Pharmacokinetics and Pharmacodynamics of Propofol and Fentanyl in Patients Undergoing Abdominal Aortic Surgery – a Study of Pharmacodynamic Drug-Drug Interactions

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Abstract

Propofol is routinely combined with opioid analgesics to ensure adequate anesthesia during surgery. The aim of the study was to assess the effect of fentanyl on the hypnotic effect of propofol and possible clinical implications of this interaction.

The pharmacokinetic/pharmacodynamic (PK/PD) data were obtained from 11 patients undergoing abdominal aortic surgery, classified as ASA III. Propofol was administered by target-controlled infusion system. Fentanyl 2-3 µg/kg was given whenever insufficient analgesia occurred. Bispectral index (BIS) was used to monitor the depth of anesthesia. A population PK/PD analysis with non-linear mixed-effect model (NONMEM 7.2 software) was conducted.

Two-compartment models satisfactorily described the PK of propofol and fentanyl. The delay of the anesthetic effect in relation to PK was described by the effect compartment. BIS was linked to propofol and fentanyl effect-site concentrations through an additive $E_{max}$ model. Context-Sensitive Decrement Times (CSDT) determined from the final model were used to assess the influence of fentanyl on the recovery after anesthesia.

The population PK/PD model was successfully developed to simultaneously describe
the time course and variability of propofol and fentanyl concentrations and BIS. Additive propofol-fentanyl interactions were observed and quantitated. The duration of fentanyl infusion had minimal effect on CSDT when it was shorter than the duration of propofol infusion. If the fentanyl infusion was longer than the propofol infusion, an almost two-fold increase in CSDT occurred. Additional doses of fentanyl administered after the cessation of propofol infusion result in lower BIS values, and can prolong the time of recovery from anesthesia.

**Keywords:** propofol, fentanyl, abdominal aortic surgery, PK/PD
Introduction

Propofol is a short-acting hypnotic, extensively used for the induction and maintenance of general anesthesia and postoperative sedation [1, 2]. It is often combined with an opioid (e.g. fentanyl) to produce two critical clinical anesthesia end-points: hypnosis and immobility. Simultaneous use of the two drugs might lead to drug interactions that can be associated with both clinical usefulness and adverse effects [3]. Fentanyl has been shown to interact synergistically [4] or additively with propofol [5] for various clinical endpoints. Ben-Shlomo et al. [5] noted the additive type of interaction during the loss of consciousness in ASA I and II women undergoing minor gynecological procedures. On the contrary, Kazama et al. [4] observed synergistic pharmacodynamic interaction between propofol and fentanyl concerning the suppression of the somatic and hemodynamic response to different surgical stimuli.

Pharmacodynamic drug interactions also play an important role in recovery from anesthesia, as modelled by Vuyk at al. [6] for various combinations of propofol and fentanyl, sufentanil, alfentanil and remifentanil. In addition, fentanyl was shown to exhibit the sparing effect concerning propofol plasma concentrations on recovery from unconsciousness after Total Intravenous Anesthesia (TIVA) [7]. Nevertheless, so far the interaction between these drugs with respect to both recovery time and concentrations has not been fully investigated, especially for patients undergoing surgical procedures. Our aim was to examine propofol-fentanyl interactions during anesthesia and after the recovery from unconsciousness in patients undergoing major aortic surgery. We studied the influence of fentanyl on the Context-Sensitive Decrement Times (CSDT) of propofol during propofol-fentanyl TIVA monitored with the BIS index. CSDT is an important pharmacokinetic parameter for
anesthetics as it describes the post-infusion decline in drug concentration.

Material and Methods

Patients:

Having received an approval from the local Research Ethics Committee and informed, written consent, 11 patients undergoing major aortic surgery, classified as ASA III according to the American Society of Anesthesiologists (ASA) physical status classification system, were enrolled in the study. The exclusion criteria were: previous cardiac surgery, ejection fraction <40%, valvular heart disease and myocardial infarction within 3 months prior to the surgery, significant renal (serum creatinine > 1.5 mg%) or hepatic dysfunction (aspartate and alanine transaminase > 50% above normal range), cerebrovascular and central nervous system diseases, history of drug or alcohol abuse, morbid obesity, and hearing abnormalities.

