

Pharmacokinetic Modeling of Propofol in Indian Children

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Abstract

Objective: To analyse the PK (pharmacokinetics) of propofol after single bolus dose in children undergoing elective general surgery and to establish a PK model of propofol after single bolus dose in children undergoing elective general surgery and to establish a PK model of propofol. **Materials and Methods:** Twelve healthy Indian children aged 5–12 years who underwent elective general surgery under general anesthesia received propofol at an intravenous bolus dose of 2.5 mg/kg. The plasma propofol concentration over the next 12 h was estimated using high-performance liquid chromatography. A total of 144 samples were analyzed, and PK parameters were evaluated using nonlinear mixed-effects modeling. Results were validated using bootstrap analysis, and visual predictive check was done to evaluate the final model. **Results:** Propofol PK in Indian children was characterized by a three-compartment model similar to adults. The model derived estimates of PK parameters are as follows: volume of the central compartment (V_1) = 598.73 ml/kg, volume of the second compartment (V_2) = 821.12 ml/kg, volume of the third compartment (V_3) = 1097 ml/kg, systemic clearance (CL_1) = 22.1 ml/kg/min, and intercompartmental clearances CL_2 and CL_3 which were 42.5 ml/kg/min and 10.4 ml/kg/min, respectively. **Conclusion:** The final PK model imparted a robust characterization of propofol PK. Inclusion of body weight as a covariate to the model exhibited a significant impact on propofol PK. The execution of this patient derived PK model should support future population PK studies that include diverse population with sparse sampling to support the dosing of propofol in Indian children undergoing surgery under total intravenous anesthesia.

Keywords: Analysis, concentration, covariate, total intravenous anesthesia, weight

INTRODUCTION

Propofol is an intravenous anesthetic agent which is increasingly being used in pediatric anesthesia for both induction and maintenance. The pharmacokinetics (PK) of propofol was studied extensively in children of different age groups in Caucasian and Chinese population with bolus dose as well as continuous infusions.^[1-7] It is well understood that race, genes, and ethnicity affect the disposition of anesthetic drugs in the body.^[6,8-10] Further, nutrition and body composition may also play an important role in the PK and pharmacodynamics (PD) of the drugs.^[11] Anthropometric studies show that there is a difference in weight for age, height for age, and growth velocity curves between the children of Indian subcontinent compared to the developed countries.^[12] However, there is paucity of information regarding the PK of propofol in Indian children. This is important as the PK evaluation in Indian adults has shown a lower volume of distribution and clearance as compared to the western population.^[13]

We undertook this study to define accurately the PK parameters of propofol in Indian children and to establish a new PK

model involving patient-specific covariates such as age, body weight, height, body surface area, and gender using nonlinear mixed-effects modeling. This propofol PK model is expected to improve the anesthetic management of children undergoing surgery under total intravenous anesthesia (TIVA).

MATERIALS AND METHODS

Study design

This study commenced after approval from the Institute Ethics Committee. Written informed consent from the parents of all the included children was obtained. This study was conducted between January 2013 and December 2015. The total number of participants in the study was 12. The children aged between 5 and 12 years with the American Society of

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Anesthesiologists' physical status I and scheduled for elective general surgery under general anesthesia were included in the study. Participants were excluded if they had (i) cardiovascular, respiratory, metabolic, renal, hematologic, hepatic, or central nervous system diseases; (ii) allergic history to any of the constituents of propofol; (iii) previous adverse anesthetic event; and (iv) anticipated potential airway management problems.

All the participants received premedication orally with 0.5-mg/kg midazolam syrup 20 min prior to surgery. Anesthesia was induced with 2.5-mg/kg propofol bolus given over a period of 20 s and maintained with isoflurane in a mixture of oxygen (40%) and nitrous oxide (60%). Propofol was not administered further during the course of surgery. Analgesia was provided with a bolus of fentanyl 2 µg/kg before induction.

Conduct of the study

Two intravenous lines (22G) were secured before induction of anesthesia: one in the antecubital vein and the other in a vein on the contralateral hand using 5% EMLA (Eutectic Mixture of Local Anesthetics) cream. The antecubital intravenous access was utilized for blood sampling. The blood samples were obtained before and at 2, 4, 6, 10, 20, 30, 60, 90, 120, 240, and 480 min after administration of propofol. A total of 12 blood samples including the predose sample were collected from each participant in heparinized tubes and centrifuged at 1200 G for 15 min. The supernatant plasma was then transferred to polypropylene storage tubes and kept at -20°C until the time of analysis. Plasma concentrations of propofol were measured within 3 weeks after sampling by modified high-performance liquid chromatography with ultraviolet (UV) detection using a previously reported method.^[14] The analysis was carried out using 250 mm × 4.6 mm column packed with 10-µm Spherisorb reversed-phase octadecylsilane particles (C 18). Propofol was monitored by a UV detector at a 270-nm wavelength. Linearity was validated by measuring area responses at the concentration range of 0.001–12 µg/ml. The minimum quantifiable amount often known as the limit of quantification is the concentration that can be quantitated reliably with specific level of accuracy and precision. The limit of detection of propofol was found to be 0.0001 µg/ml while limit of quantification was found to be 0.001 µg/ml.

