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

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Objectives: Residual neuromuscular blockade (RNB) is a common complication when using neuromuscular blocking agents (NMBA). Extubating patients with RNB increases their risk for pulmonary complications, such as airway obstruction and severe hypoxemia.[1] This study aimed to optimize dosing of rocuronium, a nondepolarizing NMBA, and reduce the risk of RNB using a population-based pharmacokinetic/pharmacodynamic (PK/PD) model.

Methods: A nonlinear mixed effect model was developed for rocuronium in patients under general anesthesia, using dose ranging (0.3–1.2 mg/kg total body weight) data from 32 patients. Total plasma concentrations and the neuromuscular block [train-of-four ratio (T4/T1)][2] were assessed up to 6 h after dosing (PK: 395 observations; PD: 242 observations). A sequential approach was used to build the PK/PD model in Monolix™ 2021R1. Age, body mass index, estimated glomerular filtration rate, serum creatinine and gender were tested as covariates. The model was used to simulate the recovery time (T4/T1 ≥ 0.9) for different age groups using Simulx™ and R.

Results: A two-compartment model with linear elimination from the central compartment described the PK of rocuronium. The transfer rate into the peripheral compartment increases with age. The PK model was linked to the PD model through an effect compartment including equal input rates from both central and peripheral compartments ($k_{1e} = k_{2e}$). This approach captures the fast onset and delayed clinical duration of rocuronium. The PD model consists of a sigmoid I-max model that captured the recovery time at different age and dose groups. The predicted median recovery times are longer for elderly patients compared to younger adults and show an increased interindividual variability in the elderly. This PK/PD model can be helpful to assess risk for residual block and assist in dose recommendations dependent on age and total bodyweight using the predicted percentage of patients experiencing RNB at the end of the surgery. It further stresses the importance of monitoring neuromuscular function in the elderly.

Conclusion: A population-based PK/PD model was developed to assist optimal dosing and reduce the risk of RNB. The recovery time is longer in elderly patients than in younger adults due to higher amounts of drug in the periphery caused by an age-dependent increase in tissue uptake. The performed simulations allow to better assess the risk of RNB at the approximate end of the surgery time. It thereby informs individual dosing and the potential need for reversal agents and reduces the risk for RNB to stay undetected. Obtaining a posteriori predictions via Bayesian estimation may help to inform adjustments on redosing prematurely recovered patients using individual PD measurements, further mitigating this risk.

References:

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