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Vecuronium pharmacokinetics in patients with major burns†

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Editor's key points

- Pharmacokinetics changes with burn injury were examined as possible mechanisms of resistance to vecuronium.
- BURN was the single most significant covariate that explained the altered vecuronium disposition in burns.
- Among burn patients, no physiological factor useful for predicting or guiding vecuronium dose was found.
- The altered drug distribution may partially explain the known resistance to vecuronium in burns.

Background. Burn patients develop resistance to non-depolarizing neuromuscular blocking agents (NDNMBAs) and require a significantly large dose to produce a desired clinical response. Pathophysiological changes related to burn injury may alter pharmacokinetics (PK) and pharmacodynamics of NDNMBAs. The purpose of this study was to compare vecuronium PK in burns *vs* non-burns.

Methods. Twenty adults, aged 23–58 yr, with 27–81% total body surface area (TBSA) burn, were studied at 4–57 post-burn days and compared with age- and sex-matched, non-burn controls. Vecuronium 0.12 mg kg^{-1} was given i.v. as a single bolus within 10 s. Blood samples (n=20) were collected over 12 h at predetermined time points. NONMEM was used to describe plasma drug concentration–time profiles for burns and non-burns.

Results. A three-compartment model best described vecuronium concentration–time profiles. Burn patients showed enhanced distributional clearance at the terminal phase (0.12 *vs* 0.095 litre min^{-1}, $P<0.0001$), which yielded shorter elimination half-life for vecuronium (5.5 *vs* 6.6 h, $P<0.001$). BURN was the single most significant covariate that explained the altered vecuronium disposition in burns.

Conclusions. The altered drug distribution between tissues may partially explain the known resistance to vecuronium in patients with major burns.

Keywords: burns; neuromuscular block; population pharmacokinetics; vecuronium

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Burn patients develop resistance to non-depolarizing neuromuscular blocking agents (NDNMBAs) and require significantly large doses to produce desired clinical response. This resistance increases over the course of therapy and depends on the extent of injury.[1] Pathophysiological changes in cardiovascular, respiratory, hepatic, and renal functions after burn injury may alter the pharmacokinetics (PK) and pharmacodynamics of NDNMBAs.[1–3] The early changes during burn shock stage immediately after the injury include protein loss, oedema formation, fluid accumulation in the lungs, and reduced cardiac output with decreases in hepatic and renal blood flow. In the subsequent hyperdynamic hypermetabolic phase, cardiac output increases to provide healing wounds a higher supply of energy and micronutrients. This augmented cardiac output enhances organ blood flow to the liver and kidneys, although full function is not regained.[2]

Vecuronium has been used for tracheal intubation as an adjunct to anaesthesia due to its relatively short duration of action and minimal cardiovascular effects. Although vecuronium PK has been described in normal subjects[4–6] and other critical illnesses,[7 8] its role to burn injury-related NDNMBA-resistance has not been well investigated. We hypothesize that pathophysiological changes caused by burn injury may alter vecuronium concentration decay over time and contribute to NDNMBA-resistance. To this end, we compared vecuronium disposition characteristics in burns *vs* non-burns as a possible mechanism of resistance.

Methods

Patients

The protocol was approved by the Institutional Ethics Committee for Human Subjects. Written informed consent was obtained from each participant. Twenty adults, aged 23–58, who suffered from >20% TBSA burn, without any renal or liver dysfunction, were enrolled. Age- and sex-matched,

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non-burned patients undergoing elective non-burn surgery served as controls. Patient characteristics, burns, and laboratory data are summarized in Table 1. Creatinine clearance (CrCL) was calculated by the Crockfort–Gault formula. Anaesthesia and surgical data are presented in Table 2.