Data handling

Propofol pharmacokinetic model building

PK analysis was executed with the Phoenix NLME software, version 1.3, 2014 (Certara L.P. Pharsight, St. Louis, MO, USA). Workflow of the propofol PK model building is depicted in Figure 1, and the steps involved are described briefly in Appendix [Electronic Supplementary Material]. Naïve-pooled method was used to identify the structural model using Akaike information criterion (AIC) value as the selection criterion and to obtain initial estimates. Nonlinear mixed-effects modeling was performed using first-order conditional estimation–extended least squares (FOCE-ELS) method to generate the base model without including covariates. Subsequently,

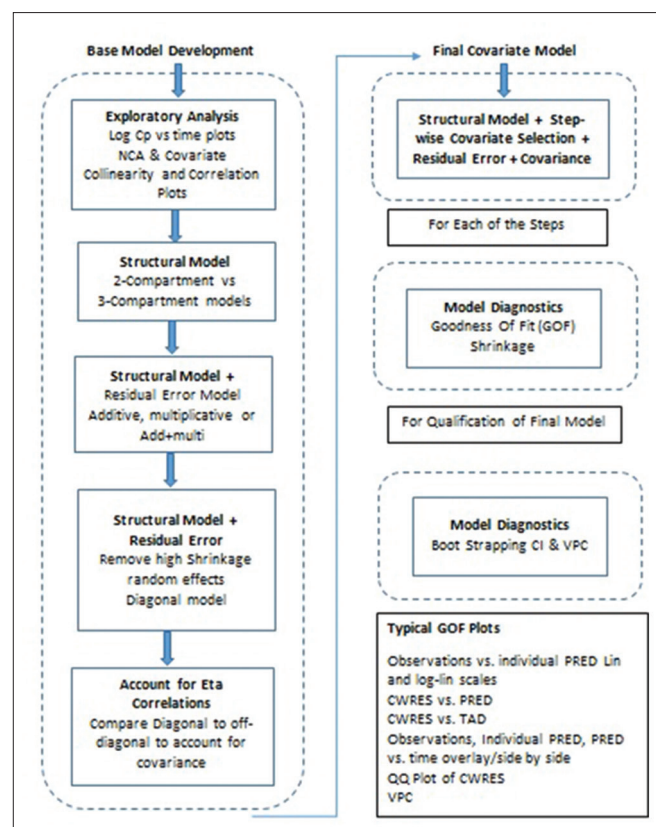


Figure 1: Propofol pharmacokinetic modeling workflow. NCA = Noncompartment analysis, CI = Confidence interval, CWRES = Conditional weighted residuals, GOF = Goodness of fit, TAD = Time after dose, PRED = Predictions, VPC = Visual predictive check

in a stepwise fashion, the covariate model was developed. Covariates such as weight, height, age, and sex were found to be possible explanatory variables in the PK model parameters. First, the covariates and PK parameters were graphically explored to gain information about the covariates which are likely to alter the variability of PK parameters. Then, the influence of the appropriate covariates on the variability of these PK parameters of propofol was further analyzed using the stepwise covariate method.

An exponential variation model was described, $P_i = P_{pop} \exp(\eta_i)$, where P_i is individual PK parameter in i^{th} subject and P_{pop} is the population mean estimate of the parameter and η_i is the deviation of i^{th} subject from the mean with the presumption that η is ordinarily distributed with mean zero and variation ω .

Random effect was modeled on CL_i and V_i . Residual unexplained variability was modeled by the proportional error model as $C_{obs,ij} = C_{ij} (1 + \epsilon_{ij})$, where $C_{obs,ij}$ is the observed plasma concentration in the i^{th} subject at the j^{th} point in time, C_{ij} is the predicted plasma concentration, and ϵ_{ij} is the proportional residual error with the presumption $\epsilon \sim N(0, \sigma^2)$.

The final model was defined after introducing the covariates into the base model using quasi-random parametric expectation maximization (QRPEM) method for more accurate population

estimates.^[15] With every inclusion of a covariate to base model, the enhancement in the fit was analyzed. Covariate was incorporated if the change in objective function value (dOFV) was >3.84 , which correlates to a statistical significance of $P < 0.05$, found on a Chi-squared distribution. During the successive backward deletion of covariates, a more conventional statistical significance criterion was applied ($dOFV > 7.879$, $P < 0.005$). Ancillary criteria for assessing the covariates incorporated were (1) depletion in unexplained interindividual variability, (2) diagnostic plots of the weighted residuals, and (3) goodness of fit plots.

Model evaluation and simulation studies

Accuracy and robustness of the final model were evaluated by bootstrap resampling method and visual predictive check (VPC) method in Phoenix NLME (version 1.3).^[16,17] The final model was integrated to 1000 bootstrap datasets to acquire the median value for each PK parameter after accounting for random-effect and fixed-effect (residual unexplained variability and interindividual variability) parameters. Median values of the nonparametric bootstrap analysis were analyzed with the original data for bias and predictive error with 95% confidence intervals.

A VPC was performed to compare the replicated and actual data. The plasma concentration versus time profiles of propofol was replicated using 1000 replicates of each participant, and the predicted concentration data and the 95% prediction interval were enumerated and analyzed with the observed concentration data.

RESULTS

The demographics of the participated children are described in Table 1. A total of 144 blood samples from 12 children were analyzed. All the data points were used for the PK modeling. Individual plasma propofol concentration against time curves is displayed in Figure 2.

Propofol pharmacokinetic model and covariate analysis

A three-compartment model fitted data better compared to a two-compartment model based on AIC values [Appendix Table 1] and individual residuals versus individual-predicted plots in initial naïve-pooled analysis. Therefore, the model was specified as volume of distribution of the central compartment (V_1), volume of distribution of

the second (rapid distribution) compartment (V_2), volume of distribution of the third (slow distribution) compartment (V_3), systemic clearance (CL_1), rapid distributional clearance (CL_2), and slow distributional clearance (CL_3).

