

CYP2B6 Genotype Guided Dosing of Propofol Anesthesia in the Elderly Based on Nonparametric Population Pharmacokinetic Modeling and Simulations

Research Article

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Abstract

Objective: The primary aim of this article is to test the hypothesis that nonparametric pharmacometric modeling will accurately identify CYP2B6 genotype subgroups based on data from a study that reported results based on parametric pharmacokinetics (PK).

Methods: Propofol concentration-time data were originally reported in the Kansaku et al., 2011 publication. Nonparametric Nonlinear Mixed Effects Modeling (NLME) was conducted using the PMETRICS R package while population pharmacokinetic model parameters were estimated using a FORTRAN compiler. Finally, model-based dosing simulations were conducted in the MATLAB Simbiology.

Results: A total of 51 patients were included in the final PK analysis. A two-compartment gamma multiplicative error model adequately described the propofol concentration-time data. The individual observed versus predicted $R^2=0.99$ and $R\text{-squared}=0.93$ for the population model predictions. Neither the UGT1A9 nor the CYP2B6 G516T gene variants resulted in statistically significant PK parameter differences while the CYP2B6 A785G gene variants resulted in statistically significant differences for the elimination rate. Model-based dosing-simulations comparing patients with the CYP2B6 AA & AG genotypes to both GG genotypes and patients from a multicenter trial suggest a 50% decrease in propofol infusion dose, to 25mg/kg/min, be made to result in approximately equivalent drug exposures.

Conclusion: Based on the pharmacometric modeling and exposure, if no dosage adjustments are made for the elderly CYP2B6 AA and AG genotypes, a 250% higher propofol blood exposure will be evident within 1-hour from the start of the infusion. Thus, based on the pharmacokinetic model, genotyping elderly patients for the CYP2B6 AA and AG gene variants will decrease the total propofol blood exposure during anesthesia and sedation when an infusion dose adjustment is made to 25mg/kg/min.

Keywords: Precision Medicine; Propofol; Genotype; Nonparametric Pharmacokinetics; Anesthesia.

Introduction

It is known that propofol is primarily metabolized by the cytochrome P450 2B6 (CYP2B6) gene, with metabolic contributions from CYP2C9, UDP glucuronosyltransferase 1A1 (UGT1A1), and UGT1A9 [1-4]. Further, it is also known that propofol is a widely used intravenous anesthetic used for the induction and maintenance of anesthesia, as well as, for sedation in mechanically ventilated patients [5]. However, despite the clinically relevant single nucleotide polymorphisms (SNPs) associat-

ed with CYP2B6 informing healthcare professionals to account for patient genotypes when prescribing, no study has proposed genotype-informed dose adjustments for patients administered propofol [6, 7].

A study by Loryan and colleagues reported that common CYP2B6 and UGT1A9 SNPs were tested in patients administered propofol; however, no significant genotype-based findings were found [8]. Similarly, Choong and colleagues reported no significant differences in neither the CYP2B6 nor the UGT1A9 SNPs on propofol

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metabolism, but found that women metabolize propofol faster than men [9]. Several studies have attempted to test whether the polymorphic CYP2B6 gene results in any significant differences in propofol clearance and consciousness following bolus doses and infusions, but none have resulted in recommendations for gene-guided propofol dosage adjustments [8, 10-13].

One consistent theme among studies is the wide interindividual variability in propofol plasma levels; however, no quantifiable pharmacometric parameter, based on genotype, has been reported for later hypothesis-testing. Further, experiments are often repeated and patients with lower frequency allele subgroups are consistently under-represented, leading to potentially incomplete results due to statistical power. These cases may be addressed by applying principles of pharmacometric modeling and simulation where Monte-Carlo simulations are conducted using mathematic model parameters from original studies of varying sizes to represent patient subgroups [14]. This article uses nonparametric pharmacometric modeling of a previously published propofol study to identify doses precisely based on the CYP2B6 genotype [10].

So, with this information as a background, the primary aim of this article is to test the hypothesis that nonparametric pharmacometric modeling will accurately identify CYP2B6 patient subgroups in a dataset that previously used parametric pharmacokinetics. If pharmacogenomic differences exist, then equivalent propofol doses will be provided for each patient subgroup. Thus, the aim of model-based dosing simulations will be to result in approximately equivalent propofol exposures, for CYP2B6 gene variants, measured as the area under the curve (AUC).