No sedative or opioid drugs were administered before the induction of anesthesia. All surgeries were performed under propofol-fentanyl TIVA. The target-controlled infusion (TCI) system Diprifusor® (Astra Zeneca, UK) was used to administer propofol. In the operating room, intravenous and arterial lines were inserted under local anesthesia, and standard monitors were applied (ECG, SpO₂). Hemodynamic measurements were carried out with FloTrac/Vigileo TM System (Edwards, USA). After the surgery the patients were mechanically ventilated in the Intensive Care Unit (ICU) until full recovery and propofol infusion was maintained until extubation.

Pancuronium 0.1 mg/kg was given to facilitate intubation and then it was administered as required. This study was initiated with a bolus injection of fentanyl (1.5 µg/kg). The propofol
infusion was started 5 min later (to study the PD interactions between the drugs) and maintained with intermittent injections of fentanyl (2 – 3 µg/kg) administered whenever inadequate analgesia was assessed throughout the surgery. The bispectral index (BIS; A-2000, Aspect Medical System, Newton, MA) was used to measure the depth of anesthesia and propofol dosage was adjusted to maintain the BIS level between 40 and 60. BIS uses highly processed electroencephalographic (EEG) signals, acquired from a single self-adhesive forehead sensor, to measure the depth of sedation and hypnosis which is expressed on a unitless scale ranging from 0 to 100 (0, coma or absence of brain electrical activity; 0 to 40, deep hypnotic state; 40 to 60, general anesthesia; 60 to 90, deep to light sedation; and 90 to 100, awake). BIS is a complex parameter composed of a combination of time domain, frequency domain and high order spectral subparameters. It is a unique quantitative electroencephalogram parameter (QEEG) which integrates several disparate descriptors of the EEG into a single variable based on the large volume of clinical data, to synthesize a combination that correlates behavioral assessments of sedation and hypnosis yet is insensitive to the specific anesthetic agents chosen [8, 9]. During the surgery crystalloid and colloid fluids were infused according to the following protocol: continuous infusion of crystalloid at a rate of \([10 \times \text{body weight (kg)}]\) ml/hour, colloid interventional infusion to preserve normovolemia (Stroke volume variation (SVV) < 12) compensatory to the volume of blood loss.

Arterial blood samples for plasma propofol and fentanyl concentration measurements were drawn before the propofol infusion, 1, 3, 5, 10, 15, 30 minutes after the beginning of the infusion, then every 30 minutes until the end of anesthesia and also after 1, 3, 5, 10, 15, 30,
60 minutes after the termination of the propofol infusion. The blood samples were transferred into heparinized tubes and they were centrifuged immediately after collection. Plasma was stored at 4°C. The propofol concentration in the plasma was measured within 8 weeks by means of high-performance liquid chromatography with a fluorescence detector [10-12]. The limit of quantification was estimated at 10 ng/ml. The within-day coefficients of variation were less than 10%. Plasma samples were analysed for fentanyl by validated high-pressure liquid chromatography (Waters 2695 Separation Module, Milford, USA) coupled with triple quadrupole mass spectrometer, equipped with electrospray ionization source (ESI+) (WatersQuattro Micro, Milford, USA). The mass spectrometer was working in the multiple-ion monitoring (MRM) mode. Fentanyl and internal standard (IS) were monitored by means of fragment ions at 387.1→238.0 and 532.0→219.1, respectively. The column used was Thermo BDS Hypersil C18 100 x 2.1 mm 3 µm (Thermo Scientific, Waltham, USA). The mobile phase was: formate buffer pH 4.0 [A] and acetonitrile [B] (J.T.Baker, Avantor, Netherlands). The flow rate was 0.2 mL/min, isocratic separation was applied – the mobile phase was used as follows: 70% [B] and 30% [A]. Fentanyl and terconazole (IS) were extracted using a single-step liquid-liquid extraction (LLE) with a mixture of ethyl acetate and hexane. The lower limit of quantification was 0.05 ng/mL for fentanyl using 0.250 mL sample volume, with a bias of 4.6% and RSD of 5.4%. The calibration curves were linear ($r^2 \geq 0.990$) over the working range of 0.05-50.0 ng/mL, using $1/x^2$ as a weighting factor. Quality Control samples at three concentration levels (LQC 0.2 ng/mL, RSD = 9.9%; MQC 1.50 ng/mL, RSD = 9.7%; HQC 15.0 ng/mL, RSD = 9.4%) were analysed for validation of analytical run.
Study Design

