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PHARMACOKINETICS AND DISPOSITION

Pharmacokinetic–pharmacodynamic modeling of the influence of chronic phenytoin therapy on the rocuronium bromide response in patients undergoing brain surgery

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Abstract
Background Antiepileptic drugs decrease the intensity of the effect of neuromuscular blocking agents. The objective of this study was to evaluate the influence of chronic phenytoin therapy (CPT) on the pharmacokinetics (PK) and pharmacodynamics (PD) of rocuronium.
Methods A total of 21 patients undergoing intracranial surgery were enrolled in the study. Ten of these were under CPT. Rocuronium was administered intravenously. Arterial blood samples were drawn, and the T1% (percentage change from the response to the supramaximal stimulus) derived from electromyogram was continuously recorded. NONMEM software was used to construct, evaluate and validate the PKPD models.
Results The PKPD of rocuronium was described using a three-compartment PK model and effect compartment model. The CPT therapy was found to increase the total plasma clearance from 0.26 to 0.75 L min^{-1}. The PD model parameter estimates were k_{e0}= 0.073 min^{-1}, IC_{50} (the steady-state plasma concentration eliciting half of the maximum response) = 836 ng mL^{-1} and γ = 3.13.
Conclusions: Chronic phenytoin therapy increases the clearance of rocuronium from 0.26 to 0.75 L min^{-1} but has no effect on the k_{e0}, IC_{50} or γ parameters.

Keywords Drug interactions · NONMEM · Population PKPD · Rocuronium

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Introduction

Antiepileptic drugs alter the time course of the effect induced by most neuromuscular blocking agents (NMBA). Therefore, to achieve a defined level of effect, NMBA dosing must be increased in the presence of chronic antiepileptic therapy [1]. It has been reported that a patient receiving chronic phenytoin therapy (CPT) or other antiepileptic drugs may possibly show a so-called "resistance" to the effects of NMBA [2–8]. Such phenomena can be caused by pharmacokinetic (PK) and/or pharmacodynamic (PD) alterations, and the best approach to clarify the mechanism of the "resistance", is to carry out a PKPD analysis of the time course of the response to NMBA.

Wright et al. used a PKPD analysis to determine the cause of the increase in the dose requirements of

vecuronium in patients receiving phenytoin chronically, which, to the best of our knowledge, is the only work addressing this problem using a population modeling approach. These authors reported that total plasma clearance and IC_{50} (the steady-state plasma concentration eliciting half of the maximum response) were significantly increased in the group of patients chronically medicated with phenytoin [2].

Rocuronium bromide is a non-depolarizing steroidal NMBA. It is mostly eliminated in unchanged form in either urine or bile, with 10% being metabolized to hydrophilic forms by decarboxylation, presumably by CYP3A4, a subunit of the P450 cytochrome system [1], although this mechanism has not been confirmed. The influence of antiepileptic drugs on rocuronium has been studied, but as yet it has not been demonstrated whether the observed increased levels of rocuronium required to maintain a certain degree of neuromuscular blocking effect are attributable to PK or PD mechanisms [6, 9].

The objective of this project was to study the PK and PD of rocuronium bromide in the presence or absence of CPT using population analysis modeling to estimate whether CPT could influence the time course of the effect of rocuronium by affecting PK and/or PD mechanisms.

Material and methods

Study design

With the approval of the Ethics Committee of the Hospital Clinic of Barcelona and after obtaining written informed consent from the participants, we enrolled 21 patients scheduled to undergo brain surgery in this observational, open label, non-randomized clinical study. Ten patients were in the CPT group, defined as having received phenytoin as the only antiepileptic drug for at least 7 days prior to surgery [2]. The remaining 11 patients were not receiving phenytoin or any other antiepileptic drug. Patients with liver or renal insufficiency were not included in the protocol. The study was designed according to the Good Clinical Research Practice for Pharmacokinetic Studies of Neuromuscular Blocking Agents as published in Viby-Mogensen et al. [10].

Anesthetic management

Three hours before being brought into the operating room, patients received 5 mg of diazepam as an oral dose. Upon arrival in the operating room, routine monitoring according to the accepted neurosurgical anesthesia protocols of our hospital was started: pulse oximetry; electrocardiogram; arterial line (for continuous blood pressure monitoring).

Before starting the induction of anesthesia, baseline samples were drawn to estimate the pre-surgical plasma concentrations of phenytoin, α_1-acid glycoprotein, albumin, and total protein levels; a blank sample without rocuronium was also taken. A sample of the rocuronium infusate was drawn to assess the exact amount of rocuronium infused to the patient.

Propofol (2 mg kg^{-1}) was used as the hypnotic agent for induction and maintenance of anesthesia, analgesia was provided by means of a continuous infusion of remifentanil (0.01–0.5 μg kg^{-1} min^{-1}) adjusted in accordance with on clinical requirements. Laryngoscopy and intubation were performed once the bolus dose of rocuronium had been injected and the surgeons had received assurance that the maximal effect was achieved.

Pharmacokinetics

Rocuronium administration

Rocuronium concentration was 10 mg mL^{-1} for the bolus dose and a 2 mg mL^{-1} solution for the maintenance infusion. To avoid undesired movement during laryngoscopy and intubation, rocuronium was administered to the patient as a bolus of 3 × $ED_{95\%}$ (0.9 mg kg^{-1}; $ED_{95\%}$ is the effective dose in 95% of patients). Single twitch height was used as the measure of rocuronium effect as explained below. After the patient recovered up to a twitch height of 25% of control twitch, a continuous intravenous infusion was started; this was adjusted during the whole procedure to maintain one response of the train of four or to clinical requirements warranting an adequate level of immobility during the whole surgical procedure until the surgeons started closing the skull, at which time the infusion was stopped. Several changes in infusion rate were made during the procedure in accordance with ongoing data on the increase and decline of effect.

Blood sampling scheme

Based on prior information on the PK model of rocuronium [11], we carried out a simple simulation exercise to decide a sampling scheme that would allow the estimation of reliable parameters defining the PK model. Briefly, PK profiles for a sample of 20 individuals were simulated under different measurement sampling designs, and model parameters were estimated from the simulated profiles and subsequently compared with the ones used in the simulations. Based on the results of the simulations, we decided to draw arterial blood samples (5 mL) at 1.5, 3, 6, 10, 30, 60 min after the bolus injection and at hourly intervals thereafter until the end of the infusion, and at 10, 30, 60 and 120 min after the rocuronium infusion was stopped. The

blood samples were centrifuged at 10 *g* and 2 mL plasma was extracted from each sample and frozen at −80°C for transport and analysis at a later date.