Methods

Literature-based Data Source

The propofol concentration-time data are referenced from the from the Kansaku and colleagues article [10]. In the study, fifty-one patients were genotyped for CYP2B6 785 A>G, CYP2B6 516 G>T, and UGT1A9 1399 C>T using blood samples. Further details may be referenced in the original study [10].

Pharmacometric Modeling

Population pharmacokinetic (PopPK) modeling was conducted using the Non-Parametric Adaptive Grid (NPAG) algorithm in the Pmetrics R package (version 1.41, Laboratory for Applied Pharmacokinetics, Los Angeles, CA, USA) [15]. Pmetrics is a nonparametric pharmacokinetic and pharmacodynamic (PK/PD) modeling and simulation package that runs in the R programming language environment (version 3.2.2, The R Foundation for Statistical Computing, Vienna, Austria) [16]. The PopPK model parameters were computed using a FORTRAN compiler [17]. The computations run in a separate DOS-based window and adheres to the ISO FORTRAN 95 Programming Language standard [17]. Moreover, G-FORTRAN supports the legacy F77, the newer FORTRAN 2003, and 2008 features [17]. As an overall diagnostic step to validate the model, a Prediction Corrected Visual Predictive Check (PC-VPC) was conducted using the PMETRICS package [15].

The following covariates were tested: age, gender, body-weight,

CYP2B6 G516T genotypes, CYP2B6 A785G genotypes, and UGT1A9 genotypes. These covariates were assessed using a step-wise additive approach, followed by a backward elimination step for the following pharmacokinetic parameters: volume of distribution in the central compartment (V_c), rate of elimination from the central compartment to the peripheral compartment (K_{cp}), rate of elimination from the peripheral compartment to the central compartment (K_{pc}), and the elimination rate from the central compartment (K_e). Selection of the final pharmacokinetic model was based on the: goodness-of-fit plots, Akaike Information Criterion (AIC), and the Prediction Corrected Visual Predictive Check (PC-VPC). Statistics for subgroup analysis were based on the Kruskal-Wallis test with Bonferroni correction, post-hoc.

Pharmacokinetic Dosing Simulations

Propofol dosing simulations were conducted based on recommendations from the propofol package insert [5]. Dosing recommendations for adults weighing 70kg were compared to model-based PopPK parameters estimated in this paper to achieve an approximately equivalent propofol drug exposure for a bolus induction dose followed by a maintenance infusion. A table of the final genotype guided dosing recommendations is reported relative to the AUC for each virtual-elderly patient subgroup. Pharmacokinetic dosing was conducted using MATLAB Simbiology (Mathworks, Natick, Massachusetts, USA).

Results

Participants

A total of fifty-one patients and 357 propofol plasma concentrations were included in the pharmacokinetic modeling process. The patient ages ranged from 42 to 81 years with a population mean \pm standard deviation (S.D.) of 65 ± 8.7 years. The body weight ranged from 40.2 to 83kg with a population average of $59\text{kg} \pm 10\text{kg}$. Propofol doses ranged from 392mg to 2430mg with a study average of $1096\text{mg} \pm 440\text{mg}$. Study infusion times ranged from 100 to 347 minutes with a study average of $228\text{min} \pm 66\text{min}$. Further details regarding the demographics for the population genotype subgroups are found in the original study [10].

Population Pharmacokinetic Model

A two-compartment gamma multiplicative error model adequately described the propofol concentration-time data. The model converged after 2581 cycles in the FORTRAN compiler environment. Figure 1 illustrates the observed versus predicted population and individual Bayesian posterior predictions. The precision of the goodness-of-fit plots resulted in an R^2 of 0.927 and an R^2 of 0.992 for the population prediction and individual predictions, respectively. Further, the final PopPK model evaluation was based on the weighted residual plots, normalized prediction distribution error plots. Results of the full individual Bayesian posterior propofol Post-Infusion Time time-output profiles from each of the 51 patients with the pharmacokinetic predictions superimposed on the observed plasma levels are shown in Figure 2 to Figure 7. Lastly, the model selection was based on the prediction-corrected visual predictive check (VPC) and is illustrated in Figure 8.

The final population pharmacokinetic parameter estimates

Figure 1. Goodness-of-fit plots illustrating the observed versus predicted propofol concentrations. The illustration on the left shows the population predicted while the right illustration depicts the individual Bayesian Posterior predictions.

