Pharmacokinetics and pharmacodynamics of rocuronium in young adult and elderly patients undergoing elective surgery

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Abstract

Objective To evaluate the impact of advanced age on rocuronium kinetic disposition in ASA I–III patients undergoing elective surgeries.

Methods Young adult (20–50 years, n = 15) and elderly patients (65–85 years, n = 14) submitted to surgery under general anaesthesia were investigated. All patients were induced with individual intravenous doses of midazolam, rocuronium, fentanyl and propofol. Rocuronium-induced neuromuscular block was monitored by train of four stimulations of the adductor muscle of the thumb on the ulnar nerve. The pharmacokinetic parameters were calculated by non-compartmental analysis. The relationship between rocuronium plasma concentration and the neuromuscular blockade was described by a sigmoidal Emax model.

Key-findings Elderly patients presented decreased Cl (2.1 ml/kg per min vs 2.8 ml/kg per min; P = 0.0123); increased AUC/dose (507.8 l g min/ml (mg/kg) vs 392.2 l g min/ml/(mg/kg); P = 0.0168) and reduced volume of distribution (285.4 ml/kg vs 435.6 ml/kg, P = 0.0434) compared to young adults. The concentrations required to achieve 50% of maximum neuromuscular block (EC50) were similar for young adult (338.8 ng/ml) and elderly (462.7 ng/ml) patients (P > 0.05).

Conclusions Elderly patients showed increased AUC/D and reduced total Cl compared to young adult patients due to the age-related reduced renal function. Differences in the PK-PD properties of rocuronium in elderly population are due to changes in drug disposition rather than to alterations in the sensitivity to the drug.

Introduction

Pharmacokinetic and pharmacodynamic processes can be changed not only by the normal ageing process, but also because of age-related diseases. Studies investigating the influence of ageing on drug kinetic disposition deserve special attention because world population is ageing, not only in developed regions, but also in less developed regions. Pharmacokinetic alterations in the elderly can be attributed to the lower gastric pH and higher duodenal pH, reduced blood flow to the gastrointestinal tract and slower gastric emptying, which can significantly alter the bioavailability of certain drugs. The total body water reduces while body fat increases with ageing thus resulting in reduced volume of distribution of hydrophilic drugs and increased volume of distribution of lipophilic drugs. Ageing is also associated with a reduction in plasma albumin concentrations. However, changes in α1-acid glycoprotein concentration are absent. The renal function and kidney size decrease with age due to loss of renal mass of both glomeruli and cortical region. Glomerular filtration rate (GFR) and renal blood flow decrease. The liver volume and hepatic blood flow also reduce with age. Considering the diversity of factors that could affect drug disposition, only clinical trials in elderly population can provide accurate evidences for...
dose adjustment to increase the safety margin of drugs used in this special population.

Rocuronium (ROC) is a neuromuscular non-depolarizing blocking agent of intermediate duration and rapid onset of action used during general anaesthesia to facilitate endotracheal intubation, artificial ventilation and the surgical procedures. Its elimination occurs mainly unchanged via biliary excretion depending on hepatocellular sequestration by OATP1A2, but also by renal excretion. In humans, rocuronium is excreted into bile in very high concentrations and its recovery in faeces within 7 days was 30% of administered dose in humans. In cats, the biliary excretion and storage in the liver represented 76% of rocuronium dose in cats. The fraction of rocuronium dose excreted unchanged in urine achieves 26% after 48 h of administration.

The drug is characterized by a large variability in terms of kinetic disposition and pharmacodynamics. The incidence of residual paralysis at the end of surgery following ROC administration was 44%. In terms of age, elderly patients have similar onset of neuromuscular blocking effect to that of young adult patients, with time to maximum block of 4.5 and 4.1 min, respectively. However, the duration of action of rocuronium is significantly prolonged in elderly patients. The present investigation aimed to evaluate whether the differences in the time for recovery from rocuronium-induced neuromuscular block are due to changes in the kinetic disposition of rocuronium. Elderly patients aged >65 years and young adults aged 18–50 years submitted to surgical procedures under general anaesthesia using midazolam, fentanyl, rocuronium and propofol were investigated.