Sampling

Anaesthesia induction and maintenance consisted of propofol 2.0–2.5 mg kg^{-1} bolus, followed by 0.1–0.2 mg kg^{-1} min^{-1} continuous infusion. This was supplemented by intermittent fentanyl 1–2 μg kg^{-1} bolus with nitrous oxide 50% in oxygen. Vecuronium 0.12 mg kg^{-1} was administered as a single i.v. bolus within 10 s. Blood samples (5 ml) were collected into EDTA tubes at 0, 1, 2, 3, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 480, 600, and 720 min (n=20). The samples were centrifuged within 30 min and plasma separated and stored in aliquots at −70°C for later assay in batches. Plasma vecuronium concentrations were analysed by high-performance liquid chromatography (HPLC) with tandem mass spectrometry.[9] The mean accuracy of the method was 95.5%, precision was <9.1%, and the lower limit of quantification (LOQ) was 5.0 ng ml^{-1}.

Pharmacokinetic analysis

Population PK model developments and simulations were performed using NONMEM ver. 7.2 (ICON Development Solutions, Ellicott City, MD, USA). NONMEM was compiled by Intel Visual Fortran Compiler 11.1 (Intel Corporation, Santa Clara, CA, USA). Window Server 2008 R2 was the operating system. NONMEM PREDPP library subroutines ADVAN 11 was used with the TRANS 4. The described population PK parameters were clearance (CL_1) and volume of distribution (V_1) for the central compartment, distributional clearance (CL_2), and volume (V_2) for the rapid peripheral compartment, and distributional clearance (CL_3) and volume (V_3) for the slow peripheral compartment [$C_p = A\exp(-\lambda_1 t) + B\exp(-\lambda_2 t) + C\exp(-\lambda_3 t)$]. The natural logarithms of observed plasma concentrations were fitted by the model to predict log-transformed concentrations.

Overall, 26% of plasma vecuronium concentration data fell below the LOQ during the initial distribution and elimination phases and were not available for analysis in both burns and non-burns (13.4% *vs* 12.6%). Thus, the likelihood for the remaining data was adjusted using the YLO variable available in NONMEM.[10] The YLO variable is set as a lower bound for the interval to correct the likelihood for observations above the LOQ. Log-transformed data were used, so that YLO was set to be equal to the log LOQ value.

The inter-individual variability (IIV) was evaluated using the exponential model as follows:

$$P_i = P_{pop} \times \exp(\eta_{Pi})$$

where P_i is the ith individual parameter, P_{pop} the mean (typical) parameter for the population, and η_{pi} a random-effect parameter with a mean of zero and a variance of ω^2. These IIV terms were initially estimated for all parameters and then removed from V_3 because of high η-shrinkage (>50%). Correlation between each term was evaluated using a BLOCK covariance matrix. The correlation coefficient between V_1 and CL was 0.77. The residual error was evaluated using a combination of the constant coefficient of variation (CCV) and additive models as follows:

$$Y_{ij} = F(P_i, t_{ij}) + \varepsilon_{addij} + F(P_i, t_{ij}) \times \varepsilon_{propij}$$

where Y_{ij} is the measured observation from the ith individual at time point j, $F(P_i t_{ij})$ is the corresponding individual prediction with a vector of the individual PK parameters for the ith subject (P_i) at a time t_{ij}, ε_{addij} the additive residual difference,

Table 1 Patient characteristics, burn, and laboratory data. Values are expressed as mean (SD) or median (min–max) whenever appropriate. TBSA, total body surface area of burn %; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; CrCL, creatinine clearance. *P<0.01, **P<0.001

	Non-burn (n=20)	Burn (n=20)
Gender (M:F)	17:3	16:4
Age (yr)	40 (25–58)	36 (23–58)
Height (cm)	170 (7)	169 (7)
Weight (kg)	70 (13)	65 (10)
ASA class (I/II/III/IV)	17/2/1/0	0/0/19/1**
TBSA (%)	N/A	51 (27–81)
Days after burn (day)	N/A	13 (4–57)
Haemoglobin (g dl^{-1})	14.4 (1.8)	11.9 (1.7)**
Albumin (g dl^{-1})	4.6 (0.7)	2.8 (0.7)**
Protein (g dl^{-1})	7.1 (0.8)	5.2 (1.6)**
AST (IU $litre^{-1}$)	21 (6)	63 (50)**
ALT (IU $litre^{-1}$)	22 (9)	50 (73)*
BUN (mg dl^{-1})	12 (4)	13 (5)
Cr (mg dl^{-1})	0.9 (0.1)	0.9 (0.2)
CrCL (ml min^{-1})	103 (18)	111 (30)