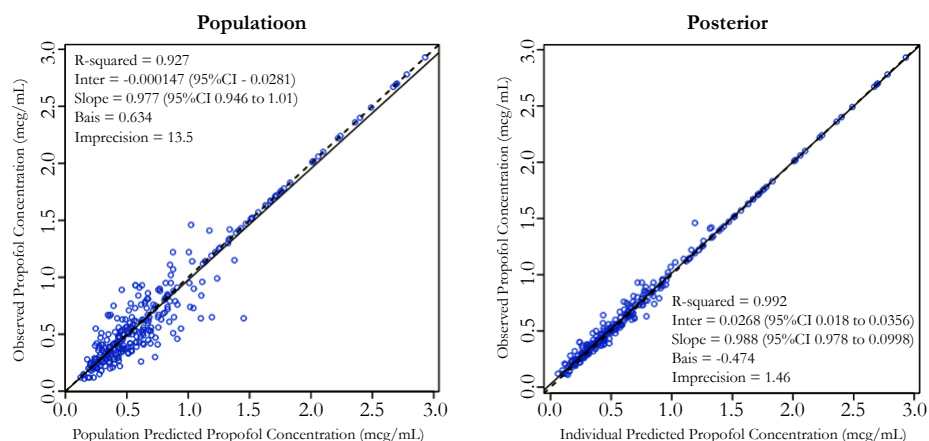


Figure 2. Results of the Individual Bayesian Posterior Propofol Post - Infusion Time - Output Profiles from Patient 1 to Patient 9.

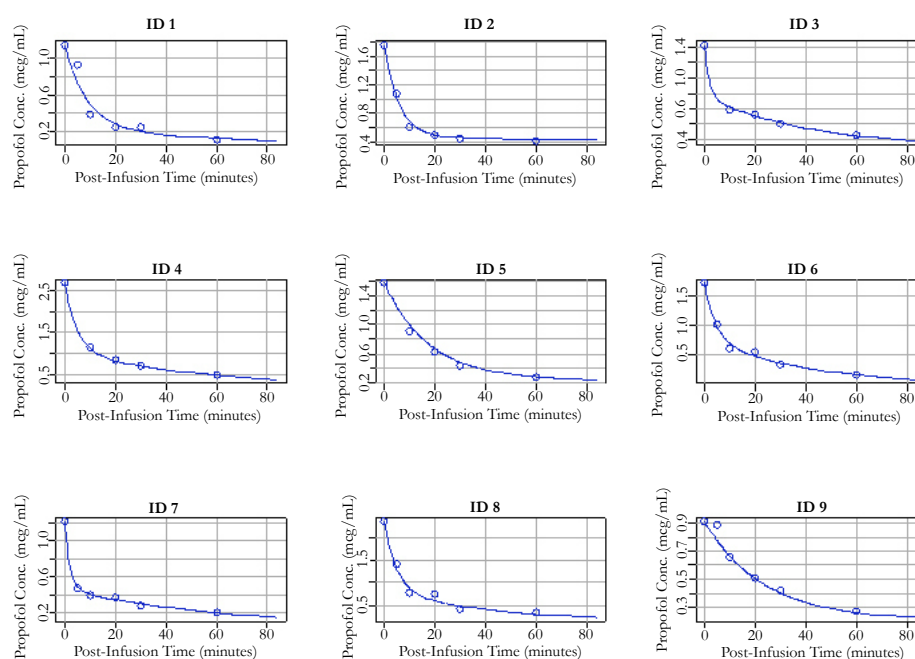


Figure 3. Results of the Individual Bayesian Posterior Propofol Post - Infusion Time - Output Profiles from Patient 10 to Patient 18.

