Recirculatory Pharmacokinetic-Pharmacodynamic Modeling of Propofol in Man

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Introduction

Induction of anesthesia with an intravenous hypnotic agent like propofol can be achieved by administration of a manual bolus followed by a continuous infusion, with an infusion rate based on (lean) body weight, age and/or sex, or by using a computer controlled infusions systems for Target Controlled Infusion (TCI). In everyday practice a large interindividual variability in the induction phase can be observed, with variation in time to loss of consciousness, depth of sedation, and incidence and magnitude of respiratory and hemodynamic side effects, as has been reviewed in the Cochrane review by Leslie et al.\(^1\) This variation is explained by the interindividual variability in pharmacokinetics and pharmacodynamics within the population. The origin of variability lies in the influence of age, weight, body composition, gender, comorbidities, hemodynamic variability like cardiac output, but also pharmacogenomics.\(^2\) During induction or maintenance of anesthesia, interaction with co-administered drugs like opioids, is evident.\(^3,4\) Opioids increase the blood concentration of co-administered hypnotic agents and shift the dose-response relationship of hypnotic agents to the left via pharmacodynamic interaction.\(^5,6\)

With the introduction of PK-PD modeling by Sheiner and colleagues\(^7\), the concept of the effect-site has been introduced: a virtual compartment that is coupled to the intravascular compartment via the transfer constant \(k_{e0}\) since the effect compartment has no apparent volume. Conventional 3-compartment models generally underpredict the intravascular drug concentration following a bolus induction dose of fast acting drugs like propofol see also chapter 2. In the study on early-phase pharmacokinetics of propofol described in chapter 6 of this thesis, we presented a recirculatory pharmacokinetic model for propofol in humans. In that study we simulated the blood concentration-time curve of a propofol bolus dose of 3 mg/kg as based on 2 pharmacokinetic parameter sets that are implemented in the commercially available TCI systems for propofol: the parameter set of Marsh\(^8\) in the Diprifusor™ by AstraZeneca and the parameter set of Schnider\(^9\) in the Orchestra Base Primea™ by Fresenius Kabi. Through these simulations we demonstrated that the peak concentrations of propofol after the administration of a bolus of 3 mg.kg\(^{-1}\) could be well predicted by our recirculatory model, but were significantly underestimated by the other PK sets.

During TCI both the effect-site concentration may be targeted, as well as the plasma site, depending on the PK-PD parameter sets available in the device. When applying effect site concentration as the target concentration, ideally, the
implemented effect site equilibration half-life is determined in the same population as the pharmacokinetic parameters are, as is the case for the Schnider effect site TCI ($k_{e0}$ of 0.456 min$^{-1}$). This is not the case for the Marsh-effect site TCI ($k_{e0}$ of 0.26 min$^{-1}$), as is used in the Diprifusor™. In targeting the effect-site concentration, the pharmacodynamic variability is superimposed upon the pharmacokinetic variability and/or inaccuracy of the pharmacokinetic model.

Knowing the poor prediction of the blood drug concentration by compartmental models in the early-phase after a bolus drug dosing, we explored the effect-site equilibration of propofol as based on recirculatory modeling with the bispectral index (BIS) as effect parameter and compared this to the effect-site equilibration of propofol as described by the compartmental models of Marsh and Schnider et al.

**Methods**

**Patients and Procedures**

The concentration-time-effect data used in this study were gathered during the study on early-phase pharmacokinetics of propofol as described in chapter 6. In this study, with approval of the Medical Ethics Committee of the Leiden University Medical Centre and written informed consent, the propofol dose-concentration-effect data of 10 patients, ASA physical status I or II scheduled for elective surgery, were studied. Based on highly frequent arterial blood sampling during the first minutes after administration of an iv bolus of 3 mg.kg$^{-1}$ of propofol, we developed a recirculatory model, using indocyanine green as a marker for the intravascular compartment.