Determination of rocuronium and phenytoin in plasma

Concentrations of rocuronium in plasma were analyzed by high-performance liquid chromatography with post-column ion-pair extraction and fluorimetric detection [12]. The assay accuracy was 5% over the range of 10–1000 ng mL^{-1}. The mean precision, as indicated by the within-day coefficients of variation, was 6.8% for rocuronium. The lower limit of quantification (LOQ) for rocuronium was 10 ng mL^{-1} in plasma.

Serum phenytoin was measured in all patients using an enzyme inmunoassay involving the inhibition of agglutination (Immulite 2500; DP Corp, Los Angeles, CA), which is the analytical technique routinely used to monitor therapeutic levels of phenytoin in epileptic patients at our institution.

Pharmacodynamics

While the patient was routinely monitored, electrodes for the electromyographic quantification of the neuromuscular blocking effect of rocuronium were placed, in accordance with the manufacturer's instructions (M-NMT Module; Datex Ohmeda, Helsinki, Finland), on the arm ipsilateral to the brain lesion. The electromyogram of the adductor pollicis was recorded using five disposable Ag/AgCl electrodes placed as follows: two stimulating electrodes along the ulnar nerve at the wrist, two recording electrodes (one at the adductor pollicis and the second on the lateral surface of the index finger) and one ground electrode between the stimulating and the recording electrodes. The arm was kept still by means of a rigid plastic frame to minimize movement artifacts and covered with drapes to avoid hypothermia that might alter the estimation of effect. The temperature of the arm was continuously monitored.

The M-NMT system was calibrated after the administration of propofol and remifentanil but before the administration of rocuronium, as described elsewhere [8]. Pulses of 200 μs, at a rate of 2 Hz, were administered, starting from 10 mA, followed by increments of 5 mA. The maximal current obtained was then increased by 15%, yielding the supramaximal stimulation. The system was set to deliver a supramaximal train of four stimulations (200 μs, at 2 Hz) every 12 s for an equilibration period of 5 min. A train of four (TOF) stimulations was given at 20-s intervals.

The percentage change from the response to the supramaximal stimulus, the so-called T1%, was continuously collected, recorded and stored. The exact times of rocuronium administration, changes in infusion rate and exact sampling times were also automatically collected online using the software program S5-COLLECT ver. 3.0 (Datex-Ohmeda, Helsinki, Finland). The resolution was one data point per second, and all data were stored in a computer hard drive for subsequent analysis.

Data analysis

The PK and PD data were fitted sequentially under the population approach using the first-order conditional estimation (FOCE) method with the INTERACTION option implemented in the software NONMEM ver. V [13]. First, the plasma concentration C) versus time profiles of rocuronium were described and then the individual model-predicted estimates of the PK parameters were used to model the time course of the response data. The PK data were logarithmically transformed. Inter-patient variability (IPV) was modeled exponentially using the expression $\theta_1 = \theta_{TV} x e^{\eta i}$, where θ_I, is the estimate of the parameter in the i-th individual, θ_{TV}, corresponds to the typical estimate of the parameter, and η_i represents the deviation between θ_i and θ_{TV}. The set of η_s constitutes a random variable symmetrically distributed around 0 and with variance ω^2. Residual variability was described with an additive error model (which in the case of the PK data corresponds to a logarithmic error).

The stepwise generalized additive model (GAM) approach was used to identify the potential important covariates and their functional relationships with the model parameters [14]. The GAM approach was performed with S-PLUS using the XPOSE software ver. 3.011 [15]. Covariates selected during the GAM approach were then evaluated individually in NONMEM. Those covariates that showed a level of significance of P=0.05 were tested and incorporated, one at a time, until the full covariate model was obtained (forward inclusion). Following the forward inclusion, a backward elimination was performed on a significance level of P=0.01.

Selection between models was based on the precision of the model parameter estimates, the visual inspection of the goodness-of-fit and residual plots and the minimum value of the objective function [−2 log(likelihood); −2LL] provided by NONMEM. A 3.84 and a 6.63 point decrease in −2LL between two nested models were considered significant at the 0.05 and 0.01 levels, respectively.

Model parameters were expressed as the estimated values together with the corresponding relative standard error computed as the ratio between the standard error and the estimate of the parameter. The degrees of inter-patient and residual variability were expressed as the coefficient of various (CV; %).

Pharmacokinetic model

Drug disposition in the plasma was described using compartmental models parameterized in terms of volumes of distribution (V_1, V_2, V_3), distribution clearances (Cl_2, Cl_3), and total plasma clearance (Cl_1).

Pharmacodynamic model

T1% variable values were fit using the effect compartment model that links the observed concentrations of rocuronium in plasma to the neuromuscular blocking effect of rocuronium with a first-order process [16]. The sigmoidal E_{MAX} model was used to relate drug effects to the predicted concentrations in the effect site (C_e).

Model evaluation

To evaluate the PK and the PD models, we calculated the prediction error (PE) for every measurement in each individual studied, as follows:

$$PE = \frac{Obs - \mathrm{Pr}ed}{\mathrm{Pr}ed} \times 100$$

where *Obs* means observation (measured plasma concentration of rocuronium or the T1% effect measured for the PK and PD models, respectively), and *Pred* means the PK or PD model individual prediction for each time there was an observation. The difference between *Obs* and *Pred* normalized to the range of the effect measure was used to evaluate the models, as described elsewhere [17]. For every patient we calculated the median prediction error (MDPE), as a measure of bias, and the median absolute prediction error (MDAPE), as a measure of inaccuracy, as described elsewhere [18]. The median across all individual values of MDPE and MDAPE were also calculated. The best and worst individuals of the CPT and non-CPT groups, respectively, according to their MDAPE were selected and graphically displayed for evaluation of the PK and PD models.

A predictive check was used to explore the PKPD models [19]. Five hundred new data sets were simulated based on the selected models. For each of the simulated data sets, the median of the first time at which the response was ≥80% after the initial bolus was computed. The difference between the median value computed from the original data and the median from all of the simulated data sets is reported as an additional measure of the performance of the proposed PKPD model.