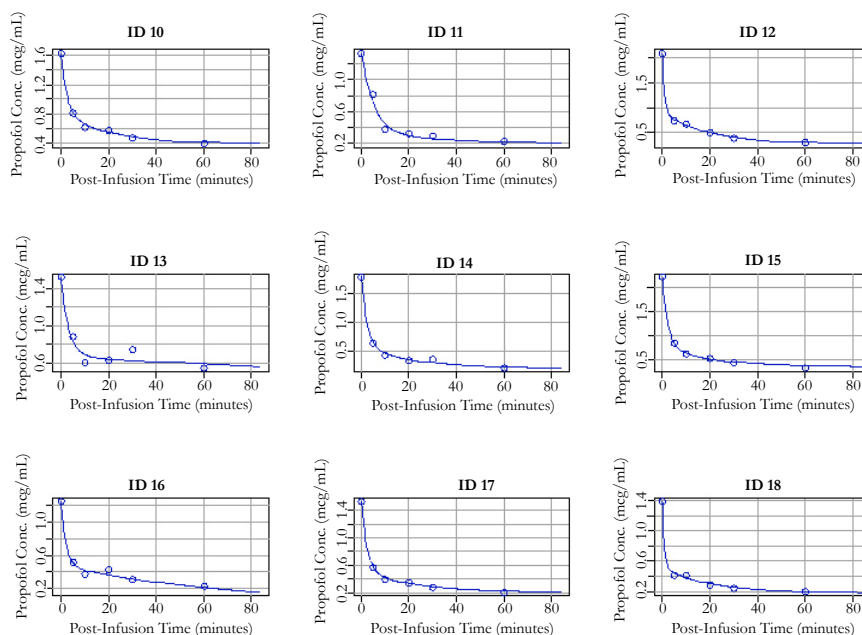


Figure 4. Results of the Individual Bayesian Posterior Propofol Post-Infusion Time - Output Profiles from Patient 19 to Patient 27.

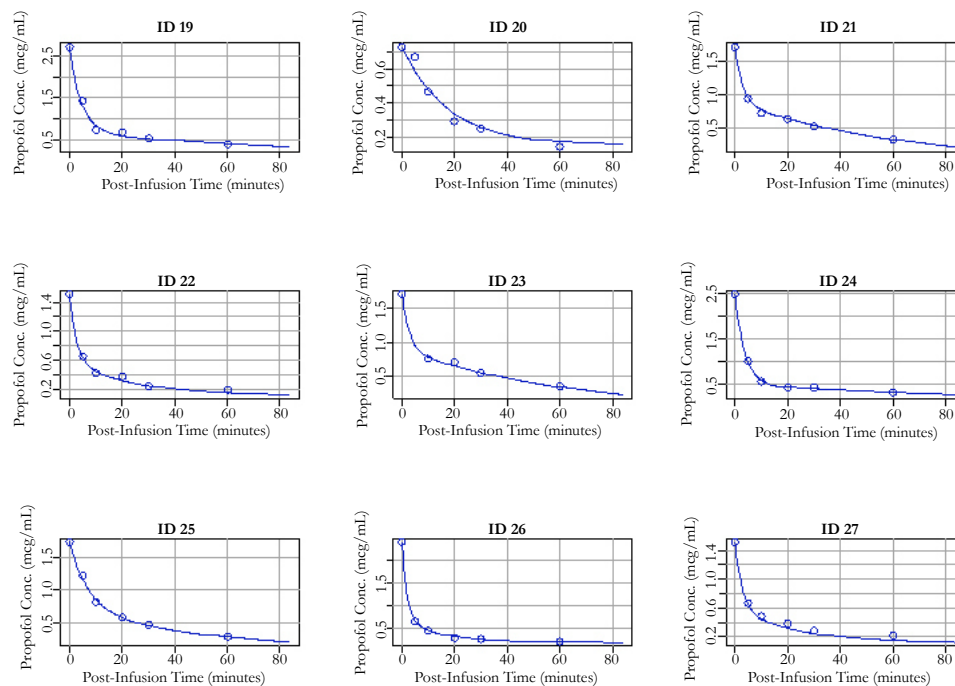
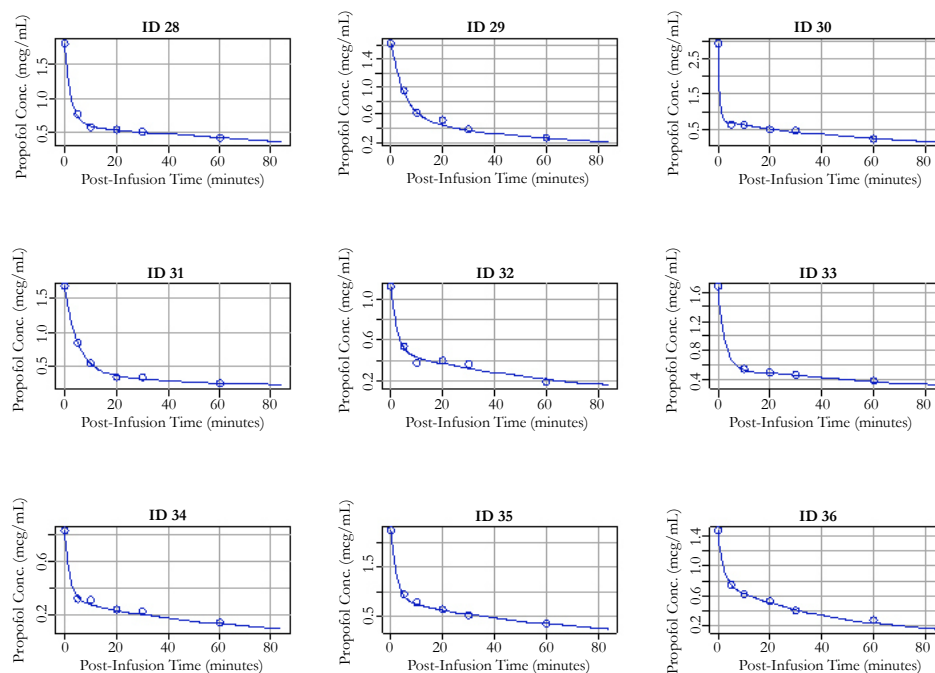