Table 2 Anaesthesia, surgery, and intraoperative data. Values are expressed as mean (SD) and median (min–max) whenever appropriate. RBC, red blood cell; FFP, fresh-frozen plasma. *P<0.01, **P<0.001

	Non-burn	Burn
Duration for anaesthesia (min)	186 (64)	181 (71)
Duration for surgery (min)	145 (62)	126 (64)
Estimated blood loss (ml)	170 (216)	830 (256)**
Fluid replacement		
Packed RBC (ml)	0 (0–400)	1000 (400–2200)**
FFP (ml)	0 (0)	360 (0–1200)**
Crystalloid (ml)	900 (350–3500)	2030 (600–5100)**
Colloid (ml)	0 (0–500)	230 (0–500)*

and ε_{propij} the proportional or CCV residual difference between the individual prediction and the observed value. The LAPLACIAN estimation method with INTERACTION was used to estimate model parameters.

Patient characteristics, laboratory, surgical, and burn injury-related data (Tables 1 and 2) were individually screened by the stepwise forward selection and backward elimination. First, the model was estimated without covariates. Plots of the individual Bayesian estimates of the model parameters *vs* the covariates were assessed for a covariate influence using linear regression. A difference between the objective function value (OFV) >3.84 ($P<0.05$) for forward selection and 6.63 ($P<0.01$) for backward elimination with degree of freedom df=1 was considered significant and covariates included in the corresponding parameter. The effect of burn injury was modelled as a percentage difference of the PK parameter estimates for non-burns, that is, $TVCL_3=\theta_{non\text{-}burn}\cdot(1+BURN\cdot\theta_{burn\_effect})$, where BURN equals 0 for non-burn and 1 for burn. Significance of covariate was evaluated based on changes in OFV, reduction in IIV, and overall model performance.

The goodness-of-fit for models were assessed graphically and numerically. Graphical diagnostics were analysed using *X*pose 4.0 (Uppsala University, Uppsala, Sweden) with typical standard plots that included scatter plots of observed, population and individual predicted (PRED and IPRED) concentrations *vs* time; observed *vs* predicted concentrations; and weighted residuals *vs* time or IPRED. The bias and precision of the model were estimated as per cent mean estimation error (MEE) and root mean squared estimation error (RMSE) as follows:

$$\mathrm{MEE}=\frac{1}{N}\times\sum_{i=1}^{i=N}\frac{\mathrm{DV}-\mathrm{IPRED}}{\mathrm{DV}},$$

$$\mathrm{RMSE}=\sqrt{\frac{1}{N}\times\sum_{i=1}^{i=N}\left[\frac{\mathrm{DV}-\mathrm{IPRED}}{\mathrm{DV}}\right]^2}.$$

The stability and predictive performance of models were evaluated by visual predictive check and non-parametric bootstrap analysis. For the former, parameter estimates were used to simulate the data for 1000 virtual patients for both burns and non-burns. The 5th, 25th, 50th (median), 75th, and 95th percentiles were calculated, and the distribution of simulated concentrations was visually compared with the measured vecuronium concentrations at each sampling time point. For the latter, 1000 bootstrap replicates were used to calculate the median with 90% confidence interval (CI) for the model parameters.

Results

One patient in the burn group received a second bolus of vecuronium followed by continuous infusion at 3 h after the first bolus of the study drug. Data obtained after the second bolus of this patient were excluded from the analysis as dosing information was not available. A total of 565 data were used to construct the model, whereas 13.4% ($n=106$) and 12.6% ($n=89$) of the expected measures were not reported in burns and non-burns, respectively, as they fell below the LOQ.