The initial estimates derived from the naïve-pooled analysis were used to generate the base model by FOCE-ELS estimation for a three-compartment model. The error model was refined by comparing the additive, multiplicative, and combined additive-multiplicative residual models. The multiplicative residual error model showed the least bias as assessed by scatter plots of conditional weighted residuals (CWRES) and population predictions as shown in Figure 3.

The potential influence of covariates on PK parameters was explored by visual inspection of correlation plots between covariates and PK parameters. Scatter plots were utilized to inspect the effect of continuous variables, and box plots were utilized for categorical variables. Sources of variability that can influence drug exposure were determined using correlation plots of individual random effects (η) with mean zero and estimated variance (ω) of parameters such as V_1 , V_2 , V_3 , CL_1 , CL_2 , and CL_3 versus the covariates. The resulting graphs were screened using visual inspection. On visual examination of exploratory plots of PK parameters versus covariates, age and body weight showed a positive correlation on random effects of V_1 , CL_1 , and CL_3 . The plots also showed the influence of gender on random effects of V_2 , CL_1 , and CL_3 .

Subsequently, the covariates were evaluated systematically by testing the influence of subject-specific covariates such as age, body weight, height, body surface area, and gender on PK parameter estimates using the structural model of propofol. All the covariates were added to automated covariate search with FOCE-ELS engine to test for the significance of the addition and deletion of the covariate from the full model. The evaluated covariate was added to the model if the decrease in the objective function value (OFV) which is $-2 \log \text{likelihood} (-2 \text{ LL}) > 3.841$, and a covariate was eliminated from the full model if the rise in OFV (-2 LL) was > 7.879 .

Table 1: Demographic data

Male (n)	7/12
Female (n)	5/12
Age (years)	7 (3.5)
Weight (kg)	21 (7)
Height (cm)	120 (20)
BMI (kg/m ²)	15 (2)
BSA (m ²)	0.87 (0.25)

All values except gender are represented as median (and interquartile range). BMI=Body mass index, BSA=Body surface area

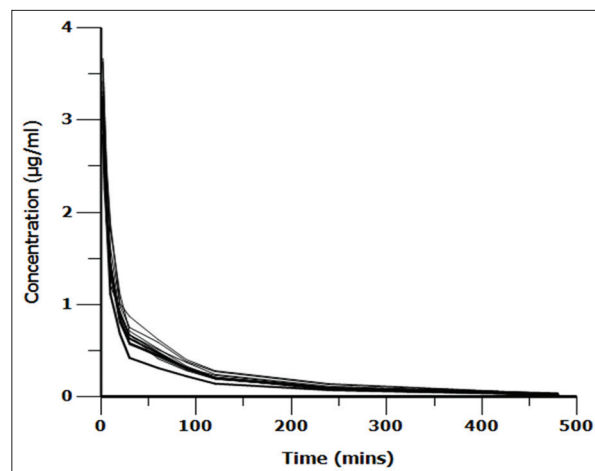


Figure 2: Individual plasma propofol concentration versus time curves

This analysis suggested a significant influence of body weight on V_1 , CL_1 , and CL_3 with a difference of 124 in -2 LL value when compared to the base model. Other covariates such as age, height, gender, and body surface area did not significantly affect the PK parameters.

Final model development

The final model was defined after introducing the covariates into the base model using QRPEM method for more accurate population estimates. The population η scatter plots were visually inspected for covariate influence and compared with the previous model that had not accounted for covariate. In addition, the final population PK model preference was on the basis of goodness-of-fit criteria as follows: (1) the log-likelihood differentiation (-2 LL) between models, (2) graphical characterization of the observed plasma against

population-predicted concentrations and the observed plasma against individual-predicted concentrations, (3) CWRES against time after dose plots to confirm appropriateness of structural model, and (4) CWRES versus population-predicted concentrations for suitability of the residual error model. A three-compartment model with a diagonal variance (ω) of V_1 and CL_3 fixed to value of 0 was used to refine the population estimates. Between-subject variability (BSV) values were found to be 6.5%, 20.1%, 18.5%, and 32.1% for CL_1 , CL_2 , V_2 , and V_3 , respectively. The relative standard error of estimation (RSE%) for the population estimates ranged from 4.5% to 21.6%. The base model and final model estimates, RSE, and BSV values are presented in Table 2.

Goodness-of-fit plots of the final PK model displayed no considerable bias. The model was robust showing appropriate fit of the final model to plasma propofol concentrations [Figure 4]. Individual-observed and population-predicted plasma concentrations were symmetrically dispersed across the line of unity, and CWRES versus population-predicted concentrations were homogeneously distributed around 0 with most of the CWRES <2 , suggesting little to no predilection in the predictions correlating to low or high propofol concentrations. Similarly, CWRES versus time after dose plot showed no bias with CWRES <2 .

Evaluation of the final pharmacokinetic model

The resampling effectively merged in the bootstrap assessment and the final model parameter estimates were within $\pm 2\%$ compared with bootstrap median. Parameter estimates were within their 95% confidence interval, as displayed in Table 3. The percentiles of the observation were plotted with the corresponding percentiles of the prediction over the time course, as shown in Figure 5. The VPC plot exhibited a good fit between the predicted and observed concentrations with most parts of percentile lines of observations which were within the predictive interval of simulations. Overall, the results of the final model demonstrated that the predictions of plasma propofol concentrations were largely unbiased, and the final model was able to describe the influence of the covariates on propofol PK.