Clinically relevant endpoints

To further explore the predictions of the proposed model and to enable possible dosing adjustments to be studied and compared between patients under CPT and patients who were not taking phenytoin, we conducted simulations based on the PKPD model. The goal of the simulations was to evaluate the effects of a dose of rocuronium on normal individuals as compared to subjects under CPT. The effect profile after a single bolus dose of rocuronium was simulated for a typical individual of the CPT group and compared to a typical individual of the control group. The size of the bolus used for simulations was $3 \times ED_{95\%}$ (0.9 mg kg^{-1}).

Indicators related to onset $T1_{10\%}$ (time to reach a T1% of 10% of the T1 control) and T_{PE} (time to peak effect), duration $T1_{25\%}$ (time to recover to a T1% of 25%) and offset $T1_{25\%–75\%}$ (time from recovery of T1% 25% to T1% of 75%) of effect were calculated for the non-CPT and CPT individuals based on the estimated parameters of the PKPD model. $T1_{10\%}$ is a descriptor of the onset of effect that depends on the dose given—the larger the dose, the shorter the time it takes to reach $T1_{10\%}$. T_{PE} is a dose-independent descriptor of the onset of effect and has been described elsewhere [20]. Simulations were conducted using PKPDTOOLS FOR EXCEL, an EXCEL add in suite of functions that allows different complex pharmacological calculations to be performed [21].

Results

The demographics, surgical procedure and other details on the characteristics of the patients are given in Table 1. Table 2 reports the covariate factors (median value and range) included in the PKPD analysis process. Figure 1 shows that CPT patients required higher doses (expressed as rates of administration) than control patients. The data from five patients (two in the control group and three in the CPT group) could not be included in the PD analysis due to anomalies in the automatic data downloading process; consequently, their data were only used in the PK part of the data analysis.

Pharmacokinetic model

A three-compartment body disposition model resulted in a significantly better fit that the one- and two-compartment models ($P<0.01$). Inclusion of IPV was found to be significant for Cl_1, volume of distribution of the shallow peripheral compartment (V_2), and distribution clearance between the central and the shallow peripheral compartment (Cl_2) ($P<0.01$). The covariance between IPV terms was not significant ($P>0.05$).

The following covariates were selected during the GAM approach: age, height and CPT on Cl_1, albumin concentration on V_2, α_1-acid glycoprotein concentration and weight

Table 1 Demographic and dosing characteristics of the patients

Identification no.	Diagnosis	Age (years)	Gender	Weight (kg)	Height (cm)	Bolus (mg)	Infusion[a](μg kg^{-1} min^{-1})	CPT (days)	DXM	Concomitant pathology
1	Tumor right hemisphere	54	Female	63	171	60	14.46	No	Yes	No
2	Glioma left hemisphere	29	Female	73	158	70	17.19	30	No	No
3	Oligodendroglioma left hemisphere	38	Female	62	159	60	15.13	300	No	No
4	Tumor right hemisphere	75	Female	58	156	50	12.38	No	Yes	No
5	Tumor left hemisphere	48	Male	64	185	60	22.54	20	No	No
6	Suprasellar tumor	19	Male	76	176	70	23.28	134	Yes	Hypothyroidism
7	Tumor left hemisphere	61	Female	60	168	60	16.77	No	Yes	No
8	Tumor left hemisphere	48	Female	53.5	156	50	13.84	No	No	No
9	Tumor right hemisphere	35	Male	92	182	80	11.86	No	Yes	No
10	Arteriovenous malformation (left temporal lobe)	47	Male	84	184	80	22.28	480	No	No
11	Tumor right hemisphere	47	Male	76	180	70	25.63	17	No	No
12	Tumor right hemisphere	76	Male	65	165	60	18.13	No	No	Diabetes
13	Tumor right hemisphere	55	Male	71	179	70	13.93	No	Yes	No
14	Tumor inter-hemispheric	61	Female	86	158	80	16.42	No	No	Hypertension, diabetes, depression
15	Tumor Posterior fossa	59	Female	75	163	70	10.55	No	No	Hypertension
16	Tumor right hemisphere	40	Female	61	166	60	21.65	7	No	No
17	Tumor pineal gland	38	Female	52	162	50	11.46	No	No	No
18	Tumor left hemisphere	52	Male	87	170	80	14.75	No	No	No
19	Giant left meningioma	77	Female	52	159	50	19.56	360	No	No
20	Tumor right hemisphere	30	Female	62	176	60	40.46	360	No	No
21	Tumor right hemisphere	53	Male	74.5	170	70	23.65	30	Yes	No

CPT, Chronic phenytoin therapy; DXM, dexametasone treatment

[a] Total dose infused has been normalized to weight and averaged to the minutes of infusion duration

on Cl_2. However, the analysis with NONMEM revealed that only CPT was a significant covariate on Cl_1 ($P<0.01$).

Table 3 shows the model estimates corresponding to the final population model in the control and CPT groups, where it can be observed that all parameters were associated with a good precision.

Goodness-of-fit measures showed that the proposed PK model had an overall good ability to describe the data. Inaccuracy was 3.63% and bias was −0.81%. Figure 2 presents the goodness-of-fit plots for the PK model. The population model (top) as well as the individual post-hoc Bayesian (bottom) predictions adequately described the measured concentrations of rocuronium. The plot of the time course of the percentage error did not show any systematic bias that could have influenced the predictions of the PK model. Figure 3 shows the best and worst individuals according to their MDAPE values in both groups of patients.

Table 2 Covariate factors analyzed in this project, compared between non-CPT and CPT groups

Covariate factors	Non-CPT (n=11)	CPT (n = 10)
Age (years)	55 (35–76)	39 (19–77)
Weight (kg)	65 (52–92)	68.5 (52–84)
Height (cm)	165 (156–182)	173 (158–185)
Gender (M/F)	7/4	4/6
Phenytoin concentration (mg L^{-1})	0	8.05 (4.6–30.2)
Phenytoin (categorical)	0	10
Dexamethasone (categorical)	5	4
Total protein (g L^{-1})	60 (44–71)	60.5 (53–68)
Albumin (g L^{-1})	39 (27–44)	37.50 (34–42)
α_1 Acid glycoprotein (g L^{-1})	0.91 (0.41–1.14)	0.85 (0.52–3.01)

Values are expressed as the median, with the range given in parenthesis

The CPT increased the typical population estimate of Cl_1 from 0.26 to 0.75 L min^{-1} and reduced the unexplained IPV found in the basic population model from 60 to 24.4%. Figure 4 displays the distribution of individual estimates of Cl_1, where it can be observed that there is no overlap between the two groups of patients.