**Data collection**

Prior to the study a cannula was inserted in a large vein in the fossa cubiti for fluid and drug administration. The radial artery was cannulated for the collection of arterial blood samples and hemodynamic monitoring. At every heart beat the arterial systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure, heart rate, cardiac output and stoke volume were gathered, provided the arterial cannula was not used for blood sampling. ECG monitoring was applied as well. Peripheral oxygen saturation and pulse rate were measured using a finger probe. Sedative data were gathered using the bispectral index (BIS) (A-2000, Aspect Medical Systems, USA); the raw and
processed electroencephalogram (EEG) data were transferred to a laptop computer every second. Control blood samples were taken for the construction of reference aliquots. Before the start of each experiment, baseline measurements of the arterial blood pressure, heart rate (HR), cardiac output (CO) and BIS were recorded for at least 15 min. After 3 min of preoxygenation with 100% O₂, each session started with the rapid intravenous administration of propofol 3 mg.kg⁻¹, mixed with ICG 10 mg (Infacyanine®, Laboratoire SERB, France) as described before.¹¹ The propofol/ICG bolus was immediately followed by a rapid bolus of 20 ml of NaCl 0.9%. A computer-controlled syringe pump combined with a fraction collector was programmed to draw 37 arterial blood samples in the first 2.5 min after propofol administration at 3 sec apart for the first 1.5 min, then at every 10 sec for the remaining min. Due to the construction of the sampling device, no mixing in the tubing could occur, as has been described before.¹¹ Five more samples were drawn manually up to 10 min after administration of the propofol bolus dose, at 3, 4, 5, 7.5 and 10 min. During manual sampling, a waste sample was drawn first. The blood samples were collected in heparinized glass tubes and processed immediately by HPLC as described in chapter 6. The study ended when the patient showed clear signs of arousal, if the BIS reached 80 or after 10 minutes.

Data processing

BIS and raw EEG data were transferred from the A-2000 monitor to a laptop and imported into a spreadsheet program (Excel 2000, Microsoft Corporation, Seattle, U.S.A.). The A-2000 calculated the BIS and other processed EEG variables based on artefact-free epochs of data, where each epoch is 2 seconds. Each calculated value was based on an average of the last n epochs, where n represents approximately 60 seconds of data (A-2000 manual).

Pharmacokinetic modeling

A recirculatory PK model was constructed for propofol, using the indicator ICG to estimate the intravascular compartment, as is described in chapter 6. A recirculatory model consisting of central and non-distributive delay compartments for the intravascular compartment, combined with a single tissue compartment and a venous lag-time, described the propofol blood concentrations best. The parameters found for propofol included a steady-state volume of 12.7 ± 1.4 L, a pulmonary volume of 0.6 ± 0.1 L, a tissue volume of 9.9 ± 1.4 L, an elimination clearance of 3.4 ± 0.2 L.min⁻¹ and a venous lag time of 0.08 ± 0.02 min. The mean cardiac output was 7.0 ± 0.5 L.min⁻¹. For the other defining parameters is referred to table 1 in chapter 6.
Pharmacodynamic modeling

The relationship between the propofol blood concentrations and the hypnotic effect measured by BIS was analyzed by coupling an effect compartment to the pharmacokinetic model via a link parameter (Figure 1). As the effect compartment is assumed to have an infinitively small volume, the link parameter is reported as $k_{e0}$. This parameter is also reported as the equilibration half-time ($t_{1/2}k_{e0} = \ln2/k$).

![Figure 1](image)

**Figure 1** Representation of the recirculatory model used to fit the propofol concentration data. The pharmacokinetic recirculatory model for propofol in chapter 6 is extended with an effect compartment. The effect compartment is coupled to the blood compartment via the first order rate constant $k_{e0}$.

The BIS data were transferred to the SAAM program (SAAM II, version 1.1.1, SAAM Institute, University of Washington, USA) and fitted to a sigmoid $E_{\text{max}}$ model using the Hill equation, which is defined by $E_{\text{max}}$, slope gamma and the $EC_{50}$ (the concentration at which 50% of the effect is achieved). Two types of the effect model were analyzed: the classic form, which is called model 1 and an alternative model in which a pharmacodynamic lag time $T_{\text{lag-PD}}$ was added to partially account for the delay in onset of the effect. This is defined as model 2 and is comparable to the pharmacodynamic modeling of the effect on BIS of propofol by Struys et al.\textsuperscript{5,6,12}
Pharmacodynamic simulations

Using the pharmacodynamic parameter sets determined for model 1 and 2 as described above, the effect site concentration was calculated. The effect site concentration was also simulated for the pharmacokinetic parameter sets described by Schnider and Marsh, combined with their respective $k_{e0}$ of 0.456 and 0.26 min$^{-1}$, as implemented in TCI systems for effect-site targeted infusion of propofol. The input for the simulation was a bolus of 201 mg of propofol administered to a female weighing 67 kg and with a length of 1.72 m, the average of our study population.

