Predicted Concentration Against Measured Concentration of Rocuronium by Published Six Pharmacokinetics Models During Continuous Infusion is Lower than that After Single Bolus

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Background: Published population pharmacokinetic models of rocuronium, which are applicable to predict plasma concentration, were developed using samples obtained after bolus without additional doses. The aim of this study was to compare the predictive performance of six published pharmacokinetic models of rocuronium after bolus without additional doses and that during continuous infusion.

Methods: After our institutional review board approval, the registration to a public clinical trial registry, and written informed consent were obtained, we recruited patients undergoing elective surgery. Patients with severe hepatic, renal, or cardiovascular disease, neuromuscular disease, a history of rocuronium allergy, body mass index greater than 30 kg/m^2, and those receiving medications known to influence neuromuscular function were excluded. Anesthesia was induced and maintained with propofol and remifentanil. Patients received 0.6 mg/kg rocuronium at 0.25, 0.5, 0.75, or 1 mg/kg/min, then trachea was intubated. When the train-of four count recovered to 1 or 2, or if necessary, a continuous infusion of rocuronium was started at 4-13 mg/kg/h over 30-240 min. The infusion rates for bolus and continuous infusion was randomly allocated to patients. Blood samples (1 mL each) were drawn via a radial artery as follows: (1) until the start of a continuous infusion of rocuronium; before, at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 150, and just before the start of continuous infusion; (2) during the continuous infusion of rocuronium; 0.5, 1, 2, 4, 8, 15, 30, 45, 60, then every 30 min, and just before the end of the continuous infusion. Plasma rocuronium concentrations were determined using high-performance liquid chromatography with electrochemical detection. Prediction error, defined as ('measured concentration' – 'predicted concentration') / 'predicted concentration' x 100 (%), was calculated for each sample. Individual median prediction error (MDPE) was calculated for the samples collected after the end of bolus before the start of the continuous infusion (MDPE_bolus) and that for the samples collected during the continuous infusion (MDPE_infusion). For each assessed pharmacokinetic models, developed by Wierda, Szenohradszky, Magorian, Cooper,

Alvarez-Gomez, and Kleijn, MDPE_bolus and MDPE_infusion was compared using Welch's t test. A P value <0.05 was regarded as significant. The data was expressed as mean±SD.

Results: Thirty-seven patients (15 males and 20 females; total body weight, 57±9 kg; height, 160±9 cm; age, 58±15 years) were included for the analysis. The MDPE_bolus *vs* MDPE_infusion were −5.5±22.6% *vs* −32.4±24.1% (P <0.001) in the Wierda model, −20.2±17.3% *vs* −50.4±18.8% (P <0.001) in the Szenohradszky model, 7.6±28.6% *vs* −33.3±26.0% (P <0.001) in the Magorian model, 4.1±25.8% *vs* −30.2±24.6% (P <0.001) in the Cooper model, 15.4±27.1% *vs* −17.1±30.0% (P <0.001) in the Alvarez-Gomez model, and −25.0±17.1% *vs* −44.8±20.2% (P <0.001) in the Kleijn model, respectively.

Conclusions: The MDPE_bolus was significantly higher than the MDPE_infusion in all assessed models, which means a measured concentration after bolus without infusion was higher than that during infusion for a predicted concentration on those models. Population pharmacokinetic model of rocuronium, which is developed based on both bolus and infusion dose regimens, is desired.