Pharmacodynamic model

The effect compartment model showed a clear superiority over the model that directly used the plasma concentration of rocuronium to describe the T1% data (P<0.05). The inclusion of IPV was found to be significant (P<0.01) for k_{e0} (the first-order rate constant governing drug distribution between the central and the effect compartment), IC_{50} (the steady-state plasma concentration eliciting half of the maximum response) and γ (the sigmoidicity parameter). Covariance between the IPV terms was not significant (P> 0.05). None of the individual patient characteristics were selected as potential significant covariates during the GAM analysis. The effect of CPT on IC_{50} was tested in NONMEM and found to be statistically non-significant (P>0.05). Table 4 lists the parameter estimates corresponding to the PD model, where it can be observed that all parameters were estimated with high precision.

In terms of the goodness-of-fit measures, the median values for MDAPE and MDPE were 8.6 and 1.05, respectively. When the observations were compared to the individual post-hoc model predictions, MDAPE was 3.4 and MDPE 0.36. Figure 5 shows the representative goodness-of-fit plots. Figure 6 shows the best and worst individuals according to their MDAPE in both groups.

Results from the predictive check showed very good agreement between the medians of the times to achieve ≥80% blockade after the first bolus administration. The median value for the observed T1% was 1.4 min and that for the simulated T1% was 1.9 min, providing an additional indication that the selected models were supported by the data.

The impact of CPT on IC_{50} was further evaluated by graphical inspection in Fig. 7 where it is clear that the

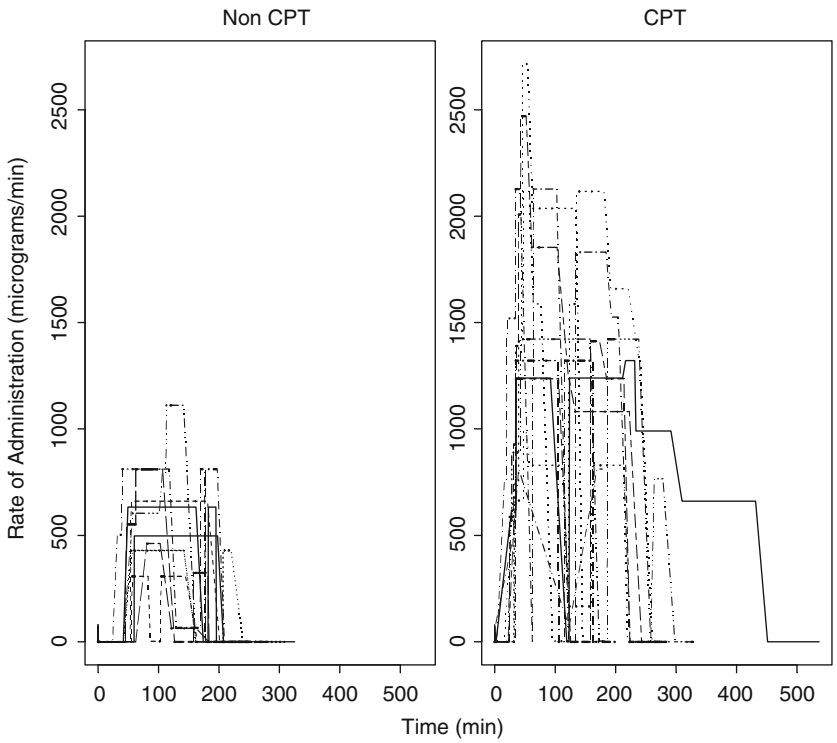

Fig. 1 Dose requirements expressed as rates of administration vs. time for the two group patients. *Left panel* Non-chronic phenytoin therapy (*CPT*) patients, *right panel* CPT patients. Each *line* represents an individual profile

Table 3 Final population pharmacokinetic (PK) parameters for rocuronium in the presence or absence of CPT

Parameter	Typical Population Estimate	Inter-patient variability
V_1 (L)	4.04 (0.07)	-
V_2 (L)	5.34 (0.13)	44 (0.4)
V_3 (L)	4.93 (0.26)	-
Cl_1 (L min^{-1})	No CPT: 0.26 (0.1)	
	CPT: 0.75 (0.06)	24.4 (0.49)
Cl_2 (L min^{-1})	0.36 (0.14)	43 (0.49)
Cl_3 (L min^{-1})	0.04 (0.15)	-
Residual (%)[a]	0.3 (0.16)	-

V_1, V_2, and V_3, Volumes of distribution of the central, shallow peripheral, and deep peripheral compartments, respectively; Cl_1, total plasma clearance; Cl_2 and Cl_3, intercompartmental clearance between the central and shallow peripheral compartments, and between the central and deep peripheral compartments, respectively

Model parameter estimates are reported with their relative standard error in parentheses. Inter-patient variability is expressed as coefficient of variation [CV(%)]

[a] Residual error in logarithmic scale

typical population estimates of IC_{50} between the two groups of individuals are very similar. The dispersion in IC_{50} in the CPT group was higher although the data did not support the estimation of a different variance in IC_{50} between the two groups ($P>0.05$).

Clinically relevant endpoints

Figure 8 shows the time course of predicted effect after a bolus dose of 63 mg (3 × $ED_{95\%}$, 0.9 mg kg^{-1}). The graph allows a comparison between groups with respect to onset, duration and offset of effect, based on the estimated PKPD parameters. The left panel shows the results of the simulation for the typical individual, representing the group of patients not taking phenytoin. The right panel represents the typical patient of the CPT group. After a rocuronium bolus dose of 63 mg, onset, defined as the time from the bolus injection to the time a T1% equal to 10% of T1% control height, was 3.2 min in the control group and 5.25 min in the CPT group. T_{PE} was 11.23 and 7.17 min in the control and CPT groups, respectively. The time from bolus injection to a recovery of T1% equal to 20% of control T1% was 45.2 min in the control group as compared to 16.75 min in the CPT. To reach a recovery of 80% of control T1% would take 85.8 min in a patient of the control group and 37.75 min in a patient taking CPT. The offset of effect was evaluated by calculating the time of recovery from a T1% of 25% to a T1% of 75% of the control T1% height; it was 32.2 and 16.75 min in the control and CPT patients, respectively.