Statistical Analysis

Descriptive statistics were generated by the SPSS statistical package (SPSS, version 17). Parameters were tested for normality using the Kolmogorov-Smirnov test. Parameters that were not normally distributed were tested for normal distribution after log transformation. If log transformation then revealed a normal distribution, the mean and standard error of the mean (SEM) were transformed back using the following equations:

$$\text{mean} = e^{\mu + \frac{\sigma^2}{2n}}$$

and

$$\text{SEM} = \sqrt{\left(\frac{e^{\sigma^2/n} - 1}{n}\right)e^{2\mu + \sigma^2/n}}$$

where $\mu$ and $\sigma$ represent the mean and SD in the log transformed dataset. Linear regression analysis was performed using the same statistical package. Means of the parameters between groups and the squared residuals of the measured versus the predicted effect data were tested for difference using the Paired Samples T-Test. Difference in goodness of fit between model 1 and 2 for each patient was tested using the F-test. Statistical significance was assumed at $p<0.05$. Data are reported as mean ± standard deviation (SD), unless stated otherwise.
Results

Patients

The 10 patients included were 2 males and 8 females, who were aged 42.2 ± 8.7 yr, weighed 67.1 ± 11.8 kg, were 1.72 ± 0.1 m with a body mass index of 22.5 ± 2.2 kg.m⁻².

The induction of anesthesia with the intravenous bolus dose of propofol (3 mg.kg⁻¹) resulted in a rapid loss of consciousness in all patients with a lowest BIS of 24 ± 9, measured at 75 (60-115) sec (median and range) after the intravenous administration of propofol. All patients had to be ventilated by mask to maintain oxygenation. When the blood propofol concentration decreased after the bolus dose administration and BIS levels increased again to a mean BIS of 72 ± 9, the data collection was terminated to assure that patients remained unconscious. The study was then terminated and anesthesia continued with propofol, remifentanil and atracurium and the trachea was intubated. The patients then were ready for their scheduled surgical procedure. The study was completed without any adverse event. No patients reported any signs of awareness.

PK-PD model

Via a data transfer protocol the raw and processed EEG variables were registered from the A-2000 monitor. A BIS value was generated every second. In order to capture the rapid change in levels of hypnosis, no averaging was performed on the generated BIS data. The data sets therefore contained 270 - 600 data points for the BIS effect measurement. Firstly, the BIS data were analyzed using a classic sigmoid E_max model, coupled to the blood concentration of propofol via k_e0 (Figure 1). This was defined as model 1. Visual inspection of the BIS data over time revealed a varying time to onset of the effect (BIS drop), after which in most patients the BIS decreased rapidly, to consequently regain higher BIS values in a slower manner. This effect pattern was only poorly reflected by the parameters k_e0 and γ in the classical model 1. To improve the quality of fit of model 1 a modification was made to the pharmacodynamic model by introducing a pharmacodynamic lag time T_{lag-PD}. This improved the fit of the PD data and was defined as model 2. The parameters determined by fitting model 1 and model 2 are represented in table 1. The parameters determined by model 1 showed a normal distribution. The parameters determined by model 2 showed a normal or lognormal
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(EC50 and ke0) distribution. All parameters differed significantly between the models according to the Paired Samples T-test (p<0.05).

**Table 1** Parameters describing the pharmacodynamics of propofol based on recirculatory pharmacokinetics, determined by two different pharmacodynamic models. In model 1 a standard sigmoid Emax model is coupled to the blood concentration via a single transfer constant ke0. In model 2 the sigmoid E_max model is linked via a pharmacodynamic lag time combined with the transfer constant ke0.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1</th>
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<th>Model 2</th>
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<tr>
<td></td>
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<td>SEM</td>
<td>Mean</td>
<td>SEM</td>
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<td>3.69</td>
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<td>Tlag-PD (min)</td>
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<td>0.47</td>
<td>0.06</td>
<td></td>
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</table>

For an illustrative patient the PK-PD model fitted to the BIS data using model 1 (panel A) or model 2 (panel B) is presented in figure 2. Improvement of fit of the induction phase with model 2, when a pharmacological lag time was introduced, is clearly visible.

