1/min)	0.655 (15)	48 (63)
Sigmoidicity parameter	γ (—)	6.57 (5.8)	18 (39)
Residual variability			
Rocuronium (proportional)	ε_1 (%)	10 (11)	n.a. (n.a.)
Rocuronium (additive)	ε_2 (ng/ml)	5.2 (43)	n.a. (n.a.)
Sugammadex (arterial plasma; proportional)	ε_3 (%)	17 (37)	n.a. (n.a.)
Sugammadex (venous plasma; proportional)	ε_4 (%)	17 (21)	n.a. (n.a.)
TOF ratio (additive)	ε_5 (%)	3.2 (13)	n.a. (n.a.)

CV = coefficient of variation; IIV = interindividual variability; PD = pharmacodynamics; PK = pharmacokinetics; TOF = train-of-four.

Application

To illustrate the application of the PK-PD model in clinical development, the possible effect of residual sugammadex in the circulation at the onset time of a subsequent (second or repeat) dose of rocuronium was simulated with the model. The onset time was defined as the time from administration of rocuronium until 90% NMB was reached (TOF = 10%). NMB was simulated after readministration of rocuronium (0.6 or 1.2 mg/kg) after earlier administration of 2 mg/kg sugammadex at reappearance of T_2 after a first rocuronium dose of 0.6 mg/kg. Figure 7 shows the percentage of the population reaching more than 90% NMB within a specified time frame of 2 to 10 min.

Discussion

The pharmacokinetic interaction model, which assumes that binding of rocuronium in the central compartment decreases the free rocuronium concentration, could predict the observed increase in total plasma rocuronium concentrations after sugammadex administration. In addition, the PK-PD interaction model assumes that sugammadex decreases the free rocuronium concentration in the effect compartment (*i.e.,* the neuromuscular junction). Using these assumptions, the rapid reversal of rocuronium-induced NMB after sugammadex administration could be predicted. This is consistent with the proposed mechanism of action of sugammadex.

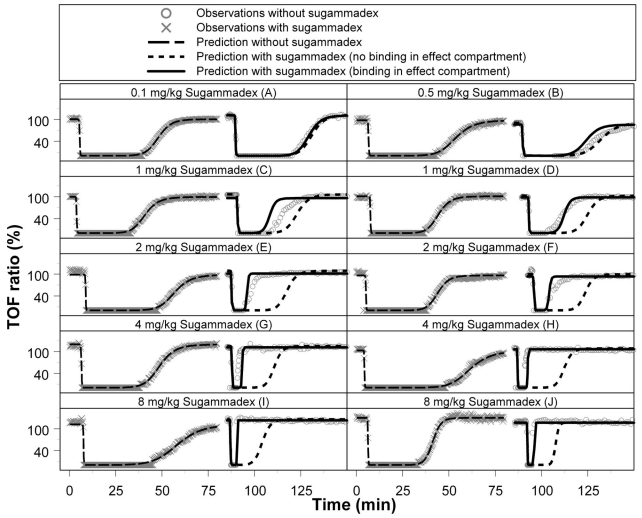

Fig. 3. Observed and predicted ratios between the first and fourth twitch height after train-of-four stimulation (TOF ratio) after administration of rocuronium 0.6 mg/kg alone or followed by sugammadex administration at 3 min at the following doses: (*A*) 0.1 mg/kg, (*B*) 0.5 mg/kg, (*C* and *D*) 1 mg/kg, (*E* and *F*) 2 mg/kg, (*G* and *H*) 4 mg/kg, or (*I* and *J*) 8 mg/kg. The *open circles* and *cross symbols* represent the observed TOF ratios in calibration study 1 without and with sugammadex, respectively. The *solid* and *dashed lines* represent the population-predicted TOF ratio without and with sugammadex, respectively.