Discussion

The patients of our study who were taking CPT required a significantly higher dose of rocuronium to maintain an adequate level of neuromuscular blocking effect. This finding is consistent with clinical knowledge and the research of other authors on rocuronium and other NMBA. We used the population PKPD modeling approach to explore at which level (PK or PD) CPT affects rocuronium response.

Disposition of rocuronium in plasma has been characterized in the past with the use of a two-compartment [22] and a three-compartment body model [23]. Regardless of the selected model fitted to the plasma concentration data, rocuronium in healthy patients is characterized by: (1) small V_1, with values ranging from 2.7 [23] to 6.76 L [22], (2) a small apparent volume of distribution at steady-state (V_{SS}), ranging from 10.5 [22] to 19.95 L [24] and (3) low Cl_1 0.2 L min^{-1} [24]. Those previous results are in accordance

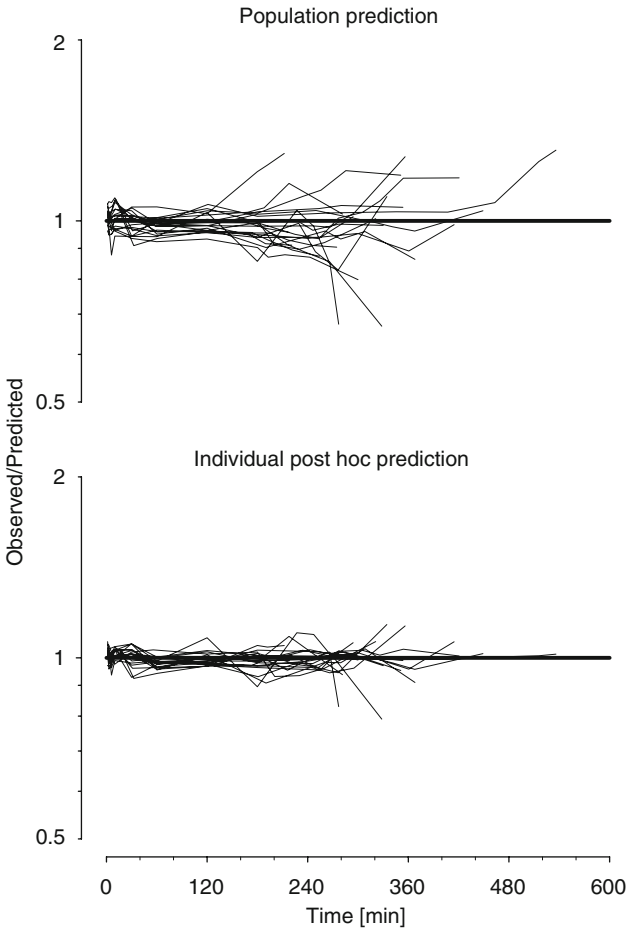

Fig. 2 Goodness-of-fit plots for the selected population pharmacokinetics (PK) model. *Top panel* Time course of the prediction error for the population PK model, *bottom panel* the prediction error for the individual post-hoc prediction. In both graphs *each line* represents a single individual, and the *bold horizontal line* is the line of identity

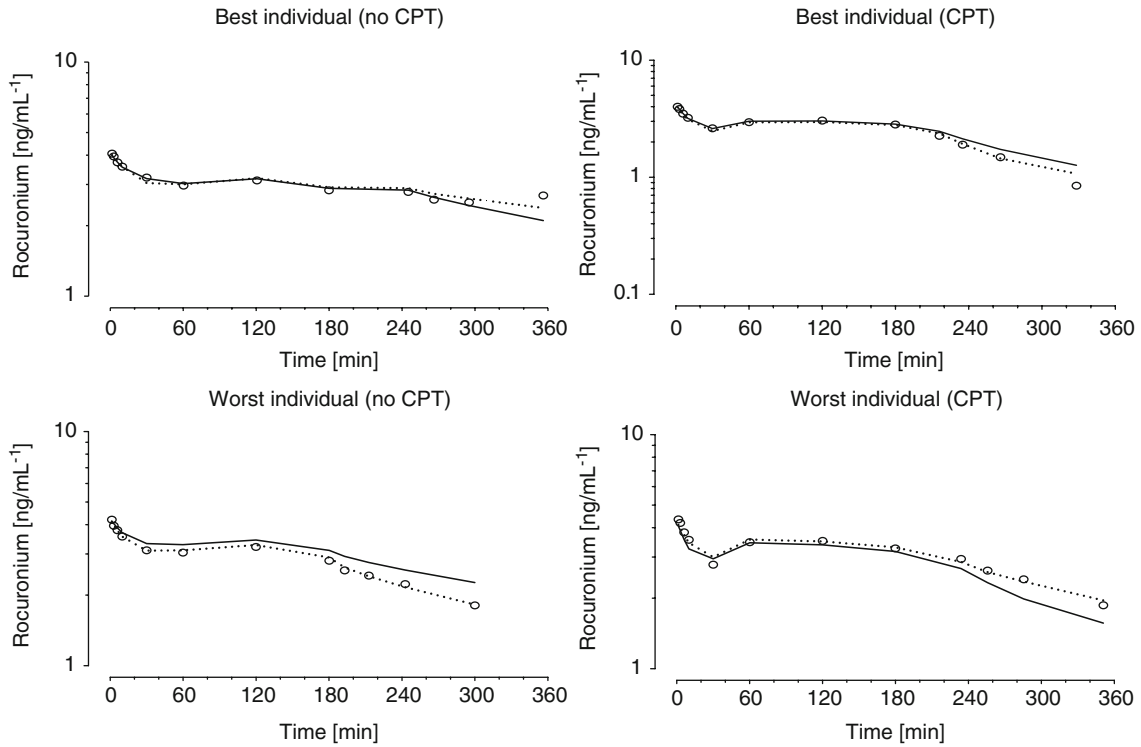

Fig. 3 Representative pharmacokinetic fits in both groups of patients. The best and worst fit in the group of patients not taking phenytoin (*left*) and those on CPT (*right*) according to their individual MDAPE values are represented in the *top* and *bottom panel* respectively. Each panel represents the time course of the observed (*circles*), population-predicted (*thick line*) and individual Bayesian post-hoc-predicted (*dotted line*) rocuronium concentrations

with the model parameter estimates obtained in the current study for patients that were not under CPT: V_1=4.03 L, V_{SS}=14.6 L and Cl_1=0.26 L min^{-1}.