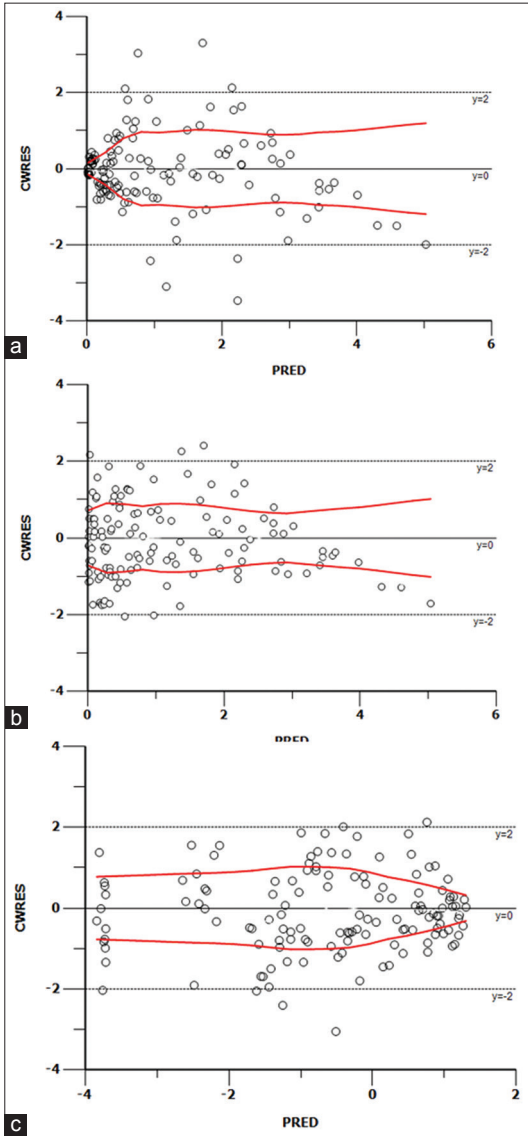


Figure 3: Conditional weighted residuals versus prediction plots of error model. (a) Additive error model. (b) Multiplicative error model. (c) Combined additive and multiplicative error models

Table 2: Population pharmacokinetic parameter estimates of the base and final model of propofol				
Parameter	Base model estimate	Final model		BSV (%)
		Estimate	RSE (%)	
V_1 (ml)	14,835.2	13,471	9.54	Fixed at 0
V_2 (ml)	25,239.7	18,475	17.43	18.5
V_3 (ml)	36,778.4	24,683	21.6	32.1
CL_1 (ml/min)	510.75	497.04	4.5	6.5
CL_2 (ml/min)	1185.5	1046.57	9.5	20.1
CL_3 (ml/min)	153.35	233.97	13.33	Fixed at 0

V_1 =Volume of central compartment, V_2 =Volume of the second compartment, V_3 =Volume of the third compartment, CL_1 =Systemic clearance, CL_2 =Rapid distributional clearance, CL_3 =Slow distributional clearance, BSV=Between-subject variability, RSE=Relative standard error

