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Population Pharmacokinetics of Etomidate in Neonates and Infants with Congenital Heart Disease

Felice Su¹, Mohammed H. El-Komy^{2,3}, Gregory B. Hammer^{1,2}, Adam Frymoyer¹, Carol A. Cohane², and David R. Drover²

¹Department of Pediatrics, Stanford University School of Medicine, Stanford, USA

²Department of Anesthesia, Stanford University School of Medicine, Stanford, USA

³Department of Pharmaceutics and Industrial Pharmacy, Beni-Suef University, Egypt

Abstract

Background—Etomidate is a rapid-onset, short-acting hypnotic medication administered for induction of anesthesia. It is currently approved by the Food and Drug Administration for use in older children and adults. Pharmacokinetic data to help guide dosing in neonates and infants is lacking.

Objective—The aim of this study was to determine the pharmacokinetics of etomidate in neonates and infants with congenital heart disease undergoing cardiac surgery.

Methods—Four neonates and sixteen infants, postnatal age 0.3 – 11.7 months, requiring open-heart surgery received 0.3 mg/kg of etomidate administered as a single intravenous dose prior to surgery. Blood sampling for plasma etomidate concentration occurred immediately following etomidate administration until the initiation of cardiopulmonary bypass. A population pharmacokinetic approach using nonlinear mixed-effects modeling was applied to characterize etomidate pharmacokinetics.

Results—The pharmacokinetics of etomidate was described by a two-compartment model with first-order elimination. An allometric weight-based model was applied to scale results to a 70 kg adult. Covariates including age and cardiac physiology were not found to significantly impact etomidate pharmacokinetics. The study population was found to have a central and intercompartmental clearance of 0.624 L/min/70-kg and 0.44 L/min/70-kg, respectively; central and peripheral distribution volume of 9.47 and 22.8 L/70-kg, respectively. Inter-individual variability was between 94–142% for all parameters and residual variability was 29%.

Conclusions—The clearance of etomidate is lower in neonates and infants with congenital heart disease compared to published values for older children without congenital heart disease. In addition, etomidate pharmacokinetics is highly variable in this pediatric cardiac population.

Corresponding Author: Felice Su, MD, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Stanford University School of Medicine, 770 Welch Road, Suite 350, Palo Alto, CA 94304 USA, felicesu@stanford.edu, Tel: (650) 498-7565, Fax: (650) 723-5201.

We have no conflicts of interest to declare.

Keywords

etomidate; pharmacokinetics; infant; newborn; congenital heart defects

Introduction

Etomidate is an imidazole derivative that induces hypnosis rapidly following intravenous (IV) injection. It is currently FDA approved for the induction of anesthesia in adults and children at least 10 years of age.⁽¹⁾ It is commonly administered off-label in infants and young children for induction of general anesthesia particularly in preparation for endotracheal intubation in emergency departments, operating rooms and intensive care units. More recently, etomidate administration for procedural sedation in children has also been published.^(2–4)

Etomidate is administered off-label to children primarily due to its favorable hemodynamic profile and minimal impact on cardiac function.^(5–7) These attributes also make etomidate a favorable induction agent for children with congenital heart disease undergoing operative repair or palliation. Despite reports of its use in this pediatric cardiac population, limited pharmacokinetic (PK) data exist for etomidate, particularly in neonates and infants.^(7, 8) Therefore, a population PK study of etomidate in neonates and infants with congenital heart disease was conducted.

Material and Methods

Study Conduct

This study was conducted applying the highest ethical standards. Following IRB approval, we enrolled 20 neonates and infants with congenital heart disease scheduled for surgical intervention. Written informed parental consent was obtained for each participant. Induction of anesthesia and insertion of central venous and arterial catheters occurred as standard of care. Patients who did not have an endotracheal tube in place prior to induction of anesthesia had inhalational induction or, if an IV catheter was in place, intravenous ketamine and fentanyl for induction of anesthesia. Patients who did have an endotracheal tube in place prior to induction of anesthesia received fentanyl and inhalational agent titrated to effect. All patients received rocuronium for neuromuscular blockade, inhalation anesthesia and fentanyl for maintenance of anesthesia. Patients were continuously monitored for heart rate and rhythm, arterial blood pressure, central venous pressure, oxygen saturation and capnography as per standard of care. Etomidate 0.3 mg/kg IV was administered to each patient over 15 seconds prior to the initiation of the surgical procedure. PK samples, 0.5 mL blood for patients up to 5 kg and 1 mL blood for patients over 5 kg, were drawn at baseline (prior to etomidate administration) and at 1, 5, 10, 15, 30, 45, 60, 90, 120 minutes after etomidate administration and every 60 minutes thereafter until the initiation of cardiopulmonary bypass. Samples were drawn from a catheter not used for etomidate administration. Blood for PK sampling did not exceed 3 mL/kg for any patient. Plasma samples were obtained by centrifugation and stored at -75°C until bioanalysis.