Figure 5. Results of the Individual Bayesian Posterior Propofol Post - Infusion Time - Output Profiles from Patient 28 to Patient 36.



are: elimination rate from the central compartment, $K_{e_{CYP2B6_{AA/AG}}} = 0.057\text{min}^{-1}$ (CV=57%) and $K_{e_{CYP2B6_{GG}}} = 0.152\text{min}^{-1}$ (CV=38%), elimination from the central compartment to the peripheral compartment $K_{cp}=194\text{min}^{-1}$ (CV=94%), elimination from the peripheral compartment to the central compartment, $K_{pc}=162\text{min}^{-1}$ (CV=69%), and the volume of distribution in the central compartment, $V_c=159\text{mL/kg}$ (CV=134%). Neither the UGT1A9 nor the CYP2B6 G516T genotypes resulted in statistically significant elimination rate parameter differences. However, the CYP2B6 A785G (rs2279343) gene variants resulted in statistically significant differences for the K_e ($p=0.044$) between the G/G (0.152min^{-1}) homozygotes and the A/G (0.053min^{-1}) heterozygotes. Further, for the population model, the CYP2B6

AA (wild-type) and AG (heterozygote) genotype elimination rates were grouped, resulting in insignificant differences, $p=0.014$, for K_e when compared to the G/G homozygous mutant alleles. Figure 9 illustrates the propofol elimination rate differences in the final model. The final nonparametric pharmacometrics model estimates are provided in Table 1.

The product of the elimination rate from the central compartment, K_e , with the volume of distribution in the central compartment, V_c , results in the clearance rate. Therefore, the calculated clearance rates for the CYP2B6 genotype subpopulations are $CL_{CYP2B6_{AA/AG}}=9.1\text{mL/kg/min}$ and $CL_{CYP2B6_{GG}}=24.2\text{mL/kg/min}$. Further, to avoid unnecessarily high blood propofol con-

Figure 6. Results of the Individual Bayesian Posterior Propofol Post - Infusion Time - Output Profiles from Patient 37 to Patient 45.