Obviously, measuring the actual free rocuronium concentration would be the ultimate test, but as these data are currently unavailable, mechanism-based modeling is a valid alternative. This is further supported by showing

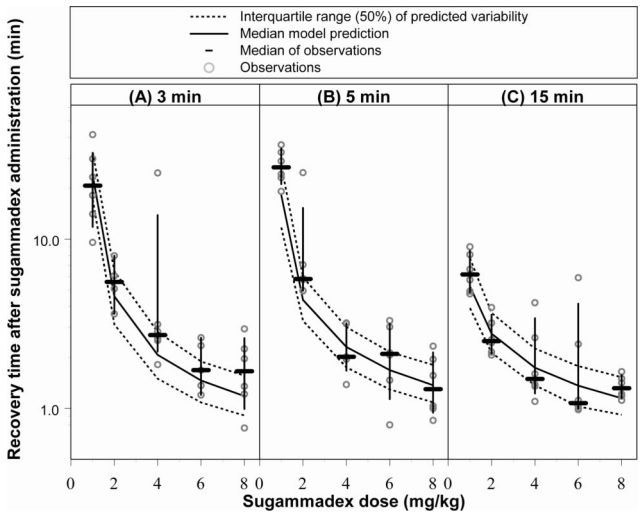

Fig. 4. Visual predictive check of the observed and predicted recovery time (time from sugammadex administration to 90% recovery of the ratio between the first and fourth twitch height after train-of-four stimulation) of rocuronium (0.6 mg/kg)-induced blockade after administration of (*A*) sugammadex 1, 2, 4, 6, or 8 mg/kg at 3 min; (*B*) sugammadex 1, 2, 4, 6, or 8 mg/kg at 5 min; and (*C*) sugammadex 1, 2, 4, 6, or 8 mg/kg at 15 min. The *open symbols* represent the observed recovery time in validation study 2. The median of the observed recovery time is shown by the *closed box symbol*. The *horizontal line* represents the uncertainty (95% CIs) in the observed median derived by bootstrap analysis. The *solid line* shows the predicted median of the recovery time and the variability in the predicted recovery time for 50% of the population is represented by the *dashed lines*.

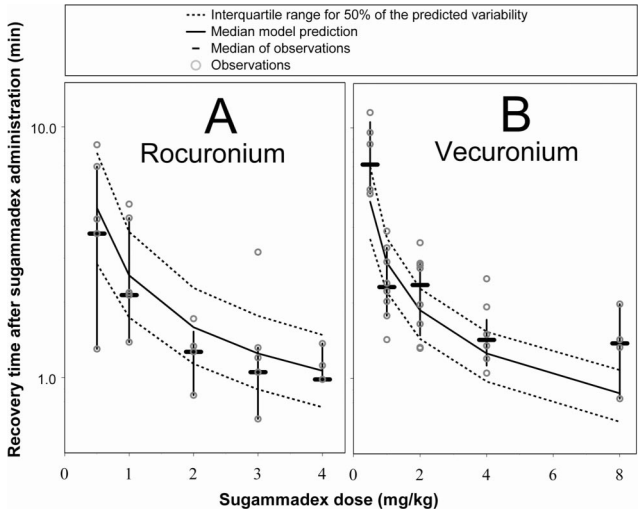

Fig. 5. Visual predictive check of the observed and predicted recovery time (time from sugammadex administration to 90% recovery of the ratio between the first and fourth twitch height after train-of-four [TOF] stimulation) after administration of (*A*) 0.6 mg/kg rocuronium or (*B*) 0.1 mg/kg vecuronium followed by sugammadex at reappearance of the second twitch (T_2) after TOF stimulation. The *open symbols* represent the observed recovery time in validation study 1 (*A*) and validation study 3 (*B*), respectively. The *closed box symbol* shows the median of the observed recovery time. The *horizontal line* represents the uncertainty (95% CIs) in the observed median, derived by bootstrap analysis. The *solid line* shows the predicted median of the recovery time, and the variability in the predicted recovery time for 50% of the population is represented by the *dashed lines*.

that the same mechanism of action also applies to another steroidal neuromuscular blocking drug, vecuronium, since the PK-PD interaction model with vecuronium-specific parameter values could also predict the