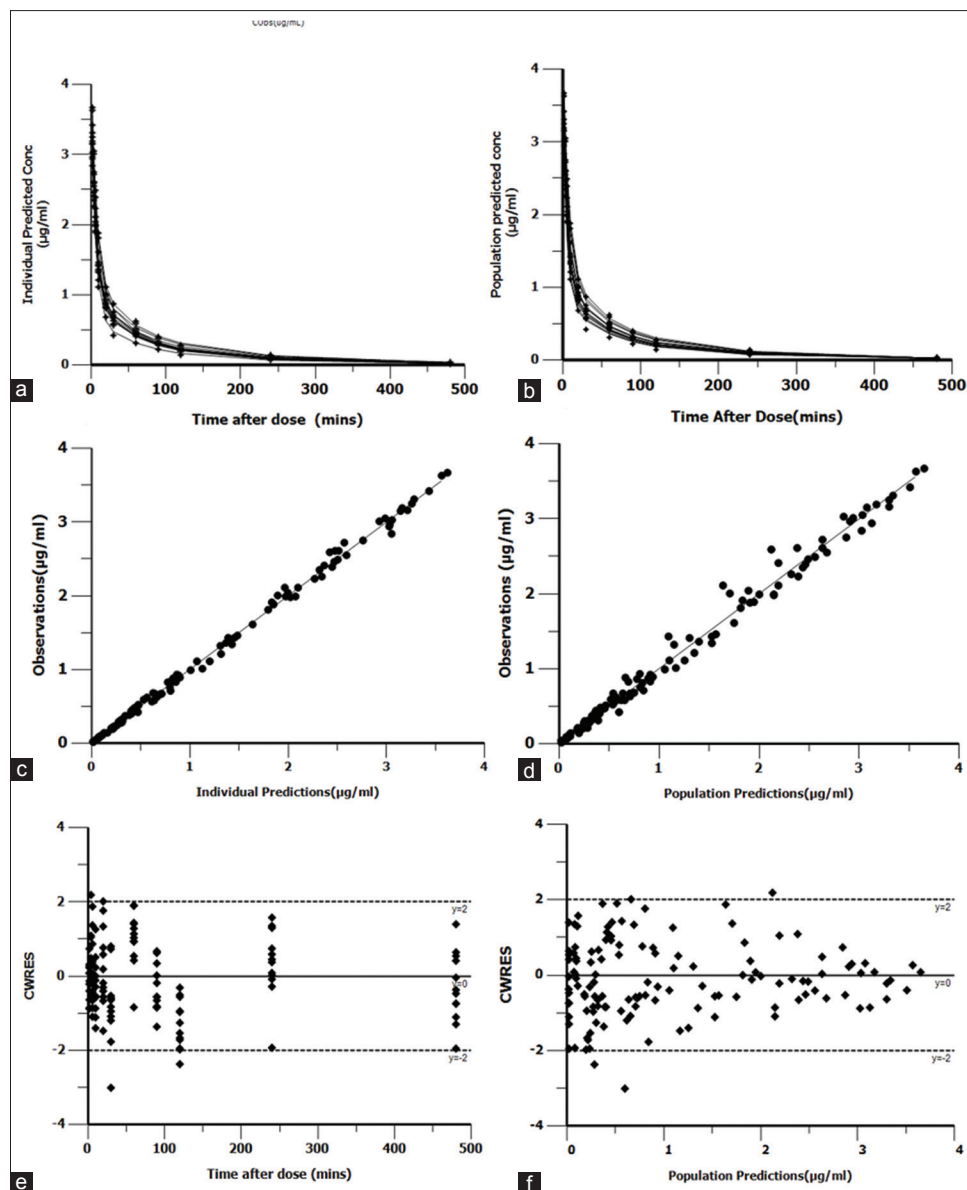


Figure 4: Goodness-of-fit graphics for propofol covariate model. Graphs depict (a) Individual-predicted concentration versus time. (b) Population-predicted concentration versus time. (c) Observed concentrations versus individual predictions. (d) Observed concentrations versus population predictions. (e) Conditioned weighted residuals versus time. (f) Conditioned weighted residuals versus population predictions. The line of identity is included in panels A and B

DISCUSSION

This study was conducted with an aim to establish a PK model of propofol for Indian children for improved management of TIVA and thus facilitating to customize its use in TCI (Target Controlled Infusion) system. Owing to significant interindividual PK and PD differences, TCI systems have a performance bias of 20%–30%.^[18] Using a PK model derived from own population and including patient-specific covariates such as age, weight, height, and sex, the performance of the TCI can be enhanced to reduce bias and improve precision. As the first step toward ideal population, PK model development is the ability to identify and confirm the best structural model, and the foundation is laid with the rich sampling schedule of the 12 subjects included in the study.

The plasma concentration of propofol was best represented applying a three-compartment model with the volume of the central compartment calculated to be 598 ml/kg and total body clearance of 22.1 ml/kg/min. Body weight was found to be a significant covariate that determines population PK of propofol in this age group. Although on the exploratory plots, age appeared to have some influence on V_1 , CL_1 , and CL_3 , it was not found significant in the stepwise covariate search analysis.

The final model represented the PK of propofol in the given population with adequate precision as concluded with goodness-of-fit plots. Less RSE% for population estimates suggested that parameters are precisely estimated and the values are reliable. Likewise, the random and homogeneous distribution of CWRES indicated that the error model described

Table 3: Comparison of population parameter estimates and the results of bootstrap validation

Population estimates		Bootstrap estimates					Percentage difference between bootstrap median value and original estimate
Parameter	Original estimate	Mean	CV (%)	Median	2.5% CI	97.5% CI	
V ₁ (ml)	13,487.4	13,507.37	1.4	13,501.55	13,169.54	13,903.58	0.10
V ₂ (ml)	18,527.6	18,518.15	8	18,508.79	15,604.2	21,267.42	-0.10
V ₃ (ml)	24,624.8	24,774.33	9.88	24,596.52	20,335.86	30,378.51	-0.11
CL ₁ (ml/min)	497.048	498.9646	2.22	498.33	479.7795	522.2448	0.26
CL ₂ (ml/min)	1045.72	1044.881	7.26	1039.55	904.3208	1190.033	-0.59
CL ₃ (ml/min)	232.307	231.2283	9.75	234	183.2099	268.734	0.77
dVdBW	0.858944	0.861088	5.14	0.86	0.788086	0.966486	-0.32
dCLdBW	0.518756	0.509603	20.93	0.52	0.253966	0.680581	1.01
dCL3dBW	0.965312	1.0024	39.74	0.97	0.324539	1.804017	0.65

V₁=Volume of central compartment, V₂=Volume of the second compartment, V₃=Volume of the third compartment, CL₁=Systemic clearance, CL₂=Rapid distributional clearance, CL₃=Slow distributional clearance, CV=Coefficient of variation, CI=Confidence interval