The concentration–time profiles of vecuronium after i.v. administration showed a poly-exponential decline in patients with *vs* without burn injury (Fig. 1A). A three-compartment model best described plasma vecuronium concentration–time profiles and significantly reduced OFV (-360 points), when compared with a two-compartment model. The IIV terms of PK parameters among all patients were moderate to high (coefficient of variation, CV%; 13.04–49.40%). A noticeable difference in PK profiles of vecuronium between burns *vs* non-burns was observed at the later distributional and terminal phases. The plasma vecuronium concentrations in patients with burn declined rapidly in the distribution phases and fell below 5.0 ng ml^{-1} within 4 h after the bolus (Fig. 1C and E). Only three out of 20 patients in the burn group had quantifiable concentrations at the terminal phases. On the contrary, 13 out of 20 non-burn patients had their plasma concentrations above the LOQ at 4 h after the bolus, although by the end of study period, only five patients had measurable concentrations (Fig. 1B and D).

The potential influence of BURN as a covariate on vecuronium disposition characteristics were examined as a percentage difference of each PK parameter estimate between the two groups. There were no major differences in CL_1 (5.4%), V_1 (4.4%), and CL_2 (7.0%) between burns *vs* non-burns; thus, the effect of the burn was removed from these parameters during the stepwise backward elimination.

Tissue distribution of vecuronium was affected by burn injury. Patients with burns had a CL_3 value 27% higher than non-burns (Fig. 2A), which indicates a rapid distribution of vecuronium into tissues. Inclusion of the burn status on CL_3 reduced its IIV from 29% to 18.03%. Similar trends were observed between CL_3 and other burn injury-related covariates (e.g. TBSA, albumin levels, and estimated blood loss). Although those injury-related variables were individually significant ($P<0.05$), their importance was not retained once BURN was added on CL_3.

In addition, a noticeable difference was observed in the extent of tissue distribution between two groups. Patients with burns have not only higher values of V_2 compared with non-burn, but also larger variability of V_2 within the group (Fig. 2B). The effect of burn injury was tested for the population mean V_2, its variability term, or both. The IIV of V_2 was found to be significantly greater in the burns than in the non-burns (43.82% *vs* 15.30%, $P<0.05$). However, a difference in the mean V_2 value between the two groups was not statistically confirmed. The final model included the effects of BURN on the population mean CL_3 (dOFV$=-6.65$) and the IIV of V_2 (dOFV$=-8.42$), and also resulted in a reduction in the proportional residual error from 24% to 13.23% (Table 3). The population mean clearance (0.51 litre min^{-1}, 90% CI 0.41–0.53 litre min^{-1}) was similar to the previously reported for vecuronium in non-burns.[4–6] The estimated typical value for central volume of distribution (V_1) was 10.25 litre (90% CI 8.55–10.66 litre). No other covariate evaluated in this study could explain the relatively high IIV for CL and V_1.

