

# Reversal of rocuronium-induced neuromuscular block by cyclodextrin Org 25969: model development and validation



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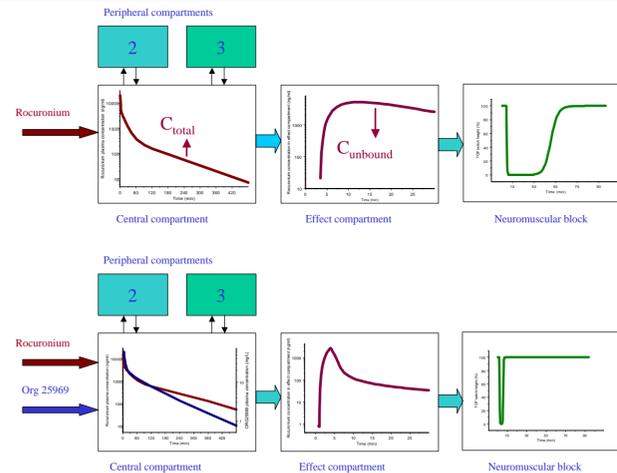


## Introduction

Org 25969 is a chemically optimized cyclodextrin designed to selectively bind to rocuronium, leading to a reversal of rocuronium-induced neuromuscular block (NMB)[1]. It is hypothesized that the reversal of rocuronium-induced NMB after administration of Org 25969 is due to a decrease in the unbound rocuronium concentration. This hypothesis was evaluated and validated using a model-based analysis. In addition, it was evaluated whether the *in vitro* dissociation constant, determined by isothermal microcalorimetry, is an adequate predictor of the complexation process *in vivo*. After validation of this hypothesis, the model can be applied for simulation of clinically relevant questions, such as selecting the dose schedule for optimal reversal of rocuronium-induced neuromuscular block.

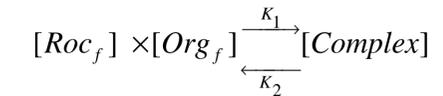
## Hypothesis

Due to specific complexation between rocuronium and Org 25969 the unbound rocuronium concentration will decrease. Consequently, the rocuronium-induced NMB will be reversed, since NMB is related to the unbound rocuronium concentration



## Model structure : Dynamic interaction model

Hysteresis between association of rocuronium to and dissociation from the Org 25969-rocuronium complex.



- The dissociation rate constant  $k_2$  was optimized
- $K_d = 0.1 \mu M$  (*in vitro* dissociation constant)
- PK of Org 25969 and the Org 25969-rocuronium complex are comparable (i.e. a three-compartmental model for Org 25969 and complex).

## Methods

### Development PK-PD model for rocuronium alone

A population PK-PD model was developed for rocuronium alone on phase-I study data, in which 10 healthy male subjects received a bolus dose of 0.6 mg/kg rocuronium. Rocuronium (arterial and venous) plasma concentration was sampled and the rocuronium-induced NMB was determined by the AMG-derived TOF ratio. A three compartmental model with first order elimination was used to model the PK of rocuronium. A hypothetical effect compartment was linked to the first peripheral compartment of the PK model and the effect of the concentration in this effect compartment was modeled using a sigmoid  $E_{max}$  model [2]. NONMEM V was used for optimization of the population mean and the inter-individual variability in the model parameters and to determine the individual-specific parameter values (posthoc's) [3].

### Development dynamic interaction model

The dynamic interaction model was optimized on data from a phase I trial, in which 0.1 – 8 mg/kg Org 25969 i.v. was administered alone to 17 male subjects on two separate occasions (Part I) and 3 minutes after a bolus dose of 0.6 mg/kg rocuronium (Part II). Data from the same subjects (n=10), who also received a bolus dose of 0.6 mg/kg rocuronium alone, were used to optimize the PK-PD model for rocuronium alone. In Part I, the subjects were awake during the whole study, whereas in Part II general anesthesia was maintained. A three compartmental model with first order elimination was used to model the PK of Org 25969. It was assumed that the PK of the rocuronium-Org 25969 complex is comparable with the PK of Org 25969 alone and can also be described with a three compartmental model, using the individual specific PK parameters for Org 25969. The dissociation constant  $K_d$  was fixed to the *in vitro* dissociation constant of 0.1  $\mu M$ . The first order dissociation rate constant of the rocuronium-Org 25969 complex ( $k_2$ ) was optimized to the data.

### Predictability PK-PD interaction model

The optimized dynamic interaction model was linked to the PD model for rocuronium alone and applied for prediction of reversal of rocuronium-induced NMB after administration of 0.1 – 8 mg/kg Org 25969. The neuromuscular blocking effect of rocuronium was related to the fraction unbound rocuronium in the hypothetical effect compartment. Instantaneous equilibrium was assumed between bound and unbound rocuronium in the effect compartment, which was calculated with the equation below, using the total concentration of rocuronium ([D]) and Org 25969 ([P]) in the effect compartment and a  $K_d = 0.1 \mu M$ .

$$f_u = \frac{2K_d}{([P] - [D] - K_d) + \sqrt{([P] - [D] - K_d)^2 + 4K_d[P] + 2K_d}}$$

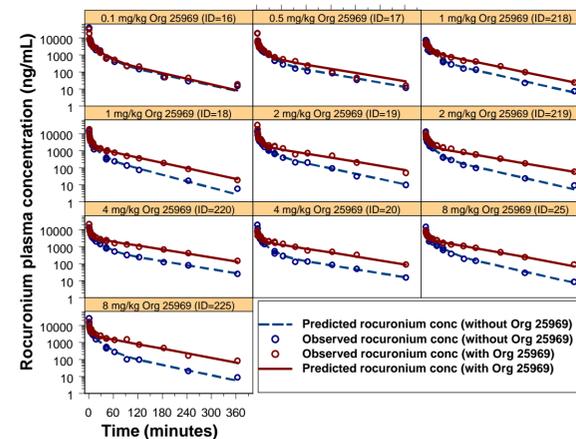
The PD parameters for rocuronium ( $E_{max}$ ,  $EC_{50}$ ,  $k_{e0}$  and  $g$ ) were fixed to the individual-specific parameters of the PK-PD model for rocuronium alone.