Our calculations revealed that no covariates other than the presence of CPT were significant at a PK or PD level. Some authors have reported changes in the level of α_1-acid glycoprotein between non-treated and phenytoin-treated patients that could justify an increase in rocuronium protein binding and partly explain a decrease in neuromuscular blocking effect [25]. We did not detect such differences between groups nor were we able to detect any effect of α_1-acid glycoprotein as a covariate factor in the modeling process. α_1-Acid glycoprotein showed no correlation with phenytoin concentrations or with the duration of CPT as other authors have also reported [26–28]. In our study, similar total protein levels or albumin were measured in

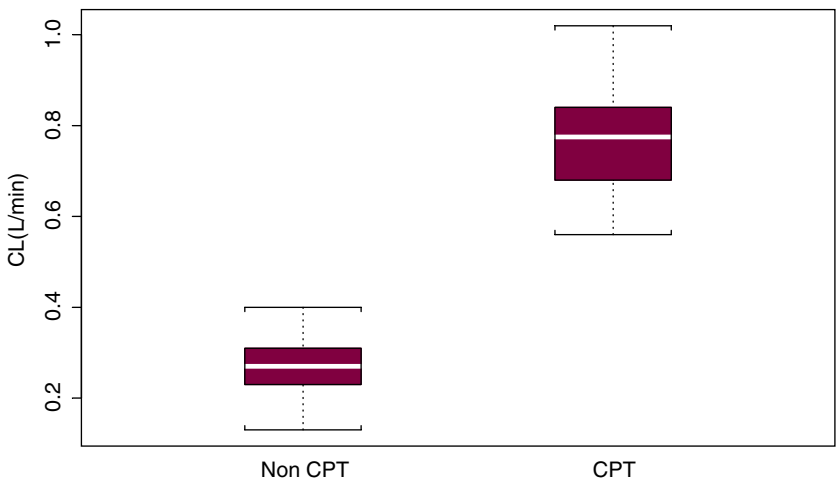

Fig. 4 Distribution of the individual estimates of clearance in each of the two groups of patients. The *length of each box* covers the 50% of the estimates, and the median is indicated by the *white line in the box*. The *distance from the median to the end of each whisker* (*lines extending from the box*) is equal to 1.5-fold the interquartile range

Table 4 Population pharmacodynamic parameters for rocuronium

Parameter	Typical population estimate	Inter-patient variability
k_{e0} (min^{-1})	0.073 (0.1)	42.4 (0.24)
IC_{50} (ng mL^{-1})	836 (0.13)	52.9 (0.15)
γ	3.13 (0.13)	52.5 (0.2)
Residual (%)	10.2 (0.25)	-

Model parameter estimates are reported with their relative standard error given in parentheses; inter-patient variability is expressed as coefficient of variation [CV(%)]

k_{e0}, First-order rate constant controlling drug distribution between plasma and biophase; IC_{50}, steady-state plasma concentration value eliciting half of the maximum neuromuscular blockade; γ, parameter governing the shape of the response vs predicted effect site concentration relationship

patients from both groups. Based on the reported findings CPT must be taken into account when using rocuronium as the neuromuscular blocking agent of choice.

In terms of covariate detection, it is worth noting the effect of factors such as weight could not be detected. It is possible that a different design of the study with a more representative group of patients of different weights and ages would give a better answer to this point. One possibility to be considered is that dosing rocuronium according to weight would not decrease the variability in the response and would not be necessary, but this area requires further exploration.

The results of our study show that CPT has an important influence on the elimination of rocuronium, increasing the value of Cl_1 from 0.26 to 0.75 L min^{-1} while decreasing IPV from 60% to 24.4, when it was included in the PK model as a covariate. A PK interaction to explain the resistance to rocuronium observed in one patient with renal insufficiency under CPT was suggested in the past [9]. A decrease in the rocuronium-induced neuromuscular blockade in patients under CPT was also observed [5]. Our contribution confirms such a hypothesis and quantifies the effect of the co-medication at the median level of the parameter Cl_1 as well as the decrease in IPV, when CPT was included in the PK model.

Our estimated values for IC_{50}, the estimate of drug potency, are consistent with those reported by other authors, which ranged from 684 [22] to 1030 ng mL^{-1} [29]. From a PD standpoint, it is worth noting that, according to our results, CPT does not affect the typical estimate of IC_{50}. Other authors have demonstrated an effect of antiepileptic therapy on the IC_{50} of different NMBA, such as vecuronium [2], although others were unable to detect changes in vecuronium IC_{50} in the presence of carbamazepine [30]. In terms of rocuronium, there has been no report of the influence of antiepileptic drugs on the potency, IC_{50}, of the drug.

Our PKPD model estimates a typical value of k_{e0} of 0.073 min^{-1} for all subjects studied regardless of CPT. These values are different from those reported previously for rocuronium bromide [22, 23, 29]. There may be several factors that can explain these differences in k_{e0} values of NMBA: differences in the effect measurement method (electromyogram vs. force transducer), in the signal acquisition method or the train of four derived parameter used for PD modeling, in the core temperature maintained during the surgical procedure, or differences related to study design, especially those related to the drug administration method (bolus, constant or variable continuous infusion or a combination of both) or to which part of the anesthesia was chosen to study the effect (induction, maintenance) [31].