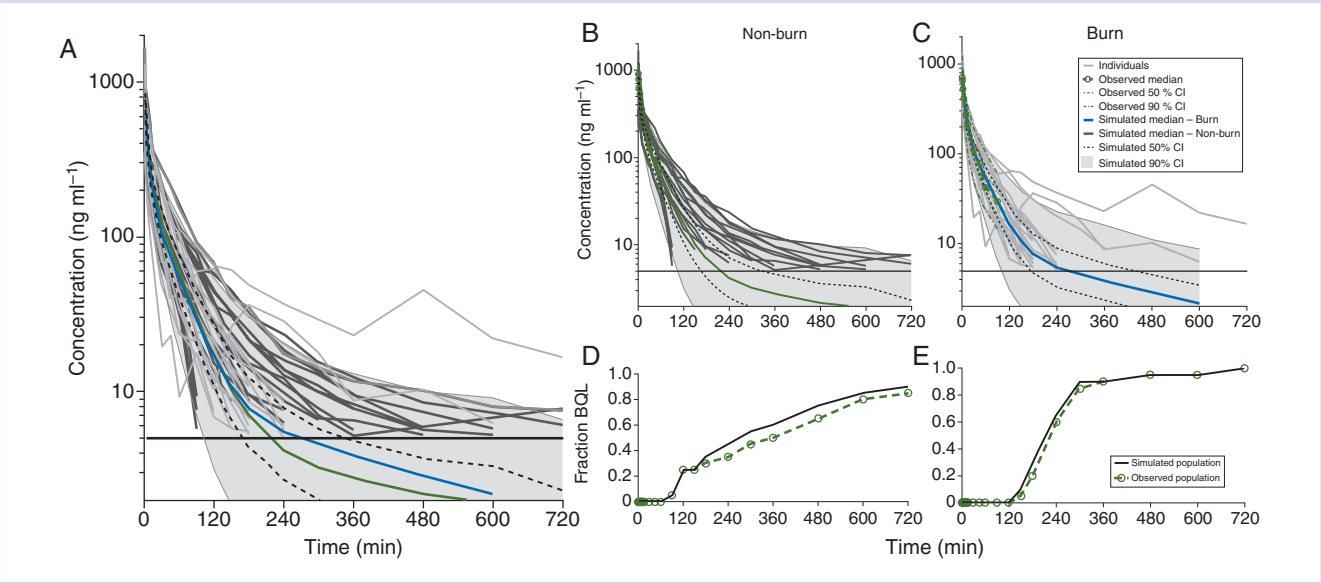

Fig 1 The observed and model predicted time courses of vecuronium plasma concentrations in non-burn and burn patients receiving 0.12 mg kg^{-1} vecuronium. The light grey lines represent the observed concentrations and the green solid line represents the median population predicted profile in non-burns; whereas the dark grey lines represent the observed concentrations and the blue solid line represents the median population predicted profile in burns. The shaded area corresponds to the simulated 90% prediction intervals and the dashed black lines correspond to the simulated 50% prediction intervals. The observed median, 50% prediction interval, and 90% prediction interval are represented with the dashed green line with open circles, dashed green lines, and dotted green lines, respectively (A–C). A total of 26% of plasma vecuronium concentration data fell below the LOQ (5.0 ng ml^{-1}, black horizontal line). The lower panels (D and E) show fraction BQL of observed (dashed green line with open circles) and simulation-based (black solid line) median in non-burns and burns.

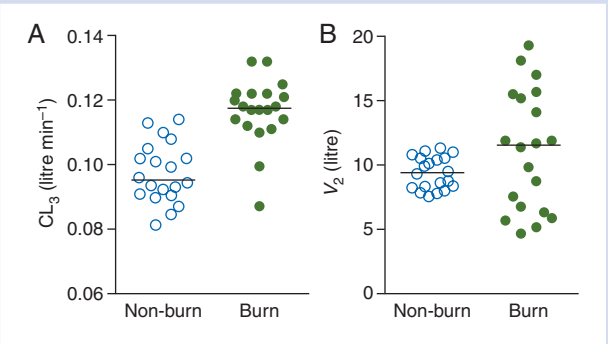

Fig 2 Effect of BURN on CL_3 and V_2. The population mean of CL_3 was 24% higher in burns compared with non-burns (A), and the variability of V_2 in burns was greater than non-burns (43.82% *vs* 15.30%) (B).

The influence of altered vecuronium disposition (V_2 and CL_3) by burn injury on the overall shape of the concentration–time curve was further assessed. The slopes of three linear phases (hybrid macro rate constants; λ_1, λ_2, λ_3) was calculated using the individual parameter estimates from the final model according to the method by Upton.[11] The terminal elimination half-life for burns was slightly shorter than that of non-burns (5.5 *vs* 6.6 h, $P<0.001$) while the differences between the two groups were minimal, <10%, in the early (λ_1) and second distributional slopes (λ_2). Although we found significant differences between the terminal half-lives, these may occur at concentrations that decrease below the therapeutic level; therefore, we estimated the context-sensitive half-time[12] for vecuronium in burns and non-burns. The context-sensitive half-time was shorter for burns than non-burns, but the difference was not statistically significant (6.90 *vs* 7.35 min, $P>0.05$).

