Saline Flush Following Rocuronium Bolus Changes Rocuronium Pharmacokinetics

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Background: We previously reported that administering a 20-mL saline flush immediately after infusion of 0.6 mg/kg rocuronium bolus shortened the onset time and prolonged the recovery phase of neuromuscular blockade.[1] It is unlikely that 20-mL saline flush changes rocuronium potency. Therefore, we hypothesized that an infusion of saline flush immediately after rocuronium bolus influences rocuronium pharmacokinetics.

Methods: Patients with an ASA physical status I or II, aged 20 to 80 years, and scheduled for elective surgery were recruited. Patients were randomly allocated to the control or saline flush group. Anesthesia was induced and maintained with propofol and remifentanil, and patients received 0.4, 0.6, or 0.8 mg/kg of rocuronium in 10-mL normal saline through a three-way stopcock which was directly connected to the intravenous catheter. In the saline flush group, 20-mL normal saline was infused immediately after the rocuronium administration. Blood samples were collected through a radial artery catheter before, 15, 30, 45, 60, 75, 90, 105, 120 s and 3, 3.5, 4, 5, 7, 10, 12, 15, 20, 30, 45, 60, 80, 100, 120, 150, 180, 240, 300 and 360 min after rocuronium administration. Plasma rocuronium concentrations were determined using high-performance liquid chromatography. Population pharmacokinetic modeling was performed using NONMEM 7.3. First, we determined a basic model structure among the following models: 2-, 3- or 4-compartment models, 2-, 3- or 4-compartment models with a standard lag time and/or a chain of presystemic compartment. Secondly, when the final basic model had a lag time and/or presystemic compartments, we assessed whether different lag times and/or different transit rate constants (K_{tr}, from a presystemic compartment to a sequential compartment) for each group (control or saline flush group) significantly improved the pharmacokinetic model. Thirdly, we examined possible covariates including total body weight, height, age, sex, heart rate just before rocuronium administration, creatinine clearance for each model parameter. A decrease in objective function value, which is −2 log-likelihood calculated by NONMEM, by 7.88 was considered as a significant improvement of the model. The data was expressed as mean±SD or median [range]. Mann-Whitney's U test was used for the comparison. $P < 0.05$ was considered as significant.

Results: We analyzed the data from seventy-two patients (60.6±10.5 kg, 163.4±9.1 cm, 46.4±19.2 years, male/female 38/34, heart rate 55.5±8.5 beats/min, and creatinine clearance 106.9±32.9 mL/min, mean±SD). The final model was described as a 4 compartment model with a lag time and two presystemic compartments. The lag time and Ktr were different between groups (Table). The total body weight and heart rate were included in the final model as covariates for V1 and lag time of the control group, respectively. The model parameters were shown in Table. The peak predicted concentrations in the control and saline flush group using the final *post-hoc* model were 20.8 [13.6-52.7] and 37.8 [8.1-65.6] (0.4 mg/kg, P =0.046), 23.5 [6.6-70.1] and 62.2 [17.3-146.2] (0.6 mg/kg, P =0.001), 40.0 [19.4–63.8] and 61.4 [37.7–142.8] (0.8 mg/kg, P =0.007).

Conclusion: A 20-mL saline flush immediately after rocuronium bolus changes rocuronium pharmacokinetics.

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Parameter	value
V_1	0.654 + 0.00463 (body weight – 60)
V_2	1.45
V_3	5.50
V_4	1.67
CL_1	0.300
CL_2	0.338
CL_3	0.133
CL_4	1.68
LAG (control)	0.335 – 0.00921 (heart rate – 50)
LAG (saline flush)	0.224
K_{tr} (control)	10.6
K_{tr} (saline flush)	42.9