A Mechanism-based Pharmacokinetic Model Describing the Interaction Between Sugammadex and Rocuronium in Patients with Normal and Impaired Renal Function

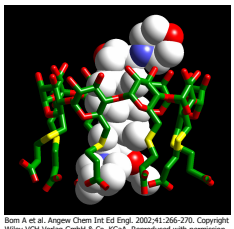
J. Smeets[1], B. Ploeger[1], A. Strougo[1], L. Liefaard[1], T. Kerbusch[2]

[1] LAP&P Consultants BV, Leiden, The Netherlands; [2] Organon, a part of Schering-Plough Corp., Oss, The Netherlands

Contacts: J.Smeets@lapp.nl; B.Ploeger@lapp.nl

Introduction

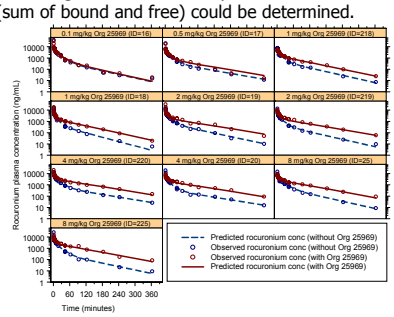
Sugammadex is a novel neuromuscular block reversal agent that acts by encapsulating the steroidal neuromuscular blocking agent rocuronium. Complex formation causes a reduction of the free rocuronium concentration in the circulation which causes an initial net flux of rocuronium from the peripheral compartments to the circulation, resulting in increased plasma concentrations of total (bound plus free) rocuronium.



Bom A et al. Angew Chem Int Ed Engl. 2002;41:266-270. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

The clearance of total rocuronium is decreased because sugammadex and the complex are primarily renally excreted at a slower rate than free rocuronium, which is also hepatically excreted. Bioanalytical separation of bound and free rocuronium and sugammadex was not possible, which means that only the total (sum of bound and free) could be determined.

The figure at the right shows the individual observed and predicted rocuronium plasma concentrations after administration of 0.6 mg/kg rocuronium and a placebo administration of Org 25969 (sugammadex) (dashed line) or 0.1 – 8 mg/kg Org 25969 (solid line) 3 minutes after rocuronium.



Aim

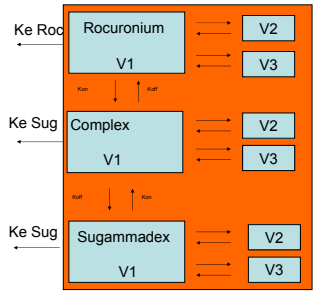
To model the pharmacokinetic interaction between rocuronium and sugammadex in patients with normal and impaired renal function based on phase I, II and III clinical data.

Methods

- Population pharmacokinetic analysis with NONMEM V.
- Development of a PK model for rocuronium in Caucasian and Japanese patients with normal renal function.
- Update of rocuronium PK model after inclusion of data from renal impaired patients. Model based upon 238 subjects from seven trials.
- Internal validation and external validation of rocuronium PK model with PK data from 26 normal and severely renally impaired (SRI) patents using visual predictive checks (VPC).
- Development of the PK interaction model for rocuronium-sugammadex: Post-hoc estimates of unbound rocuronium PK parameters were fixed. Model was fit to total (bound+unbound) sugammadex and rocuronium PK data from 147 subjects with normal and severely impaired renal function from three trials. Subjects received 0.1 – 8.0 mg/kg sugammadex at various time points after rocuronium.
- Covariates effects were investigated by first including in the model all covariates that caused a significant improvement of the objective function value (MVOF) and then excluding them stepwise, retaining only the ones that caused a significant improvement of the MVOF.
- PK interaction model was validated using internal and external datasets.