The design of this study in terms of rate of administration must be commented upon. It has been shown that the erroneous assumption that drug plasma concentrations peak at time zero and decrease monotonically after bolus administration affects the accuracy of PD parameter

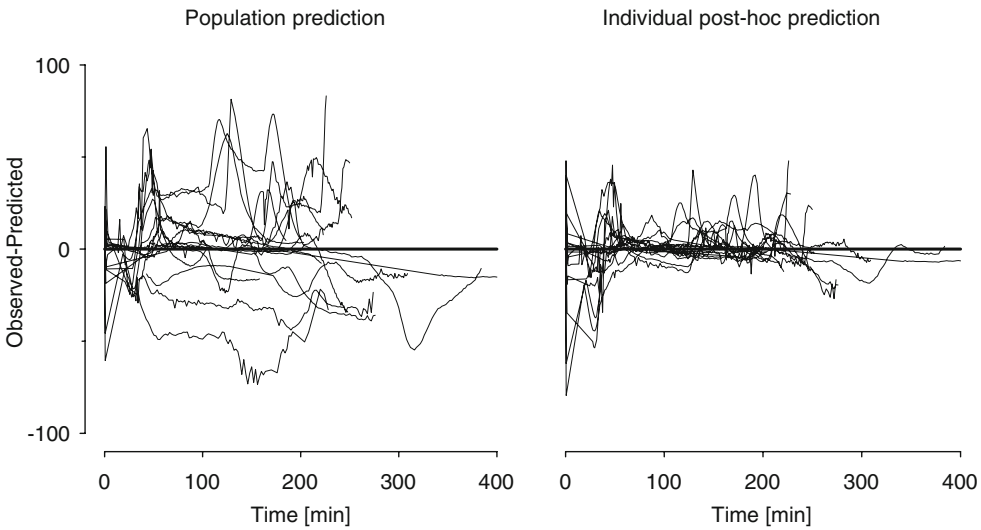

Fig. 5 Goodness-of-fit plots for the selected population PD model. *Left panel* The time course of the prediction error for the population PD model, *right panel* the prediction error for the individual post-hoc prediction. In both graphs each *hairline* represents a single individual, and the *bold horizontal line* is the line of identity

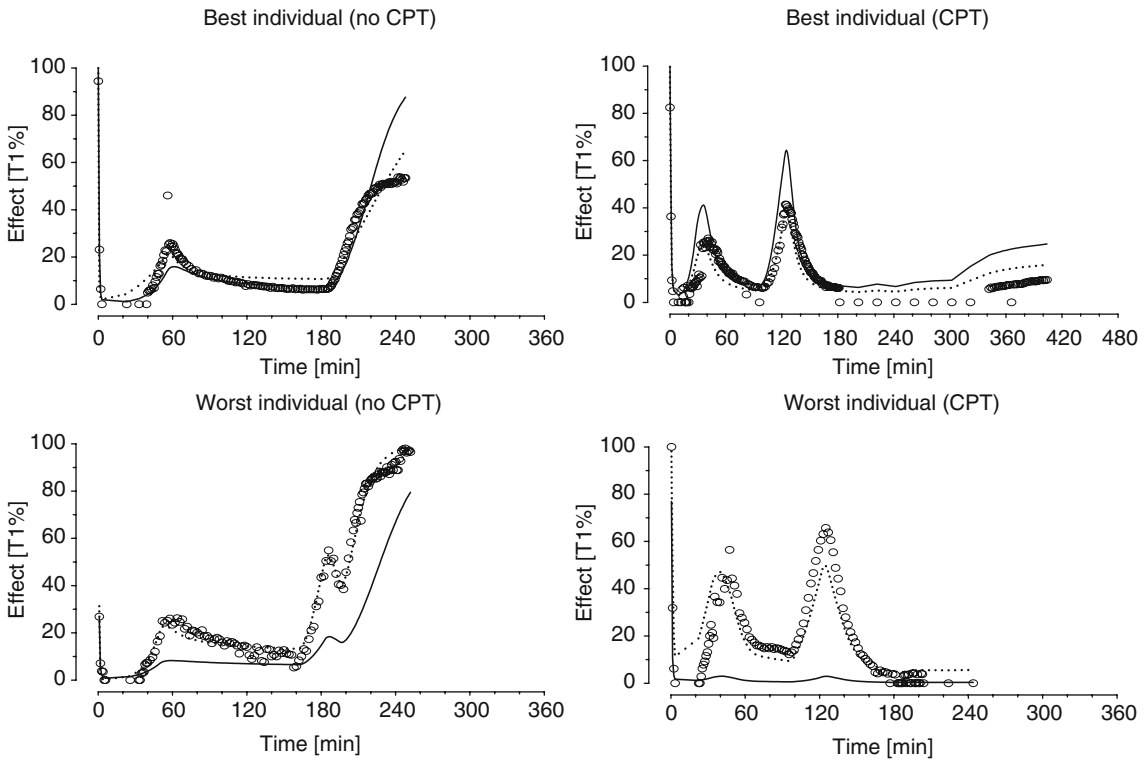

Fig. 6 Representative PD fits. The best and worst fit in the group of patients not taking phenitoyn (*left*) and those on CPT (*right*) according to their individual MDAPE values are represented in the *top and bottom panels*, respectively. Each panel represents the time course of the observed (*circles*), population-predicted (*thick line*) and individual Bayesian post-hoc-predicted (*dotted line*) rocuronium-induced effect on T1%

estimates with doses producing rapid, complete twitch depression [32]. In our study, all patients in both groups received a high initial bolus dose ($3 \times ED_{95\%}$) because of clinical concerns related to insufficient neuromuscular blockade in brain surgery patients. The concerns were based on the fact that, although the T1% effect measured at the adductor pollicis muscle could reach an effect of 100%, this is not the case at the laryngeal muscles level, where it can not reach 90% of effect, and at the adductor pollicis, although during a significantly shorter period of time [33]. This problem, which has been described for non-epileptic individuals, could be much greater in the case of patients

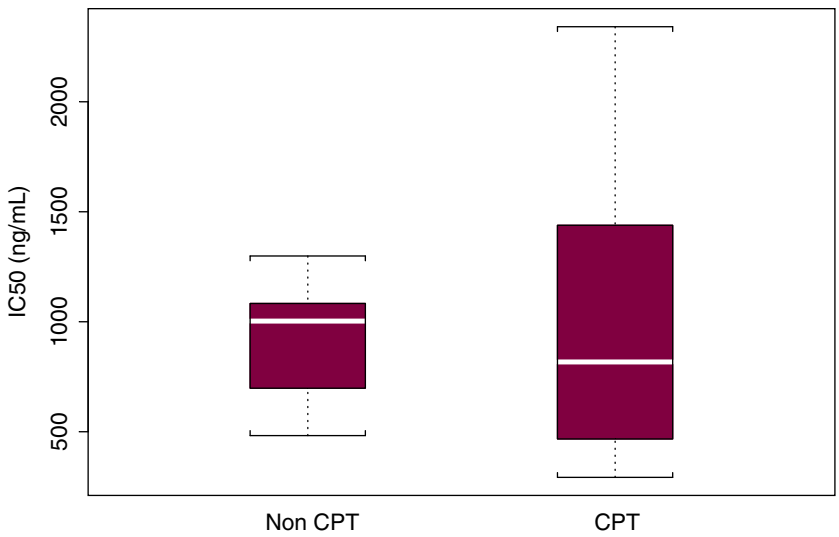

Fig. 7 Distribution of the individual estimates of IC_{50} in each of the two groups of patients. The *length of each box* covers 50% of the estimates, and the median is indicated by the *white line in the box*. The distance from the median to the end of each whisker (*the lines extending from the box*) is equal to 1.5-fold the interquartile range