Methods

Patients

Brazilian patients of both genders with surgical indication of small to medium-sized procedures and admitted at the Clinical Hospital of the Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP) were investigated. The study protocol was approved by the institutional review board (Research Ethics Committee of the School of Pharmaceutical Sciences of Ribeirão Preto–USP – Certificação number 071/2012). The study was conducted in accordance with Good Clinical Practice and to the ethical principles of the Declaration of Helsinki. All patients were informed of the clinical protocol as well as possible risks and gave their written informed consent.

Fifteen young adult patients (n = 15; 20–50 years, control group) and fourteen elderly patients (n = 14; 65–85 years; elderly group) were investigated. The demographic and clinical characteristics of patients included in present investigation are shown in Table 1. The sample size was calculated through the Power and Sample Calculation program version 2.1.30 (Vanderbilt University Medical Center, Nashville, TN, USA) based on the investigation of 15 patients with ASA I–II treated iv rocuronium, with AUC values of 296 ± 110 μg min/ml (mean ± standard deviation). A sample size of 14 patients in each group would be sufficient to detect a difference between averages of 40% with type I error probability of 5% and power of 80%.

The exclusion criteria were as follows: (1) patients taking drugs that influence rocuronium pharmacokinetics of pharmacodynamics (selective serotonin receptor inhibitors, antiepileptics, aminoglycoside antibiotics) or OATP1A2 inhibitors such as rifampicin and verapamil; (2) patients with gastrointestinal or liver disease, morbid obesity or other conditions known to interfere with the distribution or excretion of rocuronium; patients with neuromuscular disorders; (3) evidence of HIV or hepatitis C infection; and (4) pregnant patients and lactant patients.

Clinical protocol

All patients fasted for at least 10 h before surgery. During the hospital stay, the standard monitoring of patients included the monitoring of hypnosis, neuromuscular transmission, peripheral and central temperature, capnography, continuous arterial blood pressure, heart rate and oxygen saturation. Midazolam 0.03–0.06 mg/kg was given intravenously to all patients as premedication for sedation. The study was conducted only in patients under anaesthesia with intravenous propofol, as it does not change the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical characteristics of ASA I–III patients submitted to general anaesthesia using rocuronium as neuromuscular blocker (n = 29)</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td></td>
<td>Young adult patients (n = 15)</td>
</tr>
<tr>
<td></td>
<td>Elderly patients (n = 14)</td>
</tr>
<tr>
<td>Female</td>
<td>(n = 9)</td>
</tr>
<tr>
<td>Male</td>
<td>(n = 6)</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.5 (28–50)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>77.1 (56–92)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 (19.8–33.7)</td>
</tr>
<tr>
<td>ALbumin (g/dl)</td>
<td>4.2 ± 0.3</td>
</tr>
<tr>
<td>ASA Classification</td>
<td>I (n = 15)</td>
</tr>
<tr>
<td>ClCr* (ml/min)</td>
<td>88.1 ± 16.9</td>
</tr>
</tbody>
</table>

BMI, body mass index; *ClCr, creatinine clearance. "Estimated from the equations of Cockcroft and Gault using ideal body weight instead of total body weight." ASA: Classification of the American Society of Anesthesiology of physical healthy: I – completely healthy fit patient; II – patient has mild systemic disease; III – patient has severe systemic disease that is not incapacitating; IV – patient has incapacitating disease that is a constant threat to life; V – a moribund patient who is not expected to live 24 h with or without surgery. Data are expressed as mean (range) or mean ± standard deviation.
Patients were induced with propofol intravenous slowly, as indicated by the anaesthesiologist. The opioid fentanyl (2–3 μg/kg iv) was administered as the pharmacokinetic profile of fentanyl was not changed by age or the presence of liver or biliary dysfunction. Rocuronium was used intravenously as neuromuscular blocker at intravenous bolus doses of 0.3–0.9 mg/kg. The antibiotic prescribed by the attending surgeon was maintained.

After ROC administration, blood samples were collected (4 ml) at times 0, 2, 5, 10, 15, 20, 30, 60, 120, 180, 240 and 360 min for the pharmacokinetic analysis. Blood samples were collected by venipuncture in heparin-containing tubes and then centrifuged at 5000g for 10 min at 4 °C. To each sample, 0.2 ml of 1 M monobasic sodium phosphate was added per 1 ml of plasma to avoid hydrolysis of the drug. Samples were stored at −20 °C until analysis.