Linear regression analysis of the predicted versus measured effect data showed a better correlation for model 2 than for model 1 (R² of 0.940 vs 0.883, both p<0.0001, Figure 3). The residuals of the measured versus predicted effect for all data points in all patients are represented in time in figure 4. The squared residuals of model 1 differed significantly from those of model 2 (p<0.001), as determined by the Paired T-test. The F test provided further evidence that model 2 fitted the data significantly better than model 1 (p<0.0001). The fitted curve based on the pharmacodynamic parameters for model 2 in reference to the measured BIS curves of all patients is represented in figure 5.
Figure 2 Fit of the pharmacodynamic data of propofol in a representative patient, using two PK-PD models: in panel A the effect is directly coupled to the central blood compartment via $k_{e0}$ ($R^2=0.84$), in panel B a pharmacodynamic lag time ($T_{lag-PD}$) is added to the model ($R^2=0.90$). The F test showed that model 2 fitted the data better than model 1 ($p<0.0001$).
Figure 3 Measured versus predicted BIS effect data, fitted with model 1 ($R^2=0.883$) and model 2 ($R^2=0.940$, for all data points. The solid line is the line of identity ($y=x$).
Figure 4 Residuals of the measured versus predicted BIS values for all datasets, fitted with model 1 (classical model) and model 2 (model including a pharmacodynamic lag time). The squared residuals differed significantly for the 2 models (p<0.05).
Figure 5 The fitted pharmacodynamic model for BIS based on the parameters derived with model 2, including a pharmacological lag time (thick solid line) amid the measured effect curves of all 10 patients.

Discussion

Compartmental modeling poorly describes propofol concentrations during the initial mixing phase and thus may misjudge the blood-effect site disequilibrium. We explored the effect-site equilibration of an induction bolus of propofol by recirculatory pharmacokinetic modeling combined with BIS as effect parameter, and compared this to the $k_{e0}$ as based on compartmental modeling. We successfully defined the recirculatory equilibration constant ($k_{e0}$) for the effect of propofol on BIS in 2 ways. The $k_{e0}$ determined by the first, classic recirculatory PK-PD model was about 50% of the $k_{e0}$ reported in literature as determined by compartmental PK-PD modeling. This is in analogy with similar recirculatory-compartmental $k_{e0}$ comparisons e.g. for rocuronium (0.13 versus 0.24). The equilibration half-life $t_{1/2}k_{e0}$ determined by the second model, in which a variable pharmacodynamic lag time was included, generated a better fit of the median time to peak effect that was observed at 1.25 min. Compartmental pharmacokinetic models underestimate the blood propofol concentration. When modeling the effect in relation to a compartmental
pharmacokinetic model this PK-underestimation is compensated for by a consecutive overestimation of the effect-site equilibration time. With this notice we demonstrate that a reported $k_{e0}$ can only be interpreted in context with its PK-PD model.

**Limitations of the study**

Pharmacodynamic modeling of the sedative effect of propofol has been performed using multiple effect parameters like the mid-latency auditory evoked potentials$^{14}$, spectral edge frequency$^{10}$, bispectral index score$^{15}$, CUP$^{9}$ and permutation entropy$^{16}$, which are all EEG derived effect parameters. These effect parameters are derived, scaled and averaged in different ways, often undisclosed to the public. Albeit the fact that BIS is subject to a moving average (which can be adjusted from 30 to 15 sec on the monitor) and therefore shows an implicit delay, the method is widely available and has been incorporated into the standard OR equipment. Uncertainty on the mathematics by which the BIS is calculated did not outweigh the practical benefits of the BIS as effect parameter. By downloading the raw EEG data from the A-2000 monitor, we attempted to construct the fast reacting parameter permutation entropy. However, this was hampered by the occurrence of burst suppression after administration of the induction bolus of 3 mg.kg$^{-1}$ of propofol. The way that BIS handles artifacts (which can be any rapid change in the signal) by maintaining its former level, combined with the fact that excitation which is observed in the EEG at the start of induction and cannot be reflected by BIS, may account for the delay we observed in our effect measurements.$^{17}$ This phenomenon has been solved before by constructing a biphasic$^{18}$ or 2-compartment effect model for EEG.$^{19}$ Addition of a fixed lag time of 0.1 min has been described by Struys et al.$^{12}$ To deal with comparable problems, Kazama and colleagues did not start fitting the $k_{e0}$ until 1.25 min after adjusting the targeted propofol concentration in their TCI system and measuring EEG with the A-1000.$^{20}$

In our model we chose to introduce a variable pharmacodynamic lag time to account for delay in effect on mathematical grounds. However, considering the high blood peak concentrations we detected by rapid sampling, it may also reflect other phenomena like the transport through the microcirculation$^{21,22}$ and diffusion kinetics$^{23}$ that influence the equilibration ratio from the blood to the effect compartment. The $T_{lag-PD}$ showed correlation with the cardiac output ($R^2=0.524$, $p<0.02$).