Model predictions were in agreement with the observed plasma vecuronium concentrations in goodness-of-fit plots (Fig. 3). Population and individual predicted concentrations were well distributed around the line of unity (Fig. 3A and B). The individual weighted residuals had no systemic deviations (Fig. 3C and D). The visual predictive check showed that the final model predictions were in reasonable agreement with the observed values. Observed values were well overlaid with simulated values for both burns and non-burns. The 5th, 50th, and 95th percentiles were reasonably predicted up to all the measured concentrations within the first 90 min after the bolus (Fig. 1). Of the total simulated concentrations, 28% corresponded to below LOQ, which was comparable with the 26% in the observed concentrations. The estimated MEE and RMSE were calculated to be 1.45% and 18.36%, respectively. The 95% CI for MEE was 1.40–1.50%. The non-parametric bootstrap analysis indicated the stable model. The 90% CIs on structural parameters and IIV were reasonably estimated (Table 3).

Table 3 Vecuronium PK parameters in burns *vs* non-burns

Parameter	Population mean		Inter-individual variability (CV%)	
	Model estimate (%RSE)	Bootstrap median (90% CI)	Model estimate (%RSE)	Bootstrap median (90% CI)
CL (litre min^{-1})	0.51 (2.07)	0.48 (0.41–0.54)	49.40 (9.45)	50.75 (40.39–56.87)
V_1 (litre)	10.25 (1.27)	9.64 (8.55–10.66)	45.50 (14.68)	45.86 (38.27–54.58)
CL_2 (litre min^{-1})	0.66 (2.00)	0.67 (0.63–0.75)	13.04 (49.24)	15.34 (11.51–19.22)
V_2 (litre)				
Non-burn	9.70 (5.85)	9.02 (7.86–9.58)	15.30 (10.46)	22.67 (17.80–26.55)
Burn			43.82 (4.67)	47.97 (44.69–73.05)
CL_3 (litre min^{-1})				
Non-burn	0.095 (1.26)	0.090 (0.075–0.092)	18.03 (61.60)	17.85 (12.91–21.39)
Burn	0.12 (1.24)	0.11 (0.08–0.11)		
V_3 (litre)	43.79	41.99 (14.64–44.08)		
Proportional error (%)	13.23	13.01 (12.28–21.36)		
Additive error (ng ml^{-1})	2.15	2.15 (2.06–2.20)		

Discussion

The pharmacological significance of our findings can be summarized in two aspects: (i) the altered vecuronium disposition was characterized in burns compared with that in non-burns using a population PK modelling approach; and (ii) data below LOQ were analysed using a likelihood-based approach in population PK model construction.

After i.v. administration, plasma vecuronium concentrations declined poly-exponentially over time, best described by a three-compartment model. Higher variability of the volume of distribution and enhanced inter-compartmental clearance at the terminal phase contributed to the rapid reduction of plasma drug concentrations at the distributional phases in burns. The extent of tissue distribution was not only increased but also highly variable in burns compared with non-burns. Multiple factors may contribute to the distributional changes of the drug, for example, physiological changes by the thermal trauma, degree and mechanism of the injury, and site of burn. While other injury-related variables such as TBSA, albumin levels, post-burn days, and intraoperative estimated blood loss were statistically significant when individually examined, they were not able to further explain the changes among burn patients in addition to BURN. Of the burn-related covariates, no single factor explained better over the others and the BURN covariate was sufficient to account for the observed differences in PK parameters in our study. Concomitant drugs (i.e. propofol, fentanyl, and nitrous oxide) have not been described to interact with vecuronium at the doses used in the present study.[13 14]