The neuromuscular transmission was employed as pharmacodynamic parameter of the ROC, using the train of four (TOF) responses of the adductor pollicis muscle resulting from stimulation of the ulnar nerve (2 Hz for 2 s, peripheral nerve stimulator, Stimuplex (Braun, Melsungen, Germany)). The TOF monitoring was performed at the same times of blood sampling.

**GFR estimation**

Glomerular filtration rate (GFR) was assessment of renal function that is estimated based on serum creatinine values. Creatinine, an endogenous product of muscle metabolism, is completely filtered by the renal glomeruli and is not reabsorbed nor secreted. Several equations have been used to estimate the glomerular filtration rate, such as Cockcroft–Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). However, all these equations (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). However, all these equations described the renal function in elderly patients.

In geriatric population, the CG formula, slightly overestimates the renal function in elderly patients. The CG formula, slightly overestimates the renal function in elderly patients. The CG formula, slightly overestimates the renal function in elderly patients. In geriatric population, the CG formula, slightly overestimates the renal function in elderly patients. However, all these equations described the renal function in elderly patients.

The glomerular filtration rate was estimated by CG using ideal body weight: GFR (in ml/min): \[
\frac{[140 – \text{age (in years)}] \times \text{ideal body weight (in kg)}}{[72 \times \text{serum creatinine (in mg/dl)}]}^{[25]}
\]
The ideal body weight (IBW) is defined for men (in kg) as: 50 + 0.9 × [length (in cm) − 152]; and IBW for women (in kg) as: 45.5 + 0.9 × [length (in cm) − 152]

**Analysis of rocuronium in plasma**

The concentration of rocuronium in plasma was analysed by liquid chromatography coupled with mass spectrometry, as described previously by our research group. Rocuronium and the internal standard verapamil were resolved on reversed phase column LiChroSpher® 100 RP-18e Sorbent (Merck, Darmstadt, Germany) with 125 × 4 mm, 5 μm particle size, maintained at 25 °C and a mobile phase consisting of mixture of water: acetonitrile (50 : 50, v/v) added with 0.1% trifluoroacetic acid, flow at 1.0 ml/min. Briefly, samples of 120 μl of the mixture plasma, 1 m sodium phosphate buffer pH 3.0 (5 : 1 v/v), were added to 1 m phosphate buffer (50 μl), 25 μl of internal standard solution (verapamil, 100 ng/ml) and 100 μl of a saturated solution of KI. The samples were extracted using 2 ml of dichloromethane for 30 min using a horizontal reciprocant shaker. After centrifugation, the organic lower phase was separated and evaporated up to dryness. The residues were reconstituted in mobile phase and injected into the chromatographic system. The method was linear in the range of 5–2000 ng of ROC/ml of plasma, and the limit of quantification was 5 ng/ml. The relative standard deviation and relative error of the quality controls did not exceed 15%.

**Pharmacokinetic and pharmacodynamic analysis**

The pharmacokinetic parameters calculated for rocuronium were area under the curve plasma concentration versus time extrapolated to the infinity \((\text{AUC}_{0-\infty})\), \(\text{AUC}_{0-\infty}\) normalized by dose (\(\text{AUC/D}\)), total clearance (\(\text{CL}\)), mean residence time (\(\text{MRT}\)) and volume of distribution (\(\text{Vd}\)). These parameters were estimated by non-compartment analysis using Phoenix WinNonlin version 6.3 software (Pharsight Corp., Mountain View, CA, USA), with intravenous dose bolus administration.

The relationship between rocuronium plasma concentration and the percentage of neuromuscular block was described by a sigmoidal maximum effect \((E_{\text{max}})\) model using Phoenix WinNonlin version 6.3 software (Pharsight Corp.). The baseline effect was fixed at 0%. The concentration required to achieve 50% of \(E_{\text{max}}\) \((EC_{50})\) of 954 ng/ml and Hill coefficient \((\gamma)\) of 2.9 reported for ASA I–II young adult patients undergoing elective surgical procedures using ROC were used as initial estimates.