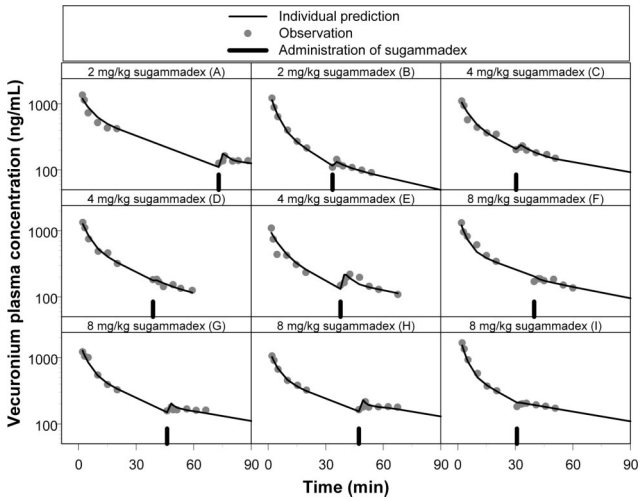

Fig. 6. Observed and predicted vecuronium concentrations after 0.1 mg/kg vecuronium followed by administration of sugammadex at reappearance of the second twitch (T_2) at the following doses (*A*, *B*) 2 mg/kg, (*C–E*) 4 mg/kg, or (*F–I*) 8 mg/kg. The *closed symbols* represent observed vecuronium plasma concentrations in validation study 3. The *solid line* represents individual predicted vecuronium plasma concentrations. The *solid vertical line* shows the administration time of sugammadex at time of reappearance of T_2.

Table 3. Pharmacokinetic and Pharmacodynamic Parameters of the PK-PD Interaction Model for Vecuronium and Sugammadex*

Parameter		Value (CV%)	IIV [%, (CV%)]
PK parameters vecuronium alone			
Clearance	Cl (l/min)	0.32 (9.6)	26 (34)
Central volume of distribution	V1 (l)	4.29 (8.9)	30 (45)
Intercompartmental clearance 1–2	Q2 (l/min)	0.47 (19)	n.a. (n.a.)
First peripheral volume of distribution	V2 (l)	4.25 (16)	n.a. (n.a.)
PK parameters interaction model			
Equilibrium dissociation constant	K_d (μM)	0.175 (—)	n.a. (n.a.)
Dissociation rate constant	K_2 (1/min)	0.00216 (—)	n.a. (n.a.)
PD parameters vecuronium			
Baseline TOF ratio = maximum effect	$E_0 = E_{max}$ (%)	107 (3.1)	9.0 (52)
Concentration at 50% of maximum effect	EC_{50} (ng/mL)	62.3 (24)	27 (61)
Distribution rate constant between first-peripheral and effect compartment	ke0 (1/min)	0.411 (18)	n.a. (n.a.)
Sigmoidicity parameter	γ	3.41 (8.5)	n.a. (n.a.)
Residual variability			
Vecuronium (proportional)	ε_1 (%)	14 (26)	n.a. (n.a.)
TOF ratio (additive)	ε_5 (%)	7.8 (46)	n.a. (n.a.)

* The parameters for sugammadex are listed in Table 2.

CV = coefficient of variation; IIV = interindividual variation; PD = pharmacodynamics; PK = pharmacokinetics; TOF = train of four.

change in vecuronium pharmacokinetics and pharmacodynamics after sugammadex administration.

The model assumes three types of interaction (binding), with increasing complexity: no binding (in the peripheral compartments), binding with instantaneous equilibrium (in the biophase) and noninstantaneous equilibrium (in plasma). It would have been more consistent to assume the same type of interaction (*e.g.,* interaction with noninstantaneous equilibrium) in all compartments. However, this would have resulted in a very complex model. It was preferred to select a parsimonious model by evaluating, for each compartment, whether including a more complex interaction resulted in a better prediction, assuming that noninstantaneous binding in plasma resulted in a better prediction, whereas the assumption of complex formation in the peripheral compartments did not (results not shown). The rapid reversal of NMB could not be predicted without the assumption of complex formation in the biophase (fig. 3). No direct information was available about the rate of distribution of sugammadex to the biophase. Therefore, we assumed this rate to be equal to that of rocuronium. Using this assumption in addition to the simplest assumption of instantaneous equilibrium in the biophase, the observed reversal of NMB could be adequately predicted (fig. 3). Using the assumption of noninstantaneous equilibrium in the biophase, it will take some time to reach equilibrium resulting in a higher free rocuronium concentration in the biophase. This would result in slower reversal, as compared with the assumption of instantaneous equilibrium, which was not observed.