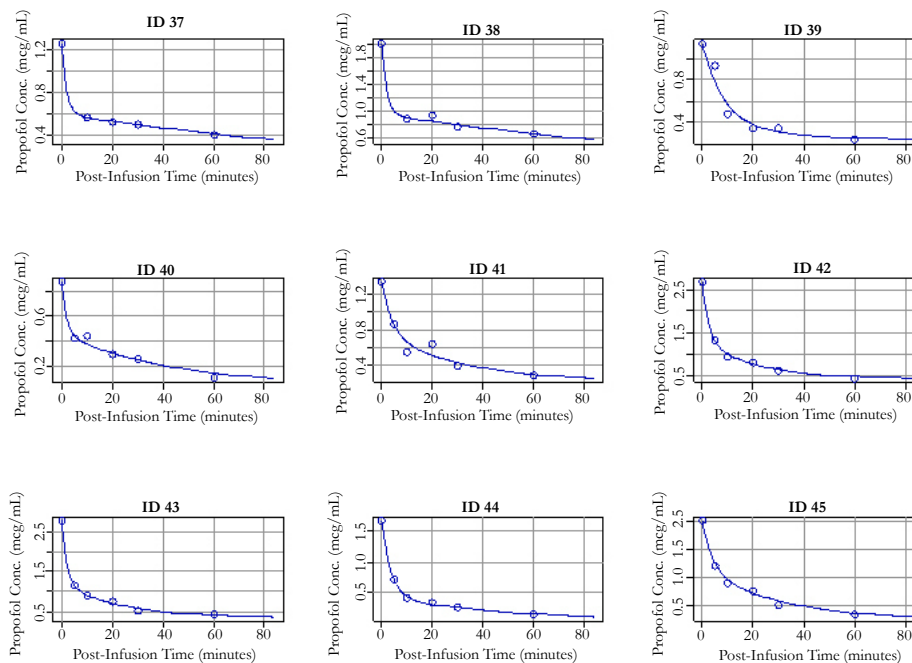


Figure 7. Results of the Individual Bayesian Posterior Propofol Post - Infusion Time - Output Profiles from Patient 46 to Patient 51.

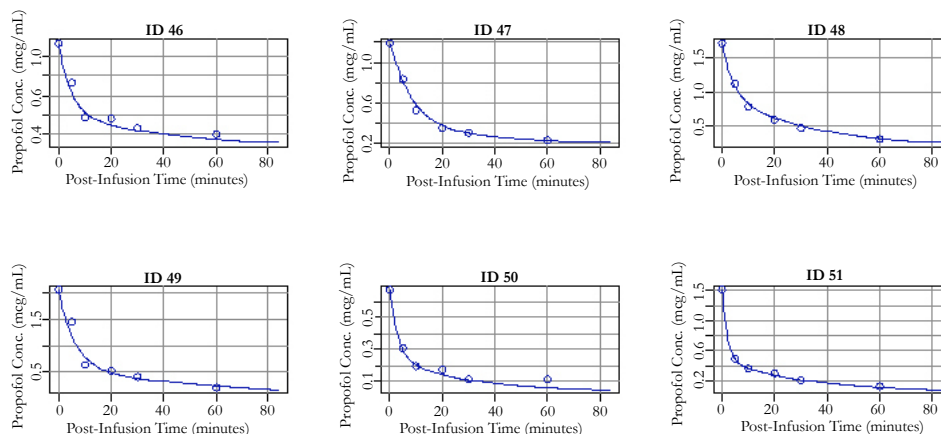


Figure 8. The Visual Predictive Check (VPC) of the Final Population Pharmacokinetic Model. The Upper, Middle, and Lower Lines Represent the 95th Percentile, 50th Percentile, and 5th Percentile, Respectively.

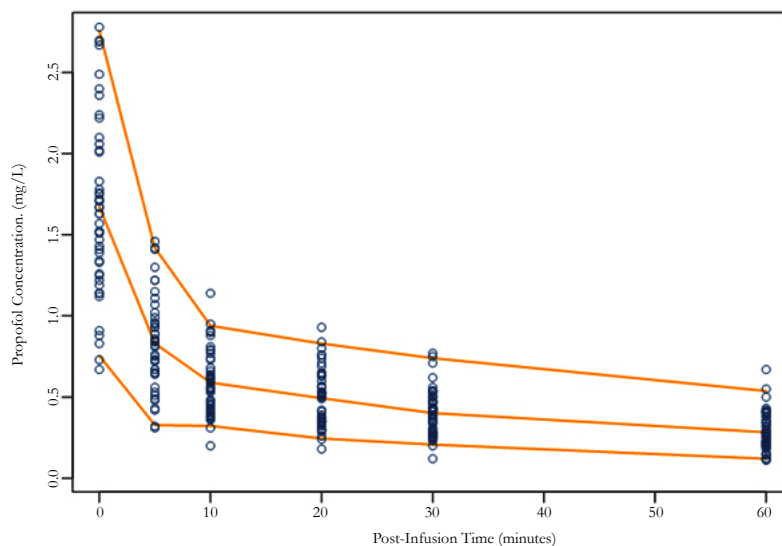


Figure 9. CYP2B6 A785G Genotype Variant Results for the Predicted Propofol Elimination Rate, K_e (min^{-1}) from the Central Compartment.