The sigmoidal \(E_{\text{max}}\) model can be described by the equation:

\[
E_t = \frac{E_{\text{max}} \times C_t^\gamma}{EC_{50}^\gamma + C_t^\gamma}
\]

where, \(E_t\) is the effect at time \(t\); \(C_t\) is the plasma concentration at time \(t\); \(EC_{50}\) is the plasma concentration, which produces 50% of maximum response, and \(\gamma\) is the slope factor or Hill coefficient.
Statistical analysis

Statistical tests were performed using GraphPad Instat® software (version 3.10, San Diego, CA, USA). The independent groups were compared using t-test for unpaired data. Pearson correlation test was performed to evaluate the correlation between creatinine clearance and total clearance of ROC. The significance level was fixed to 5% (P < 0.05).

Results

The present investigation was performed in patients submitted to surgical procedures under general anaesthesia using rocuronium, including young adults with ages ranging from 28 to 50 years (n = 15) and elderly aged 65–88 years (n = 14), nine women in the young adult group and seven women in the elderly group. The body mass index (BMI) values (mean ± standard deviation) were 26.1 ± 3.6 and 26.9 ± 3.5 kg/m² for young adult and elderly, respectively. While all patients included in the young adult group were classified as ASA I (healthy patients, n = 15), most patients in the elderly group were classified as ASA II (n = 12) due to mild systemic diseases like hypertension, dyslipidemia or osteoporosis which are age-related diseases. One male patient in the elderly group, aged 77 years, was classified as ASA III due to the presence of hypertension, diabetes and congestive heart failure. Nine patients included in the elderly group had moderate reduction in glomerular filtration rate with creatinine clearances of 30–59 ml/min/1.73 m² (Table 1). Creatinine clearance in elderly patients was significantly reduced when compared to young adults (P < 0.0001).

Rocuronium kinetic disposition after intravenous bolus doses of 0.3–0.9 mg/kg based on plasma concentration versus time curves revealed increased in AUC₀–∞/D (507.8 (µg min/ml)/(mg/kg)) in aged patients compared to young adults (392.2 (µg min/ml)/(mg/kg)) (P = 0.0168). The increased exposure was followed by the reduced total clearance (2.1 ml/(kg min) vs 2.8 ml/(kg min), P = 0.0123) and higher mean residence time (94.4 min vs 71.2 min, P = 0.0139; Table 2; Figure 1). The volume of distribution

<table>
<thead>
<tr>
<th>Group</th>
<th>AUC/dose (µg min/ml/(mg/kg))</th>
<th>Cl (ml/(kg min))</th>
<th>Vd (m/kg)</th>
<th>MRT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young adult (n = 15)</td>
<td>392.2 (328.6–455.9)*</td>
<td>2.8 (2.3–3.2)*</td>
<td>435.6 (310.7–560.6)*</td>
<td>71.2 (56.2–86.1)*</td>
</tr>
<tr>
<td>Elderly (n = 14)</td>
<td>507.8 (433.3–582.2)</td>
<td>2.1 (1.8–2.4)</td>
<td>285.4 (233.0–337.8)</td>
<td>94.4 (83.0–105.7)</td>
</tr>
<tr>
<td>P</td>
<td>0.0168</td>
<td>0.0123</td>
<td>0.0434</td>
<td>0.0139</td>
</tr>
</tbody>
</table>

AUC/dose, area under the curve plasma concentration vs time extrapolated to the infinity (AUC) normalized by dose; Cl, total clearance; MRT, mean residence time; Vd, volume of distribution. Data presented as means (95% confidence interval). *Unpaired t-test, P < 0.05.

Figure 1  Pharmacokinetic parameters in young adult and elderly patients treated with intravenous single dose of rocuronium (0.3–0.9 mg/kg) during elective surgery under general anaesthesia. AUC/dose: area under the curve plasma concentration versus time extrapolated to the infinity (AUC) normalized by dose; Cl, total clearance; Vd, volume of distribution; MRT, mean residence time. The pharmacokinetic parameters were estimated using non-compartmental analysis.

of ROC was reduced in elderly (285.4 ml/kg) when compared to young adults (435.6 ml/kg; \( P = 0.0434 \); Figure 1).