Usually a large experimental effort is needed to elucidate drug-drug interactions, mostly due to the need of measurements of various combinations of drugs under study. It is rarely possible to obtain such data in humans. In this study we used a slightly modified anesthesia protocol and nonlinear mixed-effect modelling to assess the degree of propofol-fentanyl interactions. This study was initiated with a bolus injection of fentanyl. The propofol infusion was started 5 min later and maintained with intermittent injections of fentanyl. The propofol infusion was stopped at the end of the surgery. The BIS was continuously monitored throughout the study. The delay between the fentanyl and propofol administration enabled us to study the effect of fentanyl alone on the BIS.

Population Pharmacokinetic Analysis

The population nonlinear mixed-effect modelling was done using NONMEM (Version 7.2.0, Icon Development Solutions, Ellicott City, MD, USA) and the Fortran compiler 9.0. NONMEM runs were executed using Wings for NONMEM (WFN720, http://wfn.sourceforge.net). The FOCE estimation method with the interaction option in NONMEM was applied. The minimum value of the NONMEM objective function (MOF), typical goodness of fit diagnostic plots, and evaluation of the precision of the PK parameter and variability estimates were used to discriminate between various models during the model-building process. The NONMEM data processing, simulations, and plots were carried out using Matlab® Software version 7.0 (The MathWorks, Inc., Natick, MA, USA).

A schematic representation of the proposed pharmacokinetic/pharmacodynamic (PK/PD)
model is given in Figure 1. A two-compartment model was sufficient to describe the PK of propofol and fentanyl. The delay of the anesthetic effect, with respect to plasma concentrations, was described by the effect compartment. The bispectral index (BIS) was linked to the propofol and fentanyl effect-site concentrations \((C_{e,P} \text{ and } C_{e,F})\) through an additive \(E_{\text{max}}\) model [5, 13-15]:

\[
BIS = BIS_0 \left(1 - \frac{E_{\text{max}} \left( \frac{C_{e,P}}{C_{50,P}} + \frac{C_{e,F}}{C_{50,F}} \right)^\gamma}{1 + \left( \frac{C_{e,P}}{C_{50,P}} + \frac{C_{e,F}}{C_{50,F}} \right)^\gamma} \right)
\]  

(1)

where \(C_{50,P}\) and \(C_{50,F}\) denote the concentrations of propofol or fentanyl that produce half-maximal decrease in the BIS response, \(BIS_0\) denotes the baseline BIS score (fully awake), \(E_{\text{max}}\) is the maximal effect fixed to 1 in this study (BIS value of zero at sufficiently high concentrations of propofol or fentanyl), and \(\gamma\) is the Hill coefficient. Inter-individual variability (IIV) for all PK/PD parameters was modelled assuming log-normal distribution:

\[
P_i = \theta_P + \eta_P \exp(\mathbf{v})
\]

(2)

where \(P_i\) is the set of PK/PD parameters for \(i^{th}\) individual, \(\theta_P\) is the population estimate of PK/PD parameters, \(\eta_P\) is a random effect for a particular parameter with mean 0 and variance \(\omega_{\theta_P}^2\).

Any \(j^{th}\) observation of propofol and fentanyl concentration and the BIS values for the \(i^{th}\) individual, \(C_{P,ij}, C_{F,ij}\) and, \(BIS_{ij}\) measured at time \(t_j\), were defined by the following equation:
\[ C_{P,i,j} = C_p(P_i, t_j)(1 + \varepsilon_{P,i,j}) \]
\[ C_{F,i,j} = C_F(P_i, t_j)(1 + \varepsilon_{F,i,j}) \]
\[ BIS_{i,j} = BIS(P_i, t_j) + \varepsilon_{BIS,i,j} \]  

(3)

where \( C_p, C_F \) and \( BIS \) denote the basic structural population model (Eq. 1). \( P_i \) are pharmacokinetic parameters for the \( i^{th} \) individual, and \( \varepsilon_{P,i,j}, \varepsilon_{F,i,j}, \varepsilon_{BIS,i,j} \) represent the proportional or additive residual intra-individual random error. We assumed that \( \varepsilon \) was symmetrically distributed around a mean of 0, with variance denoted by \( \sigma^2_{\text{prop}} \).