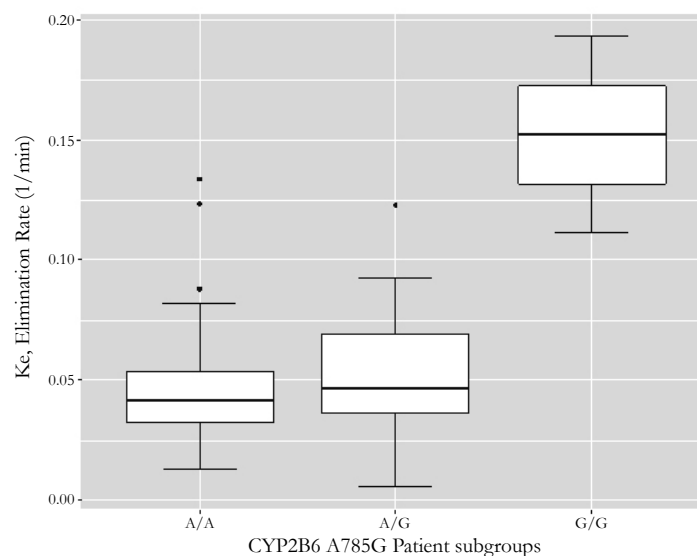
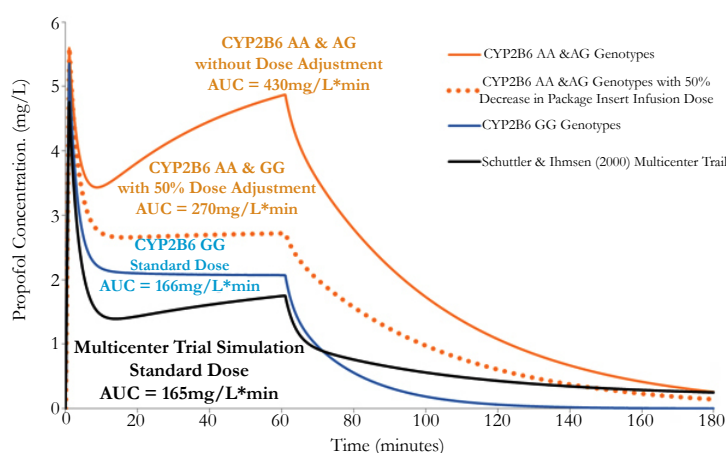


Figure 10. The model-based pharmacokinetic dosing simulations using recommendations from the current propofol package insert [5]. The dotted line represents a 25mg/kg/min infusion rate whereas all other concentration-time curves represent a propofol infusion dose of 50mg/kg/min.



centrations, which may translate to prolonged hypotension or apnea as well as other complications, dosing simulations resulting in an approximately equivalent maximum propofol concentration (C_{max}), time to maximum concentration (T_{max}), and AUC were conducted.

Propofol Dosing Simulations

The propofol package insert recommends that elderly debilitated patients receive an induction dose of 20mg every 10 seconds or 1 to 1.5 mg/kg and a maintenance infusion dose of 50 to 100 mcg/kg/min [5]. Using the genotype-stratified model parameters shown in Table 1 and referencing the Schüttler & Ihmsen multicenter ($n=270$) propofol parameters, dosing simulations were conducted [18]. The graphical results are illustrated in Figure 10 and the pharmacokinetic parameters are shown in Table 2. Based on the dosing simulation findings, if no dosage adjustments are made for the elderly CYP2B6 AA & GG genotypes, a greater than 250% increase in blood propofol exposure will occur in these patients. Therefore, at least a 50% decrease in infusion dose will be required relative to the lowest package insert (currently 50

mg/kg/min) recommendation for the elderly CYP2B6 AA & AG genotype patients.

Discussion

The hypothesis that nonparametric pharmacometric modeling would quantify the effects of the CYP2B6 A785G genotype variants on the propofol elimination rate in an elderly patient population tested true. This analysis found that patients with CYP2B6 A/A and A/G alleles cleared propofol at a rate of $CL_{\text{AAAG}}=9.1\text{mL/kg/min}$ while patients with the G/G allele cleared propofol at a rate of $CL_{\text{GG}}=24.2\text{mL/kg/min}$. The apparent propofol clearance rate for the CYP2B6 GG genotypes were consistent with the drug manufacturer's reports of 23 to 50 mL/kg/min found within the package insert, for adults [5]. However, based on the modeling and simulation, if a dosage adjustment is not made, the CYP2B6 AA & AG patients will be exposed to approximately 250% higher blood propofol levels in a short 1-hour infusion. Therefore, since the maintenance infusion dose is dependent on the clearance rate, the precision guided dose adjustments for the CYP2B6 AA & AG genotypes require a 50% decrease in infusion dose to 25mg/kg/