To measure the correlation between the two variables ROC clearance and creatinine clearance or between ROC clearance and age, the Pearson rank correlation was performed. A strong positive correlation was found between ROC clearance and creatinine clearance \( (P < 0.0001) \), and a negative correlation was found between ROC clearance and age \( (P = 0.0042, \text{Figure 2}) \). No sex differences were observed on rocuronium kinetic disposition \( (P = 0.8255) \).

Rocuronium-induced neuromuscular block was assessed by the train of four stimulations on the ulnar nerve up to 6 h after drug administration. Although the study was not powered to look at the pharmacodynamic profiles, the sigmoidal \( E_{\text{max}} \) model was fitted to the data from 10 young adult patients and 12 aged patients and either the concentrations needed to achieve 50% of maximum neuromuscular blockade \( (EC_{50}) \) and Hill coefficient \( (\gamma) \) were not different between young adult and aged patients (Table 3). The predicted neuromuscular effect of ROC based on sigmoidal \( E_{\text{max}} \) model for each young adult and elderly patient is presented on Figure 3. The weighted residuals (WRES) vs predicted neuromuscular blockade plot at Figure 3 show that all data lie within one unit from the zero ordinate.

**Discussion**

The physiological changes of ageing can alter the kinetic disposition of drugs interfering with the mechanisms of absorption, distribution, metabolism and elimination but also the pharmacodynamic processes. Such changes result in a greater variability in both pharmacokinetics and pharmacodynamics in this special population compared to young adults.\(^1\)\(^2\)\(^3\) Ageing is characterized by reduced creatinine clearance as the size of the kidneys, renal blood flow and glomerular filtration rate decrease with age.\(^8\)\(^9\) After 40 years of age, glomerular filtration rate reduces, on average, 1 ml/min/1.73 m\(^2\) per year. Although the reason is not completely known, studies indicate that in addition to the loss of renal mass, hypertension and kidney disease are the major reasons for this reduction in the elderly.\(^7\) It is relevant to point out that this investigation included young adults up to 50 years and elderly over the age of 65. Whereas an adult of 64 years would have very similar kidney function to an elderly 65, a difference of at least 15 years of age between the two groups sought to maximize the difference between the groups. In the present investigation, a significant decrease in creatinine clearance in elderly was observed when compared with creatinine clearance in young adults \( (P < 0.0001) \).
The increased exposure in elderly can be explained by the reduced total clearance and higher mean residence time (Table 2; Figure 1). Whereas ROC metabolism is considered absent in humans and considering the renal and biliary excretion are the main ROC elimination pathways,\textsuperscript{[13]} the reduction in clearance ROC in the elderly can be partially explained by reduced creatinine clearance in this population. Rocuronium metabolism is considered absent in humans despite the identification of 17-desacetyl-rocuronium in the early fractions of bile, and urine, in amounts corresponding to 0.4% and 0–0.5% of dose, respectively. This compound was also identified on the ROC ampoules at levels of 2% and 4% in release of the lot and expiration date, respectively, suggesting that the 17-desacetyl-rocuronium is an impurity and not a biotransformation product.\textsuperscript{[13]}

Considering that the fraction of dose eliminated unchanged in urine is only 0.26 for rocuronium,\textsuperscript{[13,15,16]} patients with reduced renal function to half of young adult capacity would only show a reduction of 13% on rocuronium total clearance. Another hypothesis to explain the reduced clearance of ROC in elderly patients when compared to young adult patients is the age-induced reduction on liver volume and hepatic blood flow.\textsuperscript{[8,9]} The drug carrier OATP1A2 mediates the hepatic uptake ROC. Therefore, its activity seems to be a limiting factor of the ROC elimination rate for bile duct.\textsuperscript{[12]} However, the influence of ageing on OATP1A2 activity is still now known.

