Mitigation of rocuronium induced residual neuromuscular blockade risk by means of a population PK/PD model

Miriam Happ[a,b], Leandro F. Pippa[b], Gabriela Lauretti[c], Anthony Gebhart[b], Günther Weindl[a], Francine Azeredo[b], Valvanera Vozmediano[b], Stephan Schmidt[b], Natalia De Moraes[b]

[a] Pharmacology and Toxicology Section, Pharmaceutical Institute, University of Bonn, Germany.
[b] Center for Pharmacometrics and System Pharmacology, Department of Pharmaceutics. College of Pharmacy. University of Florida, FL, USA
[c] School of Medicine of Ribeirao Preto, University of Sao Paulo, SP, Brazil.

Introduction

- High interindividual variability in recovery time of rocuronium[1]
- Frequent occurrence of residual neuromuscular blockade puts patients at higher risk for postoperative pulmonary complications[2]
- Identify impacting factors on variability in recovery time
- Reduce risk for residual neuromuscular block
- Inform dose adjustments and risk assessment

Methods

- 32 patients undergoing elective surgeries[3]
- 395 plasma concentrations
- 242 TOF ratio measurements
- Develop NLME model[4]
- Internal model validation
- Simulate covariate groups (100 patients per group)[5]
- Estimate recovery times and residual neuromuscular block risk[5]

TOF ratio: Train of Four ratio, Measurement for neuromuscular function (see Figure 2)

Modelling Workflow

Data review
↓
Structural model and residual error model
↓
Pharmacokinetic covariate model (forward inclusion, backward deletion)
↓
Correlation of population parameters and random effects
↓
Fixed pharmacokinetic parameters for pharmacodynamic model development
↓
Exposure response relationship
↓
Pharmacodynamic covariate model (forward inclusion, backward deletion)
↓
Correlation of population parameters and random effects
↓
Joint pharmacokinetic/pharmacodynamic model for simulations

Pharmacokinetic/Pharmacodynamic Model

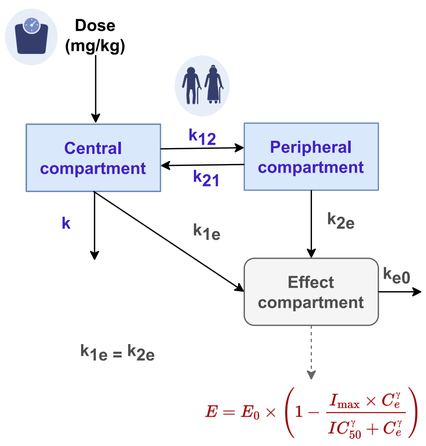


Figure 1: *Structure of pharmacokinetic (PK, blue)-pharmacodynamic (PD, red) joint model.*

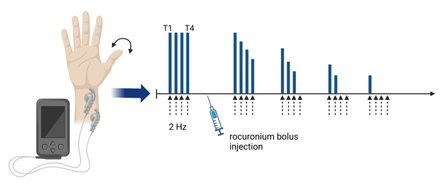


Figure 2: *Measurement of Train of Four (TOF ratio = T4/T1) at the adductor pollicis muscle as quantitative measurement of neuromuscular function.* [6]

Bootstrap (n = 500) median estimates for joint model		
	Parameter (P5–95)	**CV (P5–P95)**
V (L/kg)	0.063 (0.055–0.071)	26.4% (21.2%–32.8%)
k (h^{-1})	2.26 (2.06–2.50)	18.1% (12.0%–24.3%)
k_{12} (h^{-1})	2.51 (1.99–3.09)	48.5% (31.8%–60.7%)
k_{21} (h^{-1})	1.33 (1.14–1.54)	41.7% (26.4%–53.3%)
β_k_{12}_logtAGE	0.68 (0.46–0.98)	
IC_{50} (mg/L)	0.61 (0.45–0.75)	55.7% (28.6%–76.7%)
γ	12.12 (9.01–15.96)	68.5% (37.2%–99.6%)
k_{e0} (h^{-1})	15.34 (11.71–22.06)	
E_0	1.00 (fixed)	
Correlations		
corr_k_{12}_k_{21}	0.87 (0.67–0.93)	
Error Model parameters		
bCONC	0.25 (0.23–0.27)	
aTOF	2.42 (1.94–2.79)	

CV: Coefficient of Variation, V: central volume of distribution, k: elimination rate, k_{12}, k_{21}: transfer rates between compartments, β_k_{12}_logtAGE: age covariate parameter on k_{12}, IC_{50}: half maximum inhibitory concentration, γ: shape factor, ke0: elimination rate from effect compartment, E_0: baseline effect, aTOF: additive residual error, bCONC: proportional residual error.