Measurement of etomidate plasma concentrations was performed by iC42 Clinical Research and Development Laboratory (Aurora, CO).

Pharmacostatistical Analysis

NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD) was used for population PK analysis. All models were run using the first order conditional estimation with interaction (FOCE-I) method. RStudio Version 0.97.320 (RStudio, Inc., Boston, MA) was used for goodness-of-fit diagnostics. Selection between models was based on successful NONMEM minimization with at least 3 significant digits in each parameter estimate, decrease in objective function (OBJ) of >3.84 ($p < 0.05$), visual inspection of diagnostic scatter plots (observed vs. individual and population predicted concentrations, residual/conditional weighted residual vs. predicted concentration or time), the precision of the parameter estimates measured by the percent standard error of the mean, and changes in the inter-individual and residual variability.

Pharmacokinetic Model Development

One, two and three-compartment models were evaluated. The inter-individual variability (IIV) of parameters was described using an exponential variance model: $P_i = \theta_k \exp(\eta_{ki})$, where P_i is the estimated parameter value for individual i , θ_k is the typical population value of parameter k , and η_{ki} is the inter-individual random effect for individual i and parameter k .

Additive, proportional and combined (additive and proportional) error functions were evaluated to model the residual variability. A proportional residual error function was incorporated into the final model: $C_{obs,ij} = C_{pred,ij} * (1 + \varepsilon_{ij})$ where $C_{obs,ij}$ is the observed concentration j in individual i , $C_{pred,ij}$ is the individual predicted concentration, ε_{ij} is the residual random error.

Covariate Analysis

Biologically or clinically plausible covariates were evaluated for their influence on pharmacokinetic parameters. Covariate analysis occurred using a standard forward addition and backward elimination procedure. An increase in OBJ >7.88 ($p < 0.005$) during backward elimination was considered significant and warranted inclusion of the covariate in the final model.

Based on principles of pediatric clinical pharmacology and previous population PK models in neonates and children for a range of compounds, an allometric weight-based model scaled to a 70 kg adult was first implemented and applied to all parameters:^(9, 10)

$$P_i = P_{ref} * (WT_i / 70 \text{ kg})^{\theta_{allometric}}$$

where P_i is the typical parameter value for individual i with weight WT_i , P_{ref} is the parameter value for an individual with weight equal to the reference weight of 70 kg and $\theta_{allometric}$ is an allometric power parameter fixed at 0.75 for clearances, and 1 for volumes.^(11–13) The appropriateness of using an allometric exponent of 0.75 for clearances was also evaluated by estimating the allometric exponent parameter.

The influence of maturational processes was assessed by evaluating age-related effects on clearance. Linear, exponential and variable slope sigmoidal (Hill equation) models were tested to account for maturational differences in neonates and infants.⁽¹⁴⁾

$$\text{Hill equation: } P_i = \theta_k * \text{AGE}^{\text{Hill}} / (\text{AGE}^{\text{Hill}} + \text{EP}_{50}^{\text{Hill}})$$

where P_i is the parameter value for individual i , θ_k is the population estimate of parameter k , AGE is the patient age and EP_{50} is the AGE where the parameter value is 50% of its mature value.⁽¹⁵⁾ Both postnatal and corrected ages were evaluated. Postnatal age was defined as chronologic age after birth in months. Corrected age is defined as the age in months based on the expected date of delivery and is calculated as follows: $\text{corrected age}_{\text{months}} = \text{postnatal age}_{\text{months}} - (40 \text{ weeks} - \text{gestational age}_{\text{weeks}}) / 4.33$.⁽¹⁶⁾

Finally, the effect of the type of cardiac lesion on clearance was evaluated to assess the impact of intracardiac shunt and mixing lesions.

$$P_i = \theta_k * \text{MIX}^C$$

where P_i is the parameter value for individual i , θ_k is the population estimate of parameter k , MIX is a factor that describes the magnitude of effect if a mixing cardiac lesion is present, and C is an indicator value assigned to 1 when cardiac mixing lesion exists and 0 when there is no cardiac mixing lesion.