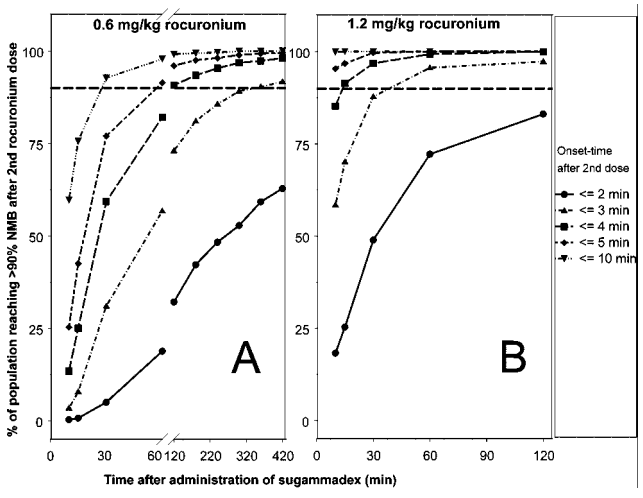

Fig. 7. Predicted percentage of the population with an onset time below a specified threshold of 2, 3, 4, 5, or 10 min after administration of (*A*) rocuronium 0.6 mg/kg or (*B*) rocuronium 1.2 mg/kg administered 10 to 420 min after reversal of rocuronium (0.6 mg/kg)-induced neuromuscular blockade (NMB) by 2 mg/kg sugammadex administered at reappearance of second twitch. The onset time is defined as the time between administration of rocuronium and reaching 90% NMB.

The identified pharmacokinetic parameters for rocuronium are consistent with previously published values.[18] Using a mean body weight of 80 kg for Caucasian patients, the rocuronium *Cl* value of 3.1 ml · min^{-1} · kg^{-1} and *V1* value of 44.8 ml/kg were very close to previously reported values of 3.2 ml · min^{-1} · kg^{-1} and 42 ml/kg,[18] respectively. Also, the pharmacokinetic parameters of vecuronium identified in this study are consistent with previously published values.[19]

The pharmacokinetics of rocuronium appeared to be different in Japanese and Caucasian patients. This difference could not be explained by observed differences in body weight, height, and/or age between the Japanese and Caucasian subpopulation. The estimated values for Cl (0.252 l/min) and V_{ss} (10.2 l) for Japanese patients are close to previously reported *Cl* (0.266–0.315 l/min)

and V_{ss} (10.2–12.7 l) values.[21] The estimated differences in pharmacokinetic parameters between Japanese and Caucasians correspond to a mean difference in total exposure to rocuronium of 17% between Japanese and Caucasians, which is considered not clinically relevant, requiring no dose adjustment.

The pharmacokinetics of sugammadex administered alone and without anesthesia or in the presence of rocuronium with anesthesia was considerably different, with higher sugammadex plasma concentrations in the latter case. This difference is reflected in a 50% lower value for *V2* and *Q2*, in addition to a 2.4-fold higher value for *Q3* and a 52% higher value for *V3* for sugammadex in the presence of rocuronium, as compared with sugammadex alone. Although an effect of complex formation on the pharmacokinetics of sugammadex cannot be excluded, the differences in the distribution of sugammadex with and without rocuronium and anesthesia could also result from anesthesia effects. As regional blood flow is likely to be different in anesthetized patients, this can explain the observed differences in the distribution parameters. However, the observed difference in sugammadex pharmacokinetics does not have clinical implications, since sugammadex will always be administered in the presence of rocuronium and anesthesia.