Increased body fat and decreased total body water and lean body mass are also observed in the elderly. Such changes explain the reduction in volume of distribution of hydrophilic drugs in the elderly when compared to young adults,\textsuperscript{[3]} such as observed for ROC in the present investigation (Table 2, Figure 1). Patients with morbid obesity were excluded of the present investigation to avoid confounding factors that could mask the age-related alterations. ROC pharmacokinetics is not altered in obese when compared to lean patients probably due to the low lipophilicity of the drug.\textsuperscript{[28]} However, the duration of action was prolonged in obese patients when ROC is dosed according to either the real body weight or ideal body weight.\textsuperscript{[29–31]} The clinical evidences suggest that dosing should be performed using ideal body weight in these special population.\textsuperscript{[30,31]}

In the present study, the neuromuscular transmission was monitored using mechanomyography (MMG) after the train of four stimulations of the ulnar nerve. MMG has been considered for many years the gold standard technique for evaluating the pharmacodynamics of neuromuscular blockers. On the other hand, acceleromyography (AMG) is simple, readily available and has been increasingly replacing MMG in clinical and research settings. However, to ensure optimal acceleration measurements

### Table 3
Pharmacodynamic analysis of rocuronium after intravenous single doses of 0.3–0.9 mg/kg in young adult and elderly patients undergoing elective surgery under general anaesthesia

<table>
<thead>
<tr>
<th>Group</th>
<th>$EC_{50}$ (ng/ml)</th>
<th>$\gamma$, Hill coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Adult ($n = 10$)</td>
<td>338.8 (299.6–753.2)</td>
<td>2.0 (1.14–2.82)</td>
</tr>
<tr>
<td>Elderly ($n = 12$)</td>
<td>462.7 (409.4–721.5)</td>
<td>3.4 (2.0–4.3)</td>
</tr>
</tbody>
</table>

$p$-Values: $P_{0.5543}$ 0.0968

Data presented as means (95% confidence interval). *Unpaired t-test, $P < 0.05$.

### Figure 3
Predicted neuromuscular effect of rocuronium vs plasma concentration in elderly ($n = 12$, full symbols) and young adult patients ($n = 10$, empty symbols) (a); weighted residuals (WRES) vs predicted neuromuscular blockade plots (b). The sigmoidal maximum effect model was used to predict the pharmacodynamic parameters $EC_{50}$ and Hill coefficient.
following ulnar nerve stimulation using AMG, it is proposed to leave the thumb totally free while other fingers should be fixed on an armboard. Several situations can affect the quality of measurements using AMG, and thus, several anaesthesiologists are reluctant to adopt AMG instead of MMG. The interferences with the thumb’s movement include (1) movements of the surgical team when in contact with the arm; (2) the restrictive role of the adhesive tapes on the patient’s hand; and (3) possible contact of the thumb with other fingers, the palm or the patient’s thigh when the arm is positioned alongside the body. 

Recent data show that the incidence of postoperative residual neuromuscular blockade is 57.7% in the elderly and 30.0% in young patients. Although the study design was not powered based on pharmacodynamic data, the pharmacodynamic study was conducted to evaluate whether the differences observed in the PK-PD of ROC in elderly patients were due to alterations in the PK, in the PD or both. The plasma concentrations required to achieve 50% of the maximum neuromuscular blockade (EC50) were similar between the two groups (338.8 ng/ml in young adults, and 587.7 ng/ml in the elderly, respectively) (Figure 3). The differences in PK-PD properties between elderly and young adults can be attributed to differences in the pharmacokinetics rather than to differences in the drug sensitivity.

Conclusion

Elderly patients undergoing elective surgeries under general anaesthesia showed increased AUC/dose, reduced clearance and reduced volume of distribution of rocuronium compared to young adult patients. Reduced clearance in elderly is partially explained by the age-related reduced creatinine clearance. Future work should look at the impact of age on OATP1A2 activity as well as the impact of OATP1A2 pharmacogenetics to the kinetic disposition of rocuronium. Differences in the PK-PD properties of ROC in elderly population are due to changes in drug disposition rather than to alterations in the sensitivity to the drug. The reduced total clearance and volume of distribution of ROC explain the need of reduced doses of the drug in the elderly compared to young adults.

Declaration

Conflict of interest

All Authors declare that there are no competing interests. This work was supported by Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) and Programa de Apoio ao Desenvolvimento Científico (PADC-FCF). The authors thank the pharmacist Gabriela Filgueira and the anaesthesiologist Bruno Lopes for help in sample and study participant data collection.

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