**Bootstrap**

Evaluation of the model robustness was based on non-parametric bootstrapping with 1000 replicates. 90% confidence intervals (5th - 95th percentile) were obtained for the parameters from the bootstrap empirical posterior distribution, as described by Parke et al. [16].

**Visual Predictive Check**

The model performance was assessed by means of Visual Predictive Check (VPC). The VPC calculation was based on 1000 datasets simulated with the final parameter estimates. Different dosing regimens and variable infusion length required the use of prediction corrected VPC (pcVPC). The pcVPCs were created by correcting the observed and simulated values for the average population prediction in the time-bin divided by population predictions for each observed and simulated value [17]. In this study the 10th, 50th and 90th percentile were used to summarize the data and VPC prediction. The pcVPC enables a comparison of the confidence intervals obtained from prediction with the observed data over time. If the
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Context-Sensitive Decrement Times were based on typical parameter estimates of our final PK/PD model. They were calculated using a computer simulation as the time needed for a varying decrease in virtual effect-site concentration after an infusion regimen designed to produce a constant level of effect-site concentrations of propofol and fentanyl [18, 20].

Results

This analysis was based on the concentration-time profiles of propofol, fentanyl and the BIS index measurements collected from 11 subjects. Table 1 lists the patients’ demographic and clinical laboratory characteristics. The available data consisted of 652 observations (118 for propofol, 121 for fentanyl, and 413 for the BIS) collected during the mean (range) duration of propofol infusion of 143 (120-182) min.

One-, two- and three-compartment models for propofol and fentanyl were screened during the model building process. The two-compartment model satisfactorily described the pharmacokinetics of both propofol and fentanyl. The additive interaction model turned out to be sufficient to describe our data. The more complex models of pharmacodynamic interactions such as the synergistic interaction model and the additive interaction model with Hill coefficient were tested, however, they were not supported by the data.

The typical goodness-of-fit plots of the final PK/PD model are provided in Figure 2. The individual predictions are very close to the experimental data, indicating good performance of the model. It is also confirmed by other goodness-of-fit plots. The pcVPC plots for the PK/PD measurements are presented in Figure 3 to assess the simulation properties of the final...
model. These results indicate that both the central tendency and the variability of the data at a particular sampling time were recaptured well. No major misspecifications were noted for the propofol PK, fentanyl PK and BIS.

Table 2 shows the final parameter estimates along with bootstrap results. The median bootstrap values of parameters are in close agreement with the population estimates in the final models, suggesting that the NONMEM parameter estimates of the models are unbiased. All parameters, inter-subject and residual error variances were estimated with low (lower than 50%) coefficients of variation (CV). All estimated IIV had low shrinkage (less than 20%). It suggests that the data is highly informative about the individual-predicted parameters.

For propofol, the typical value of the volume of the central compartment ($V_C$) was close to a plasma volume of 4.80 L, whereas the volume of the peripheral compartment was higher ($V_T = 52.4$ L). The typical systemic clearance ($CL$) of propofol and the distribution clearances were 2.22 L/min and 1.77 L/min. The IIV was estimated for the $CL$, $V_T$, and $Q$, for which it equalled 34, 57 and 62%, respectively. For fentanyl, the typical volume of the central and peripheral compartment was high and equalled 43.2 L and 124 L. The typical systemic clearance was close to that of propofol (1.79 L/min) due to the fact that both drugs are of high extraction and their clearance depends on the blood flow through the liver. The distribution clearance was higher for fentanyl than for propofol (4.06 L/min). The IIV was estimated for the $CL$ and $Q$ and it equalled 24% and 99%, respectively. The $Ce_{50}$ for the BIS was 4.97 ng/ml for fentanyl and 3.12 mg/L for propofol.
The final model was used for simulation to show the BIS response after propofol and fentanyl administrations at fixed propofol infusion and multiple dosing of fentanyl at three different doses of 0, 50 and 100 µg. The outcome is shown in Figure 4. The initial dose of fentanyl (without propofol administration) decreased the BIS values in a dose-dependent manner up to 80, observed for the highest dose. After the addition of propofol infusion the BIS rapidly decreased to about 40 and fluctuated around its pseudo-steady state values at each fentanyl administration. Also the BIS return to the baseline after the infusion cessation depended on the dose of fentanyl. To further quantitate the influence of fentanyl on recovery after anesthesia a Context-Sensitive Effect-Site Decrement Time (CSDT) was calculated for the propofol-fentanyl infusion, leading to the constant effect-site concentrations of 3 mg/L and 1.5 ng/ml. The results are shown in Figure 5 for the propofol infusion of 200 min and varying fentanyl infusion times. The graph shows that the duration of the fentanyl infusion had minimal effect on the CSDT as long as it was shorter than the duration of the propofol infusion. Interestingly, if the fentanyl infusion was longer than the propofol infusion, an almost two-fold increase in the CSDT occurred. It suggests that any additional doses of fentanyl administered after the cessation of propofol infusion led to lower BIS values, and consequently they could prolong the times of recovery from anesthesia.