The model explicitly states that once sugammadex appears in the effect compartment, reversal of NMB is rapid because of the assumption of instantaneous complex formation in the effect compartment. Hence, the distribution of sugammadex to the effect compartment, characterized by *ke0*, is assumed to be the rate-limiting step in the reversal process. However, underprediction of the reversal time for lower sugammadex doses equal to or below 2 mg/kg (fig. 4B) might arise from not considering rate limiting receptor dissociation. The predictions for vecuronium seem to support this hypothesis. As indicated by a lower EC_{50} value, vecuronium has a higher affinity for the nicotinic receptor, as compared with rocuronium. Since the onset of and spontaneous reversal of NMB are slower for vecuronium as compared with rocuronium, it is more likely that the lower EC_{50} is a result of a lower dissociation rate for vecuronium. This would imply that not taking into account the rate of receptor dissociation affects the prediction of reversal of vecuronium-induced NMB to a greater extent than prediction of the reversal of rocuronium-induced NMB. This corresponds to the observation that the PK-PD model adequately predicts the time to reversal of rocuronium-induced NMB after administration of sugammadex 0.5 mg/kg at reappearance of T_2 (fig. 5A), whereas the reversal time is clearly underpredicted for vecuronium-induced NMB after administration of the same sugammadex dose (fig. 5B).

In their theoretical approach, based on simulations with a hypothetical NMB agent and a specific binding agent, Nigrovic *et al.*[22] proposed a model that takes the association and dissociation of nicotinic receptor binding and thereby the fraction of rocuronium bound to the nicotinic receptor into consideration. Their hypothesis is that for predicting the observed fast reversal of NMB the binding agent should diffuse into the effect compartment is consistent with our finding based on actual data. Furthermore, Nigrovic *et al.*[22] showed that a two- to fourfold higher molar dose of sugammadex is required for fast and complete reversal when a binding agent is administered 3 to 5 min after rocuronium. This is consistent with our observation of under-predicting observed reversal time of rocuronium induced NMB after sugammadex doses equal to or below 2 mg/kg (fig. 4B). Our attempts to use a comparable model to the one described by Nigrovic *et al.*[22] suggest that a more complex model is not supported by the available data. Presumably, data after different rocuronium doses are required for identification of the association and dissociation rate constants for the rocuronium receptor binding.

Simulations show that with another rocuronium dose of 0.6 mg/kg administered 120 min after sugammadex, approximately 90% of patients would achieve 90% NMB within 4 min. To reduce the time after sugammadex administration, the rocuronium dose could be increased (*e.g.*, 15 min after sugammadex, reparalysis with rocuronium 1.2 mg/kg would result in 90% NMB within 4 min) or nonsteroidal NMB agents which do not bind to sugammadex (such as cis-atracurium or succinylcholine) could be used.

In conclusion, we used the data from several clinical studies demonstrating the efficacy and safety of sugammadex for reversal of rocuronium-induced NMB to describe the pharmacokinetics and pharmacodynamics of rocuronium after sugammadex administration, using one comprehensive model. Our model-based analysis is consistent with the hypothesis that reversal of rocuronium-induced NMB results from decreased availability of the free rocuronium concentration in plasma and the neuromuscular junction. We showed that the model adequately predicts observed data from other studies that were not used for model development. We were also able to use the same model to predict the observed reversal after vecuronium-induced NMB. Therefore, this model is useful to predict reversal of rocuronium and vecuronium-induced NMB for relevant clinical scenarios.

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References

1. Hunter JM, Flockton EA: The doughnut and the hole: A new pharmacological concept for anaesthetists. Br J Anaesth 2006; 97:123–6

2. de Boer HD, van Egmond J, van de Pol F, Bom A, Booij LH: Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized rhesus monkeys. Anesthesiology 2006; 104:718–23

3. Epemolu O, Bom A, Hope F, Mason R: Reversal of neuromuscular blockade

and simultaneous increase in plasma rocuronium concentration after the intravenous infusion of the novel reversal agent. Org 25969. ANESTHESIOLOGY 2003; 99:632–7

4. Gijsenbergh F, Ramael S, Houwing N, van Iersel T: First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. ANESTHESIOLOGY 2005; 103:695–703

5. Groudine SB, Soto R, Lien C, Drover D, Roberts K: A randomized, dose-finding, phase II study of the selective relaxant binding drug, sugammadex, capable of safely reversing profound rocuronium-induced neuromuscular block. Anesth Analg 2007; 104:555–62