Model Evaluation

A bootstrap analysis was performed on the PK model to evaluate parameter uncertainty and estimate 95th percentile confidence intervals. One thousand replicates of the dataset were generated by repeated sampling with replacement, and the final PK model was used to estimate model parameters for each of the 1000 data sets. The overall influence of each subject's data on the estimates of the model fixed and random effects was assessed through case deletion diagnostics using Cook's distance.⁽¹⁷⁾ In addition, a visual predictive check (VPC) was conducted to evaluate how well the final model predicted the distribution of measured etomidate concentrations.⁽¹⁸⁾ The final model was used to simulate a dataset having the same characteristics as the observed dataset (i.e., the number of subjects, dose administered, and PK sampling times) using NONMEM. For each individual in the dataset, a vector of parameters was drawn from a log-normal distribution with a variance corresponding to the inter-individual variability previously estimated. For each simulated concentration a simulated residual error was added. Simulations were replicated 1000 times. The 5th, 50th, and 95th percentiles of the simulated concentrations were calculated for each replicate. The 95% confidence intervals across the 1000 replicates were computed for these percentiles and then compared graphically to the observed data.

Simulation

A simulation study using NONMEM was performed to determine expected plasma concentrations of the lowest and highest weight patients compared to the etomidate plasma concentration associated with hypnosis in adults, 230 ng/mL.⁽¹⁾ Simulated doses were 0.3 mg/kg and 0.6 mg/kg, which were chosen to cover the dosing range currently approved for use in adults and older children by the FDA. Simulated doses were administered as a bolus

dose over 15 seconds. One thousand Monte Carlo simulation replicates were performed, incorporating the final population model parameter estimates of fixed effects, inter-individual and residual random variability.

Results

Demographics of the 20 subjects enrolled are listed in Table 1. The median postnatal age and weight of the subjects were 3.35 months (8 days – 11.74 months) and 4.98 kg (2.5 – 8.35 kg). Sixteen patients (89%) did not have an endotracheal tube in place pre-operatively and received an anesthetic regimen as described in the Methods. Two patients received additional midazolam with or without propofol for maintenance of anesthesia. The remaining two patients were intubated pre-operatively and received inhalational agent and fentanyl for maintenance of anesthesia. Median IV fluid administration during the PK sampling period was 12.3 mL/kg/hr (range 3.5–24.9 mL/kg/hr). All PK samples were processed at the iC42 Clinical and Development Laboratory. The etomidate assay was linear in the range of 3 – 20,000 ng/mL. Five percent of samples were below the lower limit of quantitation (3 ng/mL) and were not included in the data analysis. The intra-day coefficient of variation for the assay was 9.8%.

A two-compartment PK model best fit the data. Model exploration was performed using ADVAN 3 TRANS 4 subroutine with covariance between CL, V1, Q and V2 inter-individual random effects. All models minimized with successful execution of the covariance step. The addition of allometric scaling of weight to all parameters and evaluation of age and cardiac physiology did not improve model fit with large residual variability of 42%. Subsequently, an analysis for outliers using Cook's distance was performed (Figure 1). Based on this analysis, subjects 9, 15 and 18 were identified as extreme outliers and excluded from the final model development.

Concentration-time profiles for all infants are shown in Figure 2. Outlier subjects 9 and 18 are notable for peak concentrations more than twice the upper range of the remaining subjects and outlier subject 15 is notable for a ten-fold increase increase in drug concentration from the prior measurement at the final timepoint. Key model development steps following removal of outlier subjects are shown in Table 2. Diagnostic plots of inter-individual variability on clearance versus weight, postnatal age and corrected age of the base model are shown in Figure 3. Final parameter estimates and inter-individual variability including standard errors of the point estimates and bootstrap statistics for the original and final PK model excluding subjects 9, 15, and 18 are represented in Table 3. The addition of allometric scaling of weight to all parameters resulted in a 10-point decrease in the objective function following removal of the outlier subjects. Evaluation of the allometric scaling exponent for clearance resulted in an estimated power parameter of 0.73 with no significant change in the objective function compared to using a fixed exponent of 0.75. Implementation of linear, exponential, and variable slope sigmoidal models of age on clearance did not provide any further improvement in the model after scaling of clearance for weight. In addition, the type of cardiac lesion was not found to be a significant predictor of etomidate disposition. Neonates and infants were found to have a clearance of 0.624 L/min/70-kg, inter-compartmental clearance of 0.44 L/min/70-kg, central volume of

distribution of 9.47 L/70-kg and peripheral volume of distribution of 22.8 L/70-kg. Inter-individual variability in PK parameters was large (range 94–142%). The fixed effect parameters were estimated with acceptable precision as indicated by 95% confidence interval and relative standard error < 25%.