Discussion

A population pharmacokinetic and pharmacodynamic model was successfully developed to simultaneously describe the concentration-time data of propofol and fentanyl and the additive effect of both drugs on the BIS index measurements. The applied methodology had several
advantages in studying propofol-fentanyl interactions, namely: 1) the applied population analysis was based on the entire data set, 2) the drug concentrations were in close proximity to the clinically optimal values, and 3) what is important, different scenarios could be simulated from the final model [21]. A similar modelling approach, but based on a different experimental design and without the measurement of propofol and fentanyl concentrations, has already been proposed in children [22].

The interactions between propofol and opioids were studied extensively in the literature, where differences in propofol hypnosis were observed, depending on the type of opioid used [22-28]. One of the suggested reasons for such differences is the pharmacokinetic hypothesis related to the opioid-related differences is the cardiac output. However, this aspect was not included in this study. We primarily focused on the pharmacodynamic interaction of those drugs on the BIS index, which is a good factor reflecting the depth of anesthesia and time to awakening [7, 29]. The other commonly used criteria, like time to eye opening, time to extubation or time to orientation for name and place were of limited applicability in this study as aortic surgery patients are usually extubated several hours after the end of surgery.

The simple additive interaction model accurately reflected the combined effect of propofol and fentanyl on the BIS, which is consistent with literature findings [5, 13-15]. The more complex synergistic model [6] was not supported by our data, very likely due to the design limitations. Nevertheless, for the concentration range of fentanyl and propofol observed in this study, an additive model might provide a good approximation for the more complex relationship. The propofol $C_{e50}$ (3.12 mg/L) is in close proximity to the blood propofol...
concentrations associated with the loss of consciousness in 50% of patients [30-33]. The additive interactions between propofol and fentanyl suggest that in order to achieve the desired BIS value, the following equation must be satisfied:

\[
\frac{92}{BIS} - 1 = \frac{C_{e,P}}{3.12 \text{ mg/L}} + \frac{C_{e,F}}{4.97 \text{ ng/ml}}
\]

For example, to achieve the BIS value of 40 for propofol infusion leading to 3.0 mg/L concentration, the fentanyl concentration must equal 1.7 ng/ml. The biophase distribution rate constant was comparable to values reported in literature (0.174 min\(^{-1}\)) and not statistically significantly different (\(p > 0.05\), likelihood ratio test) for both drugs under study [34].

In order to reduce the patient awakening time, the optimal propofol-opioid concentrations should be maintained. Vuyk et al. [28], using a computer simulation, suggested that the fentanyl target concentration leading to the rapid emergence was approximately 1.0 to 1.5 ng/ml, which required propofol concentrations of approximately 3.0 to 3.5 mg/L to maintain adequate anesthesia. Based on our model predictions, this range of propofol and fentanyl concentrations corresponds with the BIS range of 38 - 42. On the contrary, in the study by Mi et al. [7] the patients with fentanyl concentrations of < 0.45 µg/L regained consciousness at a propofol concentration of 3.2 mg/L and BIS level of 78. It suggests that some inter-study difference, e.g. dependent on the type of surgery, might be present.