Model Structure

PK: Model structure : Dynamic interaction model



Sugammadex and rocuronium both have 3-compartmental kinetics.
The model assumes that the PK of the sugammadex-rocuronium complex is similar to that of sugammadex and that complex formation occurs in the central compartment only.
PK parameters of sugammadex and the complex were estimated simultaneously, based on plasma concentrations of sugammadex and rocuronium.
Hysteresis between association of rocuronium to and dissociation from the sugammadex-rocuronium complex is described by the association and dissociation rate constants Kon and Koff:

$$[Roc]\times[Org] \underset{K_{off}}{\overset{Kon}{\rightleftharpoons}} [Complex]$$

The association constant Ka (=Kon/Koff) was fixed to the value determined in vitro by microcalorimetry ($17.9*10^6$ M^{-1}).
The dissociation rate Koff was optimized.

Conclusions

- **The updated population PK model for rocuronium is suitable for simulations up to 5 h post dose after a single i.v. dose of 0.6 to 1.2 mg/kg. in normal and renal impaired subjects. Clearance was decreased in renal impaired patients, while other PK parameters were not affected. This leads to prolonged higher rocuronium concentrations (bound in complex) in renal impaired patients.**
- **The population PK interaction model could accurately describe the observed PK of rocuronium and sugammadex in a series of clinical trials confirming the mechanism of PK interaction.**

Results and Visual Predictive checks

Severe renal impairment (SRI) was included in the PK model of rocuronium and in the Dynamic interaction model (DIM) as a categorical covariate on Clearance (CL). Due to limitations in the data it was not possible to correlate CL to creatinine clearance. In the DIM model SRI is also a categorical covariate on Q2, V2, Q3 and V3. Clearance of rocuronium was reduced by 44% in SRI patients compared to normal patients, which is close to the reported values of 39%[1] and 32% [2]. Clearance of sugammadex was reduced 10-fold in SRI patients compared to normal patients.

PK-model rocuronium alone

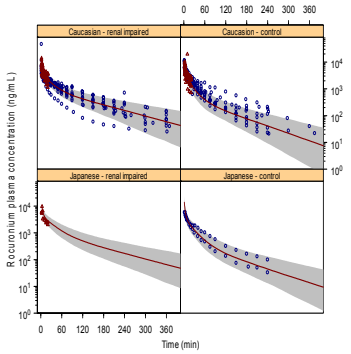
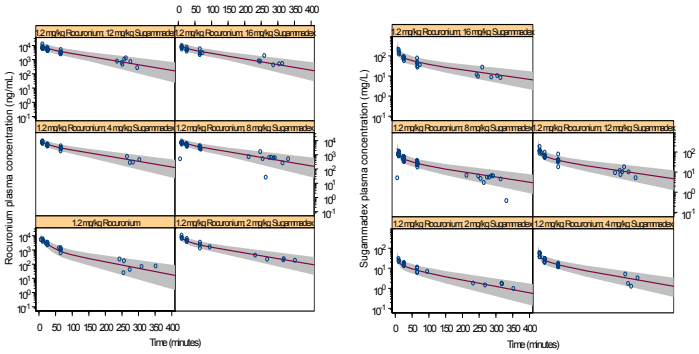


Figure 1. Validation of the PK model rocuronium alone (incl. the effect of renal impairment) using internal and external data. Shaded area represents the predicted variability in rocuronium plasma concentration for 90% of the population. Solid line shows the predicted rocuronium concentration for a typical subject. The observed rocuronium plasma concentrations in study CT 194.304 (external data) are shown as red triangles, whereas the observed data from study CT 021-009 (internal data) are shown as blue circles.

PK interaction model sugammadex and rocuronium



A B

Figure 2. External validation for the PK interaction model for rocuronium (Panel A) and sugammadex (Panel B) plasma concentration after 1.2 mg/kg of rocuronium and 0-16 mg/kg of sugammadex to surgical patients at 5 min after the administration of rocuronium. The data are shown relative to the administration of sugammadex.

References

[1]Robertson, E.N., Driessen J.J., Booij L.H (2005). Pharmacokinetics and pharmacodynamics of rocuronium in patients with and without renal failure. Eur J Anaesthesiol. 2005 Jan;22(1):4-10.

[2] Cooper R.A., Mirakhur R.K., Wierda J.M., Maddineni V.R (1995). Pharmacokinetics of rocuronium bromide in patients with and without renal failure. Eur J Anaesthesiol Suppl. 1995 Sep;11:43-4