The VPC of the final population PK model (Figure 4) demonstrated that the 2.5th, 50th and 97.5th percentiles of the observed concentrations were consistently within the 95% confidence intervals of the simulated concentration percentiles. This finding suggests that the model can adequately replicate the features of the observed data and confirms that the variability of the parameters were well estimated.

Using the final PK model, the percentage of simulated patients that achieved plasma concentrations >230 ng/mL over time is presented in Figure 5 for 2.5 kg (low weight) and 8.35 kg (high weight) patients who were administered etomidate doses of 0.3 mg/kg and 0.6 mg/kg. The median time to a plasma concentration <230 ng/mL was approximately 11 and 15 minutes for low and high weight patients administered 0.3 mg/kg, respectively, and 21 and 28 minutes for low and high weight patients administered 0.6 mg/kg of etomidate, respectively.

No adverse events occurred in relation to study conduct. All patients tolerated etomidate administration without changes in heart rate or blood pressure requiring clinical intervention.

Discussion

In this single-dose etomidate PK study, neonates and infants with congenital heart disease undergoing cardiac surgery were found to have a clearance of 0.624 L/min/70-kg, inter-compartmental clearance of 0.44 L/min/70-kg, central volume of distribution of 9.47 L/70-kg and peripheral volume of distribution of 22.8 L/70-kg. However, large variability in etomidate PK was seen between patients. A dose of 0.3 mg/kg was predicted to be adequate to reach peak plasma concentrations associated with hypnosis in adults in 96% of simulated patients.

Drug metabolism during infancy changes as the newborn matures and develops at a rapid rate. The impact of development on drug disposition is complex and is dependent on changes in body composition, organ blood flow, and metabolic enzyme maturation. In adults, etomidate undergoes rapid hydrolysis by hepatic esterases to inactive metabolites.^(1, 19) Although etomidate is a commonly used medication in pediatric patients due to its minimal effect on cardiac function, its disposition in neonates and infants has not been reported. In 2011, Lin et al. published the PK profile of etomidate administered to patients ages 6 months to 13 years.⁽²⁰⁾ They found etomidate clearance to be 1.5 L/min/70kg in a typical 4 year-old child without cardiac disease. In their study, etomidate clearance was influenced by both weight and age. Younger children were found to have a higher clearance after scaling for weight compared to older children due to the relatively larger liver mass per body weight in younger children. A six-month old, 7-kg infant would be predicted to have an etomidate clearance of 0.29 L/min based on the full covariate model by Lin et al. This is

in contrast to the etomidate clearance found in our population PK study of 0.11 L/min for a six-month old, 7-kg infant. We believe the lower clearance found in our study compared to Lin et al. is attributable to the difference in the ages of the populations studied. Lin et al. studied mainly an older pediatric population with over 70% of subjects > 2 years old. In contrast, we studied neonates and young infants with a median age of 3.4 months with only one subject > 7 months of age. The lower clearance of drugs metabolized by the liver in neonates and young infants as found for etomidate in our study is consistent with the current understanding of liver maturation and the development of drug metabolizing enzymes.^(21–23) Therefore, the PK model by Lin et al., in which clearance increases as age decreases, is likely inappropriate to apply to neonatal and younger infant populations in which liver maturation needs to be accounted.

In adults, a standard dose of 0.3 mg/kg of etomidate results in a duration of hypnotic effect of approximately 3–5 minutes and is associated with a plasma concentration of >230 ng/mL.⁽¹⁾ Concentrations associated with hypnosis in children have not been established. In our study, fifteen minutes following an etomidate dose of 0.3 mg/kg, 45% of subjects had plasma concentrations > 230 ng/mL (median 512 ng/mL, range 288–1220). At thirty minutes, 20% of subjects continued to have concentrations associated with hypnosis in adults. The findings in our study show a lower etomidate clearance scaled for weight in neonates and infants with congenital heart disease when compared to older children and adults, resulting in increased plasma concentrations and potentially prolonged hypnotic effect in most patients. These findings were further explored by performing a simulation study. Our simulations showed a prolongation in hypnotic effect in the dosing range currently FDA approved for older children and adults. The median duration of plasma concentrations >230 ng/mL was 11 to 28 minutes for the dose range 0.3–0.6 mg/kg. Thirty percent of 2.5 kg simulated patients who received etomidate 0.6 mg/kg had plasma concentrations >230 ng/mL beyond 30 minutes compared to 47% of 8.35 kg simulated patients.