This study confirms that a population model of the BIS index measurements has to take both the pharmacokinetics of propofol and fentanyl into consideration. Nevertheless, it is rarely done in modelling practice, limiting the interpretability and comparability of results across
different studies. The interaction model considerably reduces the unexplained variability and this might explain the misfits often presented in BIS modelling efforts [35]. Also, the higher sensitivity to propofol anesthesia observed in ASA III patients in clinical studies [36-38] might be explained by the lack of the opioid effect on the BIS. In the study by Wiczling et al., which was conducted on patients scheduled for abdominal aortic surgery, no interaction with fentanyl was taken into consideration in data analysis [36]. The calculated $C_{e50}$ of propofol was significantly lower than in our current study (2.19 mg/L vs 3.2 mg/L).

In this study the CSDT was used to describe the role of post-infusion PK of propofol and fentanyl on the recovery from anesthesia (Fig. 5). We noted that the fentanyl infusion time had minimal effect on the CSDT of propofol as long as it was delivered for a shorter time than the duration of propofol infusion. When the fentanyl infusion is longer than the infusion of propofol, an almost two-fold increase in the CSDT can occur. This increase is greater for higher percentage CSDT.

**Conclusion**

The presented simulation suggests that any additional fentanyl doses administered upon the discontinuation of propofol infusion lead to lower BIS values, and consequently can prolong the time to recover from anesthesia. An integrated PK/PD model was proposed and successfully applied to describe propofol concentrations, fentanyl concentrations, and the depth of anesthesia, as reflected by the BIS index. The developed model describes the data reasonably well and can be used to facilitate understanding of the complex interplay of the drugs under study in anesthetized patients.
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Table 1. The patients’ demographic characteristics.

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<th>Parameters</th>
<th>Median (std) or Number</th>
</tr>
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<tr>
<td>Number of patients</td>
<td>11</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.0 ± 14.3 [60 - 100]</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.0 ± 7.5 [51 - 77]</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.84 ± 0.2 [1.65 - 2.27]</td>
</tr>
<tr>
<td>Propofol dose, mg</td>
<td>1097 ± 600 [632 - 2690]</td>
</tr>
<tr>
<td>Propofol infusion length, min</td>
<td>143 ± 20.8 [120 - 182]</td>
</tr>
<tr>
<td>Propofol infusion rate, mg/min/kg</td>
<td>0.0842 ± 0.0366 [0.0175 - 0.114]</td>
</tr>
<tr>
<td>Fentanyl dose, µg</td>
<td>800 ± 199 [650 - 1200]</td>
</tr>
<tr>
<td>Initial Systolic Blood Pressure, mmHg</td>
<td>145.0 ± 31.8 [106 - 208]</td>
</tr>
<tr>
<td>Initial Diastolic Blood Pressure, mmHg</td>
<td>73.0 ± 11.8 [50 - 98]</td>
</tr>
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Table 2. The final population PK/PD parameters and inter-subject and residual error variance estimates of propofol, fentanyl and the BIS. The bootstrap estimates (n = 500) are given for comparison.