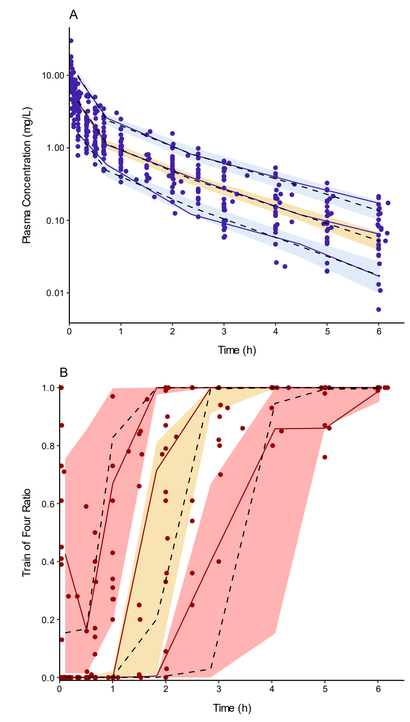
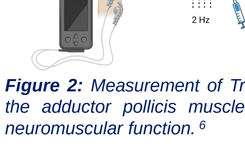


Figure 3: *Visual predictive checks of PK (A, blue) and PD (B, red) of the joint model, with observed data (●), empirical 10th, 50th, and 90th percentiles (—), model-predicted 10th, 50th, and 90th percentiles (- -) and prediction intervals.*

Clinical Implications

Pre-Surgery:

Dose individualization based on patient age, body weight and anticipated surgery length



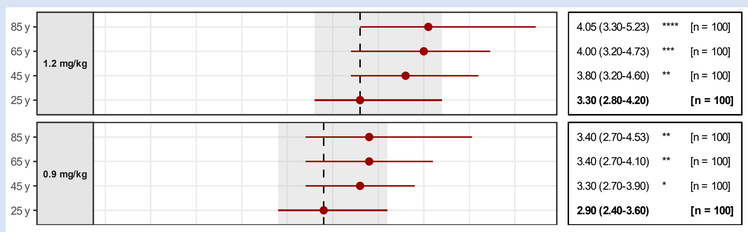
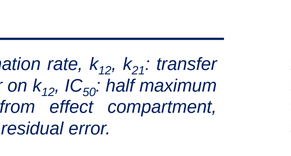


Figure 4: *Simulated recovery time (time to TOF ≥ 0.9), groups defined as average age ± 0.1 SD, same individuals across doses. 45, 65, and 85-year-old groups compared to 25-year-old group (—) by Mann-Whitney U test.[7] $p < 0.05$. (*) $p < 0.05$; (**) $p < 0.01$; (***) $p < 0.001$; (****) $p < 0.0001$.*

During Surgery:

Continuous monitoring and risk assessment before extubation to assess need for reversal agents and state of recovery



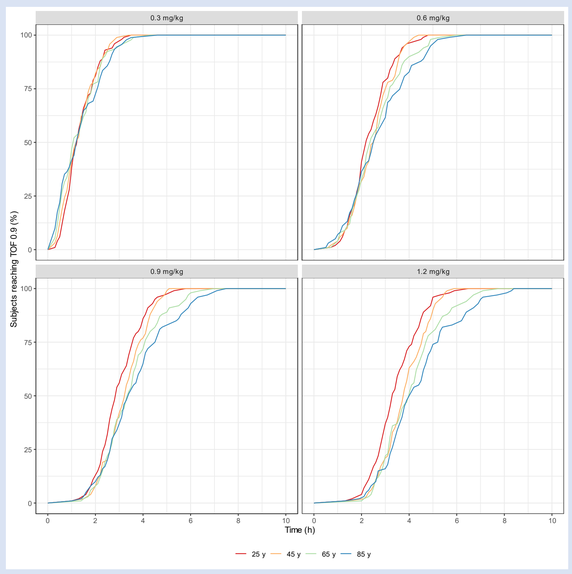
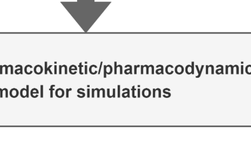


Figure 5: *Percentage of recovered simulated patients over time (recovered: TOF ≥ 0.9), groups defined as average age ± 0.1 SD, same individuals across doses. Subjects not achieving TOF < 0.9 were excluded.*

Post-Surgery:

Safe extubation after full recovery is achieved at TOF ratio ≥ 0.9



Conclusions

- Geriatric patients are at higher risk for residual neuromuscular blockade
- Model shows promising opportunities for application to
  - Reduce risk of residual neuromuscular block
  - Reduce need for expensive reversal drugs
  - Model informed precision dosing

Future Directions

- External validation and extension to other patient populations
- Bayesian Estimation tool to support multiple dosing
  - Incorporating real-time TOF measurements
  - Developing easy to use bedside tool for clinicians

References

(1) Maybauer et al. Anesthesia 62: 12-17 (2007)
(2) Murphy et al. Anesth Analg 107: 130-137 (2008)
(3) Varrique et al. J Pharm Pharmacol 68: 1351-1358 (2016)
(4) Monolix 2021R1, Lixoft SAS, a Simulation Plus company
(5) Simulx 2023R1, Lixoft SAS, a Simulation Plus company
(6) Figure was modified from Boon et al. F1000Research 167 (2018)
(7) R Statistical Software (4.2.2; R Core Team 2022)
Elements of Figure 1, Figure 2 and Icons in this poster were created with Biorender.com