Etomidate inhibits cortisol production in the adrenal gland primarily through the inhibition of 11- β hydroxylase.^(24, 25) Etomidate administration has been associated with increased morbidity and mortality in adult patients with sepsis or septic shock but this finding remains controversial in the current literature.^(26–29) A single dose of etomidate for the induction of anesthesia in children undergoing cardiac surgery resulted in significantly decreased cortisol levels when compared to ketamine both during and at 24 hours following surgery.⁽³⁰⁾ With the lower etomidate clearance and higher plasma concentrations found in our neonatal and young infant population, prolonged exposure may result in increased impact on adrenal function. The clinical significance of stress response modulation during pediatric cardiac surgery has yet to be elucidated in the setting of etomidate administration, exogenous steroid administration, cardiac disease and cardiopulmonary bypass.^(31–33) Many patients receive a large dose of corticosteroid during cardiopulmonary bypass, and this may mitigate the effect of etomidate on adrenal function.

Children with congenital heart disease constitute a very heterogeneous, complex population with dynamic organ dysfunction and alterations in organ blood flow. In general, our small sample size limited our ability to evaluate the etiology of the large variability seen in our

study population. Similar variability in etomidate PK has also been found in adult healthy volunteers in whom the inter-individual variation in clearance was 81% and residual variability was 32%.⁽³⁴⁾ Despite intended enrollment of infants with a wide age range, only 1 patient was older than 7 months of age. This severely limited our ability to adequately account for the influence of age on PK parameters. Similarly, our study population enrolled a limited number of neonates. This did not allow for covariate exploration based on age groups comparing neonates and infants to identify any potential influence of age on etomidate clearance. We were also unable to identify any clinical etiology or covariate to account for extreme outlier subjects 9, 15 and 18. An additional limitation is that the induction of anesthesia was not standardized in this study and may have contributed to the large variability seen in our measurements due to cardiovascular effects of anesthetic agents as well as potential drug-drug interactions. Similarly, there is a relatively wide range of IV fluid administration that occurred during the PK sampling. While etomidate PK is linear in adults in the dose range of 0.2–0.6 mg/kg, it is possible that at the upper range of adult etomidate dosing recommendations (0.6 mg/kg) infants may not exhibit linear PK as this has not been studied and infants may be exposed to higher plasma concentrations and durations of effect than our simulations predict.⁽³⁵⁾ Finally, the effect of etomidate on adrenal function, which remains an important topic of debate, was not elucidated in this study.

Conclusion

Etomidate clearance is highly variable and appears diminished in neonates and infants with congenital heart disease. In our simulation studies, this results in prolonged etomidate exposure and hypnotic effect in this population. A dose of 0.3 mg/kg of etomidate adequately achieves concentrations associated with hypnosis in adults in >95% of simulated neonates and infants but may result in prolonged exposure in some patients. Increased awareness for this potential prolonged exposure, increased hypnotic effect and impact on adrenal function is important in this population. Larger PK studies are needed in this age population to further delineate appropriate dosing adjustments due to the high variability.

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Figure 1.
Cook's distance plot evaluating for outliers in the original dataset. Subjects 9, 15 and 18 were identified as extreme outliers with Cook's distance > 5 .

Figure 2.
Concentration-time profiles for subjects included in the final PK model presented on both linear scale and logarithmic scale. Outlier subjects 9 (red), 15 (blue) and 18 (green) were removed from the final PK model.

Figure 3. Interindividual variability on clearance (η_{CL}) versus weight, postnatal age and corrected age of the base model with outliers removed.

Figure 4.

Visual predictive check of the final allometric pharmacokinetic model. Dashed lines represent the 5th, 50th, and 95th percentiles of the observed concentrations. Solid lines represent the 5th, 50th, and 95th percentiles of the predicted concentrations. Shaded areas represent the 95% confidence intervals for the 5th, 50th, and 95th percentile of simulated concentrations. Circles represent the observed concentrations.

Figure 5.