Table 1. Final Population Pharmacokinetic Model Parameters for CYP2B6 Genotypes.

| Parameter Descriptions | Value | CV % |
|---|-------|------|
| $K_{e_{CYP2B6 AA \& AG}}$ (min^{-1}): elimination rate from the central compartment for CYP2B6 AA & AG genotypes | 57 | 57% |
| $K_{e_{CYP2B6 G}}$ (min^{-1}): elimination rate from the central compartment for CYP2B6 GG genotypes | 152 | 38% |
| K_{cp} (min^{-1}): elimination from the central compartment to the peripheral compartment | 194 | 94 |
| K_{pc} (min^{-1}): elimination from the peripheral compartment to the central compartment | 162 | 69 |
| V_c (mL/kg): volume of distribution in the central compartment | 159 | 134 |

Table 2. Dosing Simulation Comparisons for Propofol in the Elderly.

| | CYP2B6 AA & AG Genotype | CYP2B6 AA & AG Genotype | CYP2B6 GG Genotype | Schüttler&Ihmsen 2000 Multicenter Trial [15] |
|------------------------|----------------------------------|--------------------------------|----------------------------------|---|
| Virtual Patient Weight | 70-kg | 70-kg | 70-kg | 70-kg |
| Induction Dose | 1mg/kg | 1mg/kg | 1mg/kg | 1mg/kg |
| Infusion Dose | 50mg/kg/min | 25mg/kg/min New Dose | 50mg/kg/min | 50mg/kg/min |
| Infusion Time | 1-hour | 1-hour | 1-hour | 1-hour |
| AUC (mg/L*min) | 430 | 270 | 166 | 165 |
| Cmax (mg/L) | 5.5 | 5.5 | 5.3 | 4.7 |
| Tmax (min) | 1 | 1 | 1 | 1 |
| Notes | Dosing as per package insert [5] | 50% dose decrease | Dosing as per package insert [5] | 70-year-old patient. Dosing as per package insert [5] |

min, as stated and shown in the results.

In the original study, propofol concentration-time data were analyzed using parametric pharmacokinetics, which assumes the estimated model parameters are normally distributed for the given population [10]. However, it is well-established that non-normally distributed populations of under-represented polymorphic alleles are analyzed using non-parametric statistics. In nonparametric statistics no assumptions are made about the underlying distribution of the population modeling parameters under test [19]. Thus, these results provide insight that nonparametric pharmacometric modeling software may be preferred when attempting to identify subgroups and population outliers during the process of drug discovery and quantitative pharmacology.

The clinical realities of dosing propofol in the elderly without consideration for the CYP2B6 genotype are reported in a case report published by Yonekura and colleagues in December 2016 [20]. In this case, the author attributes the CYP2B6 and UGT1A9 genotypes as being the causal factor for a 71-year-old patient experiencing 3-hours of delayed emergence from anesthesia [20]. In a retrospective analysis of 17,540 patients, with 4033 being over the age of 65 years, patients over 70 years of age experienced a dose-dependent increases in hypotension [21]. Further, a study by Mikstacki and colleagues recently reported that the CYP2B6 gene and patients' body mass index were associated with propofol metabolic rates and optimizing of propofol anesthesia [22].

Overall, it is important to note that the potential clinical impact of CYP2B6 A785G (rs2279343) gene variants guiding propofol infusion dosing, in the elderly, may be quite beneficial due to reported allele frequencies of the CYP2B6 AA and AG genotypes of: 16.7% in African-Americans, 9.3% in Asians, 4.0 to 32.6% in

Caucasians, 14.3% in Hispanics, and 9.3% in Japanese persons [23, 24]. So, in accordance with the national Precision Medicine Initiative, the results from this study provide support to clinicians and researchers who use preemptive genotyping to help avoid excessively high blood propofol levels in geriatric patients during surgery and procedures requiring propofol for sedation [25, 26].

Conclusion

This study has shown that nonparametric pharmacometric modeling, by not assuming a normal parametric distribution when estimating population pharmacokinetic parameters, effectively allows data from the individual patients to create useful parameter distributions. Clinically, the CYP2B6 AA and AG patient genotypes are estimated to require a 25mg/kg/min infusion dose during the maintenance of general anesthesia, whereas the CYP2B6 GG genotypes do not require a dosage adjustment outside of the propofol package insert under geriatric dosing recommendations. These findings provide insight into the pharmacogenomics of propofol anesthesia and should be further confirmed.

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