### External validation PK-PD interaction model

The developed PK-PD interaction model was validated using a predictive check, in which both the observed rocuronium plasma concentration and reversal of rocuronium induced NMB after administration of 0 – 8 mg/kg 3 minutes after 0.6 mg/kg rocuronium to 33 subjects that were scheduled for surgical procedures with an anticipated duration of anesthesia of at least 75 minutes (Phase II data). In a predictive check the outcome of this trial was simulated for 1000 hypothetical subjects by means of a Monte Carlo simulation using the developed PK-PD interaction model. Differences in the position and overlap of the simulated and observed distribution shows the validity of the developed model to adequately predict the observed data.

## Development dynamic PK interaction model

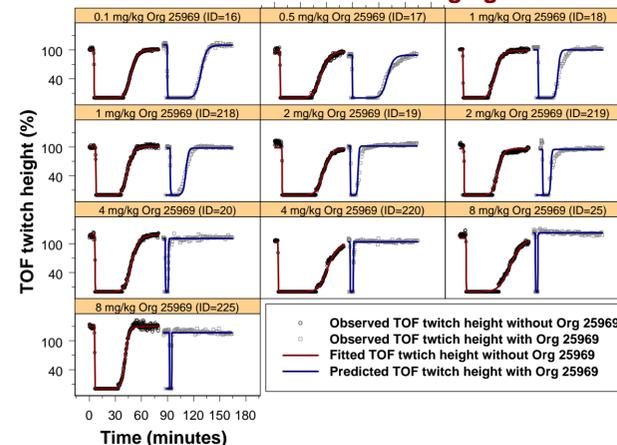
PK rocuronium after 0.6 mg/kg with and without Org 25969 (0.1-8 mg/kg) (Phase I data)



- Adequate prediction of observed increase in the rocuronium plasma concentration after Org 25969 administration using the *in vitro*  $K_d$  of 0.1  $\mu M$
- Optimized dissociation rate constant ( $k_2$ ) = 0.002  $min^{-1}$

## Predictability PK-PD interaction model

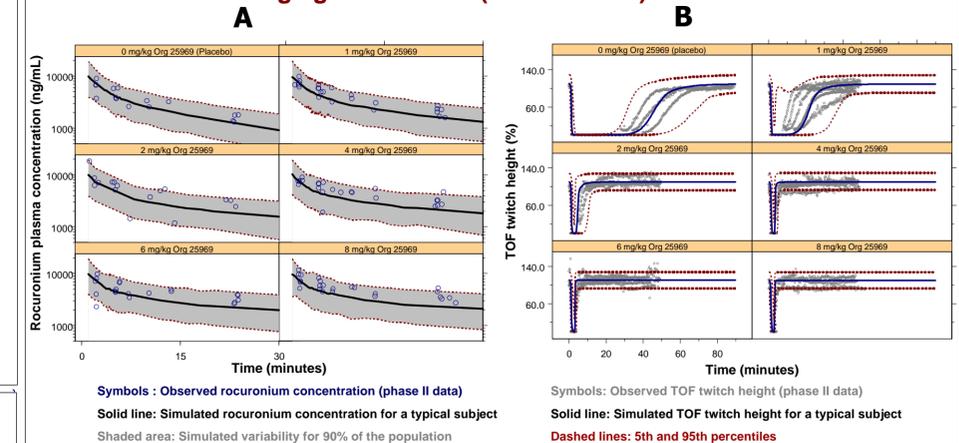
Reversal of rocuronium induced NMB after 0-8 mg/kg Org 25969 administered 3 minutes after 0.6 mg/kg rocuronium (Phase I data)



- After fixing the individual specific posthoc-estimates of the PK-PD model for rocuronium alone, the dynamic interaction model predicts the observed reversal of rocuronium-induced NMB after administration of 0.1 – 8 mg/kg Org 25969 adequately

## External validation of PK-PD interaction model

(A) Observed and simulated variability in PK of rocuronium and (B) reversal of rocuronium-induced NMB after 0-8 mg/kg Org 25969 administered 3 minutes after 0.6 mg/kg rocuronium (Phase II data)



## Conclusions

- Model based evaluation showed that the reversal of rocuronium-induced NMB by Org 25969 is due to a rapid decrease of the unbound rocuronium concentration.
- The pharmacokinetic interaction between Org 25969 and rocuronium can be adequately predicted using the *in vitro* dissociation constant, which is determined by isothermal microcalorimetry.
- The observed variability in the PK of rocuronium and reversal of rocuronium-induced NMB of a phase II study that was not used for model optimization can be adequately simulated by the dynamic PK-PD interaction model

[1] Angew.Chem.2002, 114(2), 275-279  
 [2] Europ.J.Anesthesiol. 1994, 11(Suppl. 9), 66  
 [3] NONMEM Users Guides. Version V., San Francisco: NONMEM project group; UCSF