Percentage of simulated patients with a plasma concentration associated with hypnosis in adults (>230 ng/mL) over time after a single etomidate dose. Patients ($n=1000$) were simulated at each weight (2.5 kg low weight and 8.35 kg high weight) and dose (0.3 mg/kg and 0.6 mg/kg) using the final pharmacokinetic model.

Table 1

Subject demographics and baseline characteristics.

Subject	Gestational Age (weeks)	Postnatal Age (months)	Corrected Age* (months)	Weight (kg)	Gender	Cardiac Lesion
1	34.0	4.2	2.8	4.95	Male	Pulmonary atresia
2	41.7	1.7	2.1	4.30	Male	Pulmonary valve stenosis
3	38.7	0.7	0.4	4.10	Male	Tetralogy of Fallot
4	39.0	6.7	6.5	7.05	Male	Coarctation of the aorta & ventricular septal defect
5	38.7	3.3	3.0	5.85	Female	Atrioventricular canal defect & pulmonary stenosis
6	39.0	4.1	3.9	6.50	Female	Hypoplastic left heart syndrome
7	38.9	0.3	0.0	2.60	Female	Tetralogy of Fallot
8	36.0	1.3	0.4	2.50	Male	Tetralogy of Fallot
9	39.3	1.5	1.3	3.96	Male	Transposition of the great arteries
10	39.7	1.2	1.2	3.50	Male	Ventricular septal defect, branch pulmonary artery stenosis
11	40.0	11.7	11.7	6.90	Male	Tetralogy of Fallot, pulmonary atresia, major aortopulmonary collateral arteries
12	40.0	4.6	4.6	8.35	Male	Pulmonary stenosis, pulmonary artery hypoplasia, coronary artery stenosis
13	37.0	2.4	1.7	5.00	Female	Pulmonary atresia
14	36.0	5.7	4.8	5.43	Female	Pulmonary atresia
15	39.0	5.6	5.4	5.00	Male	Tetralogy of Fallot, pulmonary atresia, major aortopulmonary collateral arteries
16	39.4	3.0	2.9	4.55	Male	Tetralogy of Fallot, pulmonary atresia, major aortopulmonary collateral arteries
17	39.0	6.3	6.0	7.25	Female	Transposition of the great arteries, pulmonary stenosis, ventricular septal defect
18	40.0	3.5	3.5	4.95	Female	Tetralogy of Fallot, pulmonary atresia, major aortopulmonary collateral arteries
19	37.0	6.0	5.3	5.90	Female	Atrioventricular canal defect
20	39.7	0.6	0.5	4.22	Male	Tetralogy of Fallot, pulmonary atresia, major aortopulmonary collateral arteries

* Corrected age=months = postnatal age+months – (40 weeks – gestational age)/weeks/4.33.

Table 2

Key model development steps for model development following removal of outlier subjects 9, 15, and 18.

Model Run	Compared to	Description	MVOF	Change in MVOF
1		Base model, proportional error model	1378	
2	1	Base model, additive error model	1626	248
3	1	Allometric weight effect	1368	-10
4	1	Postnatal age effect (Hill equation)	1370	-8
5	1	Postnatal age effect (linear)	1368	-10
6	1	Postnatal age effect (exponential)	1383	5
7	1	Corrected age effect (linear)	1368	-10
8	1	Intracardiac shunt effect	1389	11
9	3	Allometric weight effect and postnatal age effect (linear)	1382	14
10	3	Allometric weight effect and corrected age effect (linear)	1368	0

Table 3

Parameter estimates from the original (full dataset) and final etomidate population PK model with outliers removed. IIV is the inter-individual variability, RSE is the relative standard error and CI is the confidence interval obtained from bootstrap analysis.

Parameter	Estimate	%IIV	%RSE	Bootstrap 95% CI
Original (Full dataset)				
CL (L/min/70 kg)	0.466	129	15.5	0.25, 0.78
V1 (L/70 kg)	8.07	151	11.6	3.4, 17.8
Q (L/min/70 kg)	0.289	219	17.5	0.1, 0.76
V2 (L/70 kg)	19.7	171	17.1	7.6, 46.3
Residual Variability (CV%)	42		35.1	27.2, 53.3
Final (Outliers removed)				
CL (L/min/70 kg)	0.624	94	11.7	0.4, 0.99
V1 (L/70 kg)	9.47	121	16.4	5.5, 18.4
Q (L/min/70 kg)	0.44	142	22.3	0.23, 0.96
V2 (L/70 kg)	22.8	127	23.6	12.4, 48
Residual Variability (CV%)	29.2		19.2	21.3, 33.1