<table>
<thead>
<tr>
<th>Parameter [unit]</th>
<th>Θ</th>
<th>ω² (%CV) [Shrinkage]</th>
<th>Θ, Bootstrap Estimate Median (5th-95th percentile)</th>
<th>ω² (%CV), Bootstrap Estimate Median (5th-95th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc,P, [L]</td>
<td>4.80 (37.9)</td>
<td>-</td>
<td>4.84 [3.00 - 7.93]</td>
<td>-</td>
</tr>
<tr>
<td>CL,P, [L/min]</td>
<td>2.22 (10.8)</td>
<td>33.8 (33.3) [2.4%]</td>
<td>2.22 [1.89 - 2.67]</td>
<td>39.2 (15.1 - 51.8)</td>
</tr>
<tr>
<td>Q1,P, [L/min]</td>
<td>1.77 (25.1)</td>
<td>61.5 (42.5) [16.9%]</td>
<td>1.84 [1.19 - 2.79]</td>
<td>52.3 (0.6 - 85.1)</td>
</tr>
<tr>
<td>V1,P, [L]</td>
<td>52.4 (35.5)</td>
<td>57.3 (20.1) [13.8%]</td>
<td>53.2 [34.0 - 102]</td>
<td>53.3 (10.1 - 73.6)</td>
</tr>
<tr>
<td>Vc,F, [L]</td>
<td>43.2 (22.1)</td>
<td>-</td>
<td>43.0 [24.8 - 58.6]</td>
<td>-</td>
</tr>
<tr>
<td>CL,F [L/min]</td>
<td>1.79 (10.8)</td>
<td>23.9 (17.5) [14.1%]</td>
<td>1.79 [1.30 - 2.12]</td>
<td>21.4 (0.2 - 30.5)</td>
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<tr>
<td>Q1,F [L/min]</td>
<td>4.06 (33.5)</td>
<td>99.2 (31.6) [12.7%]</td>
<td>4.00 [2.12 - 6.38]</td>
<td>91.1 (29.9 - 156)</td>
</tr>
<tr>
<td>V1,F, [L]</td>
<td>124 (17.2)</td>
<td>-</td>
<td>124 [84 - 193]</td>
<td>-</td>
</tr>
<tr>
<td>BIS, [ ]</td>
<td>92.0 (3.5)</td>
<td>-</td>
<td>91.8 [87.0 - 97.3]</td>
<td>-</td>
</tr>
<tr>
<td>EMAX, [ ]</td>
<td>1 fixed</td>
<td>-</td>
<td>1 fixed</td>
<td>-</td>
</tr>
<tr>
<td>Ceso,F, [ng/ml]</td>
<td>4.97 (57.9)</td>
<td>65.9 (54.4) [16.8%]</td>
<td>5.11 [2.50 - 18.4]</td>
<td>59.7 (0.4 - 122)</td>
</tr>
<tr>
<td>Ceso,P, [mg/L]</td>
<td>3.12 (29.0)</td>
<td>68.3 (26.2) [35.0%]</td>
<td>3.09 [2.03 - 5.14]</td>
<td>62.3 (30.4 - 93.3)</td>
</tr>
<tr>
<td>γ, [ ]</td>
<td>1 fixed</td>
<td>-</td>
<td>1 fixed</td>
<td>-</td>
</tr>
<tr>
<td>k eo,F = k eo,P, [1/min]</td>
<td>0.174 (27.0)</td>
<td>82.0 (36.0) [4.5%]</td>
<td>0.184 [0.122 - 0.307]</td>
<td>75.1 (35.7 - 134)</td>
</tr>
</tbody>
</table>

**Residual variability**

<table>
<thead>
<tr>
<th>σ²</th>
<th>Parameter</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>σ²</td>
<td>prop, P, %</td>
<td>33.5 (12.3) [7.9%]</td>
<td>33.3 [26.8 - 39.8]</td>
<td></td>
</tr>
<tr>
<td>σ²</td>
<td>prop, F, %</td>
<td>37.2 (12.2) [4.4%]</td>
<td>36.5 [29.0 - 43.1]</td>
<td></td>
</tr>
<tr>
<td>σ²</td>
<td>add, BIS</td>
<td>7.97 (12.5) [3.4%]</td>
<td>7.96 [6.46 - 9.8]</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. The PK/PD model of propofol/fentanyl.
Figure 2. Goodness of fit plots for the final PK/PD model. The blue open circles denote propofol concentrations, the green solid circles denote fentanyl concentrations, and red solid squares denote BIS measurements.
Figure 3. The prediction corrected visual predictive check plots (pcVPC) for propofol/fentanyl concentrations and the BIS measurements. The pcVPC plots show the simulation-based 95% confidence intervals around the 10th, 50th, and 90th percentiles of the PD data in the form of blue (50th) and light blue (10th and 90th) areas. The corresponding percentiles from the prediction corrected observed data are plotted in black.
Figure 4. The propofol concentration, fentanyl concentration and the BIS index simulations from the final model. The following infusion parameters were used: (propofol) initial dose 100 mg, rate of infusion 10 mg/min and duration of infusion 160 min, (fentanyl) multiple dose at 40 min intervals at a dose of 0 (dotted line), 50 (grey line), and 100 µg (solid line). The propofol infusion started 40 min after the first dose of fentanyl to illustrate the effect of
fentanyl alone on the BIS.

Figure 5. Context-sensitive effect-site decrement times for propofol-fentanyl infusions showing the time for decreasing the effect-site concentrations of a given percentage (20 - 80%) from the maintained effect-site concentration after propofol infusion cessations with a varying duration of fentanyl infusion. The propofol and fentanyl biophase concentration were kept at 3.0 mg/L and 1.5 ng/ml, which corresponds to the BIS of about 41.