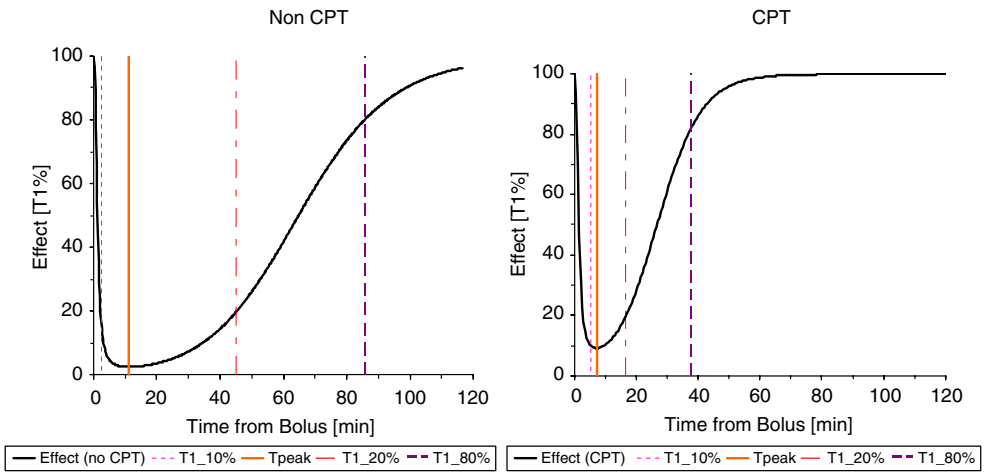

Fig. 8 Simulation of the time course of effect after a bolus dose of rocuronium in the CPT group as compared to the control group. The simulated bolus dose is 63 mg (3 × $ED_{95\%}$, 0.9 mg kg^{-1}, assuming a weight of 70 kg) administered to the typical patient of the control group (*left panel*) and the typical patient of the CPT group (*right panel*) according to the proposed PKPD model. Indicators of onset ($T1_{10\%}$, T_{PE}) and duration of effect ($T1_{20\%}$, $T1_{80\%}$) as described in the text are represented in both graphs to allow for a better evaluation of the influence of CPT on neuromuscular blocking effect after a bolus dose of rocuronium

under chronic antiepileptic therapy, thereby placing them at a greater risk of insufficient blockade during induction. To overcome the limitations of a large initial bolus, we considered that a combination of a bolus and a variable continuous infusion, where several points of onset and offset of effect could be measured, could be a good approach to estimate PKPD parameters, as other authors have already demonstrated for anesthetic drugs such as propofol [34, 35].

It is also worth noting that an increase in the dose would increase the time of ablation of T1% which, in turn, would decrease the amount of data obtained on the relation between Cp and effect as well as decrease the number of data points related to onset of effect. This two facts might increase the bias and variability of the estimation of k_{e0} [32]. Bergeron et al. studied the PKPD of cisatracurium using three different bolus doses of 1.5-, three- and sixfold the $ED_{95\%}$ of cisatracurium. They found that there was a direct relation between doses and IC_{50}—i.e. the larger the dose the greater IC_{50}—while the k_{e0} was inversely related to dose—a larger dose decreased the estimate of k_{e0}, thereby increasing onset time [36]. Kuipers et al. estimated a k_{e0} for rocuronium of 0.24 min^{-1} ($t_{1/2ke0}$ 2.9 min) after a bolus dose of 1 × $ED_{95\%}$ [22], while the estimates for k_{e0} of rocuronium in studies where 2 × $ED_{95\%}$ was administered ranged from 0.09 through to 0.17($t_{1/2ke0}$ 4.12–7.7 min) [23, 29]. Our estimate of k_{e0} is lower than those reported, probably because of the influence of the initial 3 × $ED_{95\%}$ bolus dose.

Model misspecification could also contribute to explaining the lack of agreement between the pharmacodynamic results previously published by other authors and the results of our study. The attainment of 100% of effect might not be the real maximal effect but rather the level at which the signal disappears although the effect is still building up. The use of the sigmoidal E_{MAX} model would not be adequate to model such data when the supramaximal effect is reached.

With regard to the results of simulating a bolus dose administered to a typical 70-kg subject belonging to each of the two groups studied in our study, it must be noted that although T_{PE}, a dose-independent indicator of onset of effect, indicates a shorter time to reach maximal effect in the CPT group, the onset is slower when the same dose is administered to both subjects. This is probably due to the fact that the increase in Cl_1 makes less drug available to reach the biophase and the effect is less intense and with a shorter duration. Consequently, in order to reach the same level of effect after a bolus, a larger dose of rocuronium must be administered to those patients under CPT. The calculated descriptors of duration and offset of effect predict a shorter duration and faster recovery in the group of patients under CPT; therefore, to maintain the same level of effect than in the control group, doses must be increased in the patients under CPT.

Caution must be taken in interpreting the simulations presented. Since our estimates of k_{e0} seem to be dependent on the dose administered, our results can only be valid when similar dosing schemes are used. Using the estimated parameters to study the time course of rocuronium effect on T1% may give erroneous conclusions when the simulated dose is a submaximal one, since for doses like 2 × $ED_{95\%}$ the estimated k_{e0} and possibly $IC_{50\%}$ might be greater and affect the expected time course of neuromuscular blocking effect.

In conclusion, a three-compartment PK model combined with the effect compartment model provided the best approach for describing the disposition and time course of the neuromuscular blocking effect of rocuronium bromide. When combining a large bolus dose with a variable

continuous infusion of rocuronium, the effect of CPT is to increase metabolic clearance with no apparent effect on C_{50} or k_{e0}. The effect of as large a bolus dose as that used in our study might affect the estimation of parameters such as C_{50} and k_{e0}. Chronic administration of phenytoin must be considered to be a relevant factor when deciding the dosing guidelines of rocuronium in such patients.

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