6. Sparr HJ, Vermeyen KM, Beaufort AM, Rietbergen H, Proost JH, Saldien V, Velik-Salchner C, Wierda JM: Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomized multicenter study: Efficacy, safety, and pharmacokinetics. ANESTHESIOLOGY 2007; 106:935–43

7. Sorgenfrei IF, Norrild K, Larsen PB, Stensballe J, Ostergaard D, Prins ME, Viby-Mogensen J: Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: A dose-finding and safety study. ANESTHESIOLOGY 2006; 104:667–74

8. Shields M, Giovannelli M, Mirakhur RK, Moppett I, Adams J, Hermens Y: Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block. Br J Anaesth 2006; 96: 36–43

9. Suy K, Morias K, Cammu G, Hans P, van Duijnhoven WG, Heeringa M, Demeyer I: Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. ANESTHESIOLOGY 2007; 106:283–8

10. de Boer HD, Driessen JJ, Marcus MA, Kerkkamp H, Heeringa M, Klimek M: Reversal of rocuronium-induced (1.2 mg/kg) profound neuromuscular block by sugammadex: A multicenter, dose-finding and safety study. ANESTHESIOLOGY 2007; 107:239–44

11. Sacan O, White PF, Tufanogullari B, Klein K: Sugammadex reversal of rocuronium-induced neuromuscular blockade: A comparison with neostigmine-glycopyrrolate and edrophonium-atropine. Anesth Analg 2007; 104:569–74

12. Danhof M, de Jongh J, De Lange EC, Della Pasqua O, Ploeger BA, Voskuyl RA: Mechanism-based pharmacokinetic-pharmacodynamic modeling: Biophase distribution, receptor theory, and dynamical systems analysis. Annu Rev Pharmacol Toxicol 2007; 47:357–400

13. Bom A, Bradley M, Cameron K, Clark JK, Van Egmond J, Feilden H, MacLean EJ, Muir AW, Palin R, Rees DC, Zhang MQ: A novel concept of reversing neuromuscular block: Chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. Angew Chem Int Ed Engl 2002; 41:266–70

14. Beal SL, Sheiner LB, Boeckmann AJ. *NONMEM users guides.* Ellicott City, Maryland; Icon Development Solutions; 1989–2006

15. Post TM, Freijer JI, Ploeger BA, Danhof M: Extensions to the Visual Predictive Check to facilitate model performance evaluation. J Pharmacokinet Pharmacodyn 2008; 35:185–202

16. Wierda JM, Proost JH, Schiere S, Hommes FD: Pharmacokinetics and pharmacokinetic/dynamic relationship of rocuronium bromide in humans. Eur J Anaesthesiol Suppl 1994; 9:66–74

17. Plaud B, Proost JH, Wierda JM, Barre J, Debaene B, Meistelman C: Pharmacokinetics and pharmacodynamics of rocuronium at the vocal cords and the adductor pollicis in humans. Clin Pharmacol Ther 1995; 58:185–91

18. De Haes A, Proost JH, Kuks JB, van den Tol DC, Wierda JM: Pharmacokinetic/pharmacodynamic modeling of rocuronium in myasthenic patients is improved by taking into account the number of unbound acetylcholine receptors. Anesth Analg 2002; 95:588–96

19. Zhang L, Beal SL, Sheiner LB: Simultaneous *versus* sequential analysis for population PK/PD data II: Robustness of methods. J Pharmacokinet Pharmacodyn 2003; 30:405–16

20. Eleveld DJ, Kuizenga K, Proost JH, Wierda JM: A temporary decrease in twitch response during reversal of rocuronium-induced muscle relaxation with a small dose of sugammadex. Anesth Analg 2007; 104:582–4

21. Suzuki T, Saeki S, Takeda J, Ozaki M, Iwao Y: Neuromuscular blocking effects, pharmacokinetics and safety of Org 9426 (rocuronium bromide) in Japanese patients [Article in Japanese]. Masui 2006; 55:419–27

22. Nigrovic V, Bhatt SB, Amann A: Simulation of the reversal of neuromuscular block by sequestration of the free molecules of the muscle relaxant. J Pharmacokinet Pharmacodyn 2007; 34:771–88