Studies of atracurium in burn patients have shown an increase in plasma protein binding due to increased α_1-acid glycoprotein (AAG) plasma concentrations.[1] The free fraction of vecuronium in humans has been reported to range between 31% and 35%,[15] and it can be inferred that the plasma protein binding of vecuronium may increase after burn injury, similar to observations in atracurium, which translates into a lower fraction of drug in plasma (<31%). This may in part explain the observed differences in the distribution of vecuronium in burns. Nevertheless, increased AAG plasma concentrations have not been found to significantly contribute to vecuronium resistance.[16]

Changes in plasma protein concentrations are observed in burn patients. During the first 48 h after burn injury, albumin concentrations decrease (acute phase) and remain low for close to 60 days (hypermetabolic phase). The albumin concentrations in burn patients [2.8 (0.7) g dl^{-1}] were significantly lower than in the non-burns [4.6 (0.7) g dl^{-1}] and negatively correlated to the TBSA [51% (27–81%)]. The TBSA showed a trend with CL_3, but this correlation was not confirmed because BURN was sufficient to account for the differences between burns and non-burns. In addition, all patients in the present study were recruited during the hypermetabolic phase (post-burn 4–57 days). Post-burn days showed a trend with the V_1, but this correlation could not be confirmed due to limited data for days more than 30.

While vecuronium PK has been previously modelled using two[7 8] or three[4–6] compartment PK models, an accurate description of the tissue distribution of vecuronium has been challenged by incomplete data at the terminal phases that result from insufficient sampling periods, data censoring, or both during quantitative analysis. Consequently, parameter estimates that describe the rate and extent of tissue distribution are mostly incomparable among the studies.

In this study, vecuronium concentrations fell below the quantifiable level by 4 h after the bolus to a greater extent in burns than in non-burns, accounting for 26% of the total data being below LOQ. To overcome this problem, a likelihood-based approach was used to adjust the likelihood of the data above the LOQ as previously suggested.[10] The importance of proper handling below LOQ data in PK/PD analysis is widely recognized, and studies have demonstrated that the use of a likelihood-based approach could prevent potential biases in parameter estimations, compared with ignoring below LOQ observations.[10 17 18] Although implementation of the likelihood-based method improved the overall performance of our model, many patients