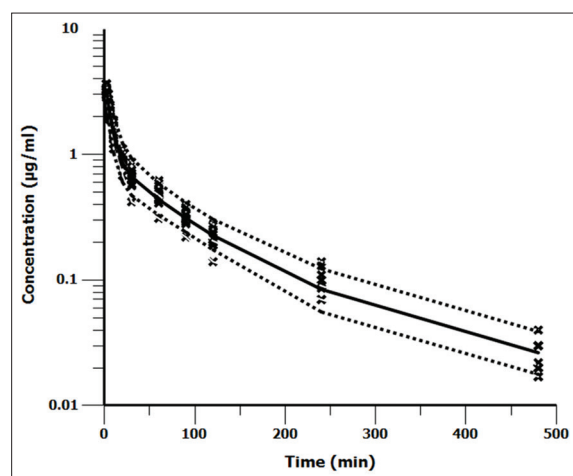


Figure 5: Visual predictive check plot. The black dots represent the observations, the dashed black lines are the 5th and 95th percentiles of the model simulation, and the solid black line depicts the model-predicted median

the variance of the data precisely. There were no random effects included in the final model for V₁ and CL₃, suggesting that the study included homogeneous population that would not allow us bring out BSV. BSV was reported to be 6.4% for CL₁ and ranged from 18.5% to 32.1%, suggesting that variability in these secondary parameters (V₂, V₃, and CL₂) expected. Moreover, the reliability of this final model was confirmed with bootstrap analysis, which exhibited narrow confidence intervals for the parameter estimates. The VPC stipulated an adequate probability of the final model. Overall, the final population estimates from this study are reliable.

Our study population demonstrated a remarkably higher volume of the central compartment (598.73 ml/kg) compared to adults of Indian origin (211.9 ml/kg).^[13] These results are similar to those obtained in children of other racial origins, as shown in Table 4. This is in tune with the existing knowledge regarding PK differences between adult and pediatric population. Majority of the available studies reported a volume of the central compartment between 500 and 600 ml/kg.

There are contrasting reports on Chinese children; V₁ was significantly higher (730 ml/kg) in a report by Shangguan *et al.*^[19] in children of 5–9 years' age group, but Jones *et al.*^[4] reported 597 ml/kg in children of 4–12 years' age group. Although Saint-Maurice *et al.*^[2] also reported the V₁ as 722 ml/kg, the studied population was younger (4–7 years) which could be the reason for higher V₁. From this study, we could infer that the Indian children in this age group would require a higher induction dose, than that required by adults. The systemic clearance obtained in our study was 22.1 ml/kg/min, which is less compared with other pediatric studies [Table 4] except for the report by Shangguan *et al.* in Chinese children. The differences between these studies may be attributable to the dissimilarity of the population studied, anesthetic techniques performed, and different time points for collection of blood sample. Lower clearance compared to other population may also indicate a need for a lower maintenance dose of propofol in our population. However, a comprehensive evaluation of simultaneous PK and PD may be required in a large population with sparse sampling to confirm the findings of this study.

Our study also compared well with the other studies for defining the important covariates influencing the PK of propofol. Previous studies emphasized that weight is a significant covariate whereas age is not, for defining the PK estimates and hence plasma concentrations for propofol.^[1,3,4,19,20] Therefore, induction dose of propofol in Indian children should be considered by weight of the children regardless of the age whereas the maintenance dose for achieving a target concentration may need further evaluation. This study can aid us further to design better population PK studies in the near future by including diverse population.

The clinical importance of lesser clearance of propofol obtained in this population needs to be explored. The conventional wisdom may suggest a lesser maintenance dose requirement. However, this limitation can be overcome by incorporating the variables from this model into a TCI algorithm dedicated for use in children. Another limitation of

Table 4: Reported population pharmacokinetic parameter values for propofol and their comparison with the current study

Study	Age (years)	Patients (n)	Sampling site	V ₁ (ml/kg)	CL (ml/kg/min)	Reference
Marsh <i>et al.</i>	1-12	20	Vein	340	34	[1]
Kataria <i>et al.</i>	3-11	53	Vein	520	34	[3]
Valtonen <i>et al.</i>	3-10	40	Vein	530	32	[20]
Saint Maurice <i>et al.</i>	4-7	10	Vein	722	30.6	[2]
Jones <i>et al.</i>	4-12	12	Vein	597	40.4	[4]
Shangguan <i>et al.</i>	5-9	11	Vein	730	12.5	[19]
Current study	5-12	12	Vein	598	22.1	-

V₁=Volume of central compartment, CL₁=Systemic clearance

this study was the lack of evaluation of PD aspect of propofol use in children.

CONCLUSION

The final PK model developed in the current study is a robust representation of propofol PK in Indian children. The execution of this patient-derived PK model can provide a safe and effective TIVA practice in children, which would allow titration of target concentrations. This structural PK model of propofol can aid future population PK studies to support the dosing in children.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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APPENDIX

Appendix: Steps involved in propofol pharmacokinetic model building

- Exploratory analysis was carried out initially, and log-linear plots of concentration versus time [Appendix Figure 1] for each individual subject data were reviewed for plausible number of compartments for compartmental modeling (i.e. to identify the structural model for base model). Based on these exploratory plots, the data fit to either two- or three-compartment model since there are two or three straight line regions in the plots. However, comprehensive quantitative assessments along with other diagnostic plots are required to select the best model
- Noncompartmental analysis was carried out for gathering rough initial estimates for central compartment. These summary Pharmacokinetics (PK) parameters are useful for initial estimates of clearance and volume of distribution of central compartment. The Phoenix NLME has an interactive tool for selecting the initial estimates for other compartments upon visual inspection for fit
- Structural model confirmation was done using naïve-pooled method and with additive, multiplicative, and additive + multiplicative residual error models
- Three-compartment model with multiplicative error model provided lower Coefficient of variation % values for all parameter estimates when compared to two-compartment model
- Three-compartment model found to be appropriate based on the Akaike information criterion (AIC) value [lower AIC value for three-compartment model as shown in Appendix Table 1] and diagnostic plots such as population prediction (pred) versus time plots (better fits and less deviation of observed data from model predicted) and residuals versus pred plots (less bias and randomly distributed)
- A three-compartment model with multiplicative error is selected as the final base model before doing the covariate search to select significant covariates to be added to the model. As the first step, correlation plots for various PK parameters and covariates were visually inspected for the correlation. Correlation among the covariates was also considered to identify collinear covariates so that only one of the collinear covariates was included in the model
- Body weight was added as covariate, shrinkage values examined, and random effects for V2, V3, Cl, and Cl2 were included in the model (<13%)
- Eta scatter plots were evaluated for covariance effects [Appendix Figure 2]. The statistical tests revealed no significant covariance effect after accounting for covariance Cl and V2, Cl2 and V2, and V3 and V2.
- The final model has PK parameters that can be described as follows:

$$V = tvV * (BW/\text{median}(BW))^{\wedge}dVdBW$$

$$V2 = tvV2 * \exp(\eta V2)$$

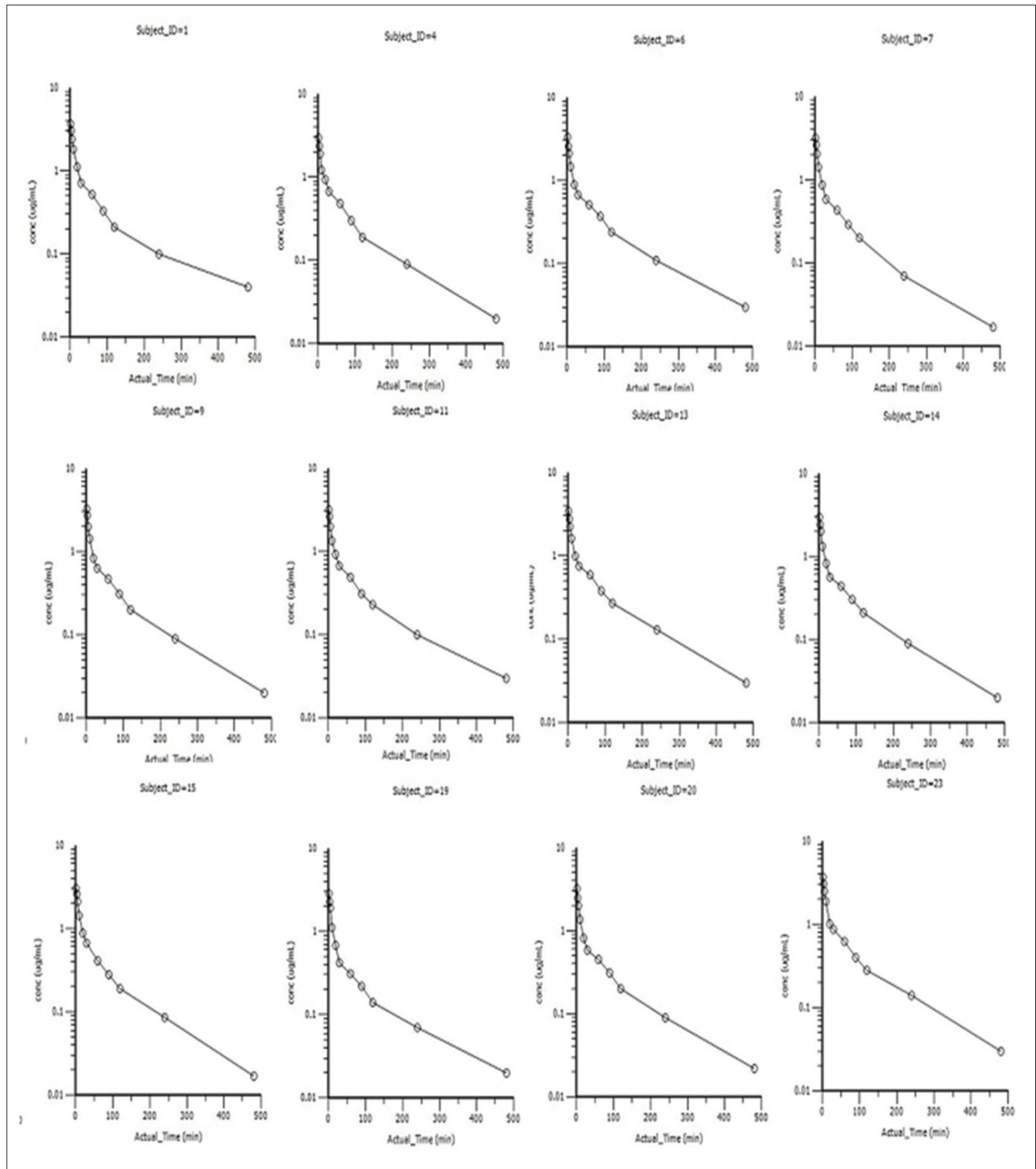
$$V3 = tvV3 * \exp(\eta V3)$$

$$Cl = tvCl * (BW/\text{median}(BW))^{\wedge}dCldBW * \exp(\eta Cl)$$

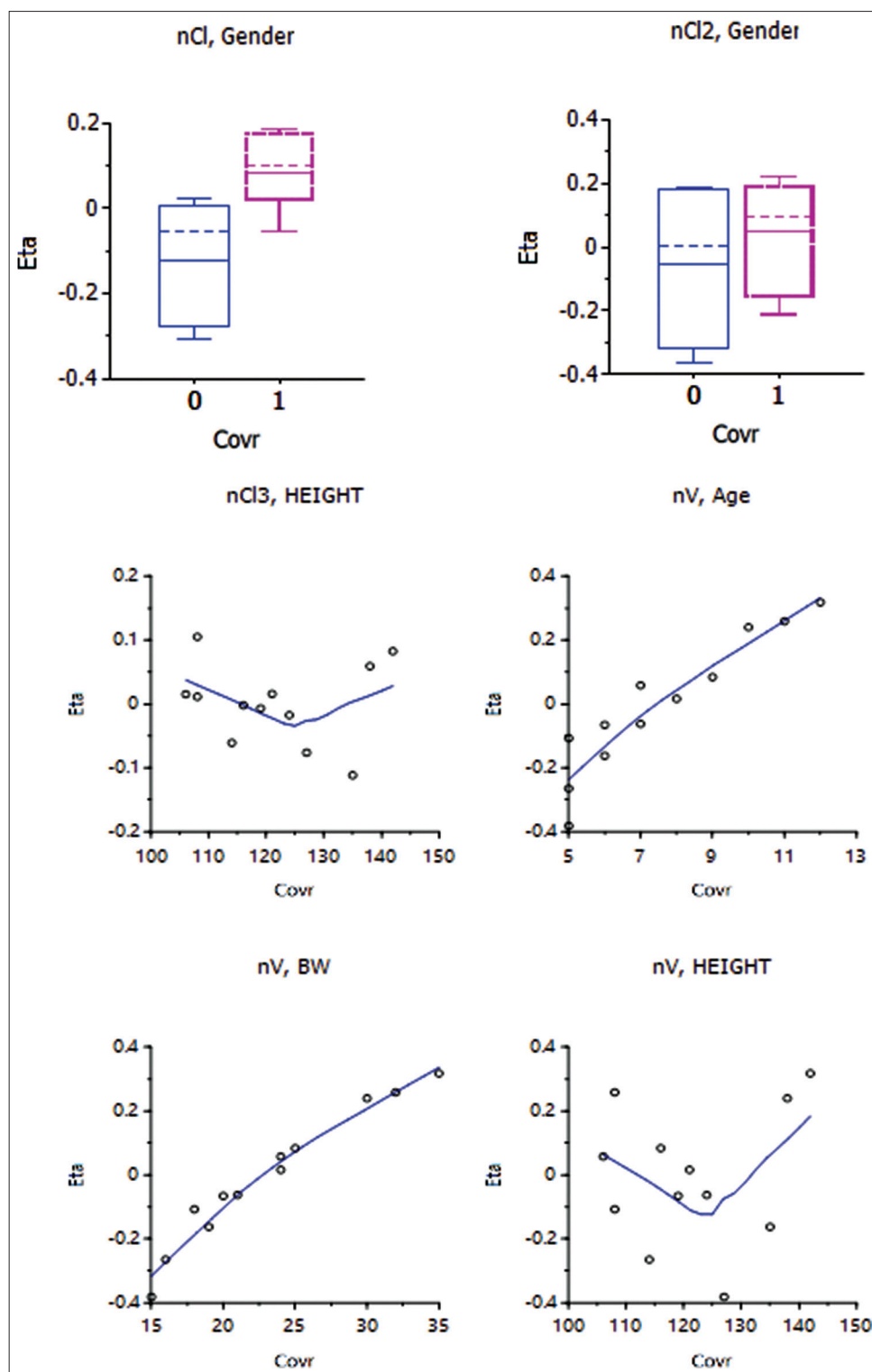
$$Cl2 = tvCl2 * \exp(\eta Cl2)$$

$$Cl3 = tvCl3 * (BW/\text{median}(BW))^{\wedge}dCl3dBW$$

- Diagonal variance (DV) versus population prediction (POP PRED) plot of the final model is shown in Appendix Figure 3
- Bootstrap and visual predictive check were conducted to evaluate the final model and it was found to be qualified.



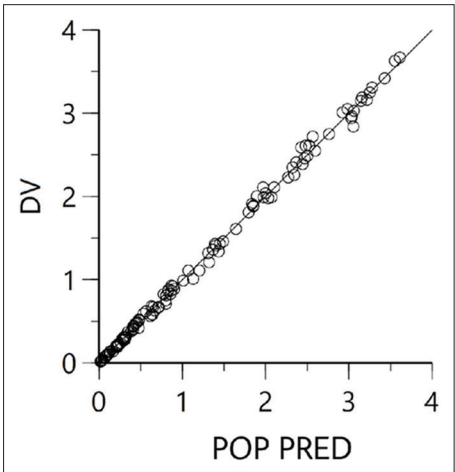
Appendix Figure 1: Log-linear plots of plasma concentration versus time profiles of all participants following IV bolus dose of propofol



Appendix Figure 2: Representative covariate plots for evaluating the correlation between η and covariates. (After accounting for covariance Cl and V2, Cl2 and V2, and V3 and V2)

Appendix Table 1: Comparison of Akaike information criterion values of all participant in two- and three-compartment model												
Naïve-pooled multiplicative model	Subject ID											
	1	4	6	7	9	11	13	14	15	19	20	23
	AIC value											
Two compartment	-10.75	-17.93	-20.84	-22.7	-21.65	-17.45	-21.22	-28.14	-27.96	-26.19	-23.17	-19.24
Three compartment	-30.21	-32.3	-37.98	-45.06	-35.62	-40.45	-32.99	-39.66	-47.26	-35.58	-37.63	-27.66

AIC: Akaike information criterion



Appendix Figure 3: Diagonal variance (DV) versus population prediction (POP PRED) plot of the final model