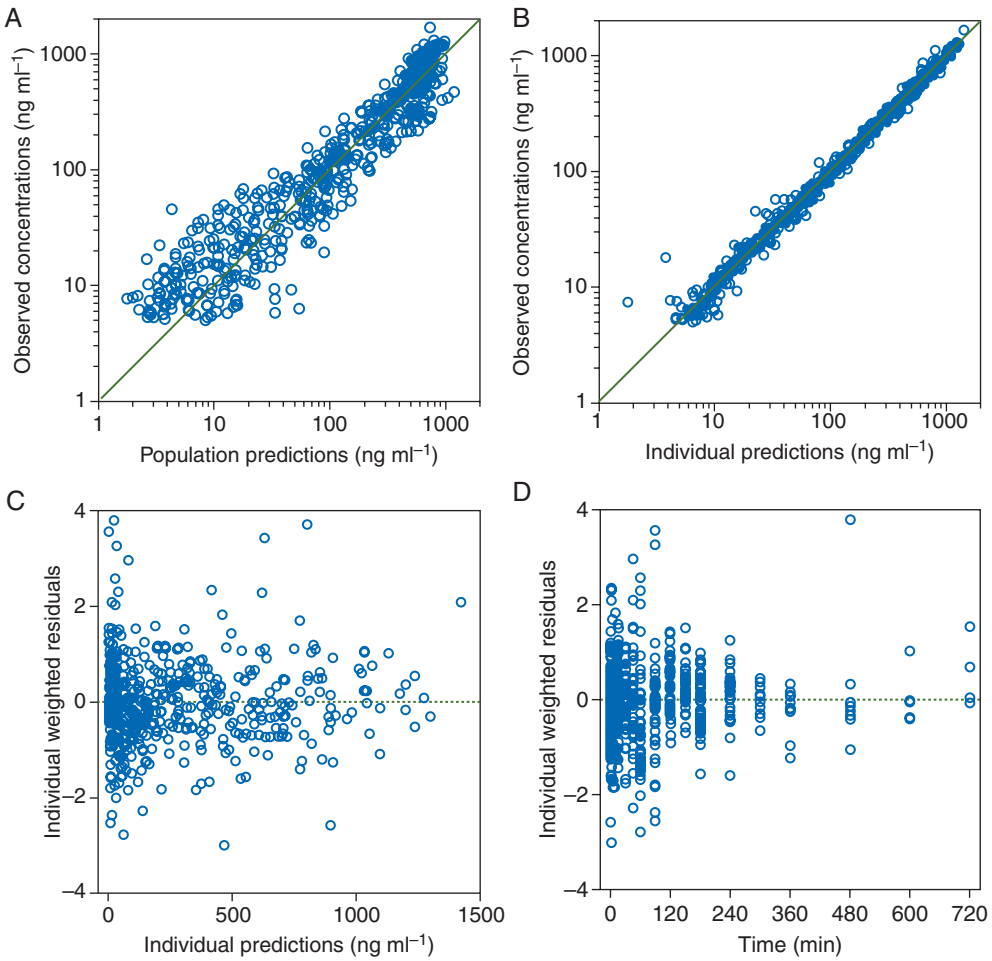

Fig 3 Goodness-of-fit plots for population and individual predictions including observed *vs* population predicted (A) or individual predicted concentrations (B); and individual weighted residuals *vs* individual predicted concentrations (C), or time (D). Solid lines represent the line of unity.

did not have observed data at later time points, which prevented further delineation of the effect of burn injury on vecuronium disposition. Adjusting the likelihood for the observations above LOQ has been shown to partially correct the bias related to ignoring below LOQ observations; however, this approach has some limitations. The method used in this study does not consider information about the time points recorded for observations below LOQ, which can lead to distinctive bias. Future studies that provide the LOQ observations can use a different approach that maximizes the likelihood for all data by treating the below LOQ observations as censored.[10]

The clinical relevance of the covariate effects was examined by simulations. While simulations demonstrated that the terminal half-life and context-sensitive half-time of vecuronium are shorter in patients with burns, the difference did not reach a statistical significance; thus, a new dose regimen for burns could not be estimated.

The underlying mechanism of resistance to NDNMBAs in burns cannot be explained by differences in PK parameters alone, and it may result from a combination of various factors associated with burn injury. A previous report on rocuronium, which belongs to the same aminosteroidal family as vecuronium, suggested that resistance to NDNMBA may be due to burn-related changes in pharmacodynamic (PD) properties, that is, drug–receptor interaction.[19] The studies have suggested that resistance may result from an increase in the number of acetylcholine receptors in the neuromuscular junction, which may require higher NDNMBA dose to exert the desired response.[3] A study in paediatric patients showed a correlation between the effective dose of vecuronium (34–65 $\mu g\,kg^{-1}$) and twitch suppression relative to TBSA.[20] Further investigation of the relationship between vecuronium disposition and burn-related changes in PD properties using a comprehensive PK/PD modelling approach may help to understand resistance to this NDNMBA in burn patients.

In summary, our PK analysis suggests that the rate and extent of tissue distribution of vecuronium are increased in burn patients, resulting in the rapid reduction of plasma vecuronium concentrations at the distribution and terminal phases. This may partially contribute to the known resistance to vecuronium in patients with major burns. Among burn patients, however, no physiological factor useful for predicting or

guiding anaesthetic drug dose was found. Thus, drug dosing in major burns has to be carefully individualized and titrated based upon clinical response.

Authors' contributions

K.R.V.-V. performed the PK analysis and wrote the manuscript. K.K. designed and coordinated the study. S.Y. designed and coordinated the study. S.W. performed the PK analysis and wrote the manuscript. T.H.H. designed and coordinated the study, and wrote the manuscript.

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Declaration of interest

None declared.

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