The number of patients enrolled in this study is relatively small. However, the vast amount of data generated by the high sampling frequency of blood
concentrations as well as effect measurements, allowed for accurate fitting and less need for interpolation. The variability on the pharmacodynamic parameters is therefore not due to a large variability in the pharmacokinetics.

The real $k_{e0}$?

The findings in this study once more demonstrate that no such parameter as the real $k_{e0}$ for propofol exists. Up to now a number of studies have been performed, generating various values for the $k_{e0}$ (and its equilibration halftime) for propofol. Billard et al. reported a $k_{e0}$ of 0.20 ($t_{1/2k_{e0}}$: 3.5 min);\(^{10}\) Schnider et al. reported a $k_{e0}$ of 0.456 ($t_{1/2k_{e0}}$: 1.51 min)\(^{9}\) and Struys et al. of 1.21 ($t_{1/2k_{e0}}$: 0.57 min)\(^{24}\) and later of 0.58 ($t_{1/2k_{e0}}$: 1.2 min) for a bolus and 0.32 ($t_{1/2k_{e0}}$: 2.2)\(^{12}\) for infusion based on BIS, whereas a $k_{e0}$ of 0.26 ($t_{1/2k_{e0}}$: 2.6 min) based on auditory evoked potentials is incorporated in the Diprifusor (preliminary results presented by M. White).\(^{25}\) Kazama et al. compared 4 age groups, receiving a step-up schedule of propofol TCI. For each age group a different $k_{e0}$ could be determined, even with or without taking EEG activation into account. Values for $t_{1/2k_{e0}}$ varied between 2.29 and 4.33 min.\(^{20}\) The implications of combining different PK data sets with various $k_{e0}$ values is clearly described by Glen.\(^{25}\) Misinterpretation may lead to underdosing with the risk of awareness, or overdosing with the possibility of eliciting side effects like hemodynamic and cardiac depression. To illustrate this we simulated the calculated effect-site concentration, based on our recirculatory pharmacokinetic model that is presented in chapter 6. We compared this to the calculated effect-site concentrations produced by the PK-PD model described by Schnider and by Marsh (Figure 6).

Due to lack of information on the complete pharmacodynamic model on which the $k_{e0}$ of Schnider (0.456) and Marsh (0.26) are based, we could not simulate the BIS effect which would be expected at the calculated effect site concentration. Both the Marsh and Schnider models are implemented in commercially available TCI systems.

The simulations of the effect-site concentration show the influence of the parameter sets on the calculated effect-site concentration and its time-course. Interpretation of the effect-site concentration involves knowledge of the $EC_{50}$ which determines the desired target concentration. Furthermore, the $k_{e0}$ is influenced by the mode of administration, i.e. bolus or infusion\(^{12}\). In our study $k_{e0}$ showed correlation with cardiac output as well ($R^2 =0.600; p<0.01$).
Figure 6 Simulations of the effect-site concentrations calculated from the PK-PD models described by Marsh\textsuperscript{25}, Schnider\textsuperscript{9} and model 2 presented in this study. Note the high Ce from the Schnider model and the delay in time to peak effect (max Ce) with the Marsh model. The mean time to peak effect measured in our study was 1.2 min.

Conclusion

We explored the effect-site equilibration of an induction bolus of propofol by recirculatory pharmacokinetic modeling combined with BIS as effect parameter, and compared this to the $k_{e0}$ as based on compartmental modeling. We successfully defined the recirculatory equilibration constant ($k_{e0}$) for the effect of propofol on BIS. The classically determined $k_{e0}$ was about 50\% of the $k_{e0}$ reported in literature as determined by compartmental PK-PD modeling. Effect data were best fitted after inclusion of a variable pharmacodynamic lag time.

Compartmental pharmacokinetic models underestimate the blood propofol concentration after induction of anesthesia. When modeling the effect in relation to a compartmental pharmacokinetic model this PK-underestimation is compensated for by a consecutive PD-overestimation of the effect-site equilibration constant ($k_{e0}$). With this we draw attention to the fact that a $k_{e0}$ may only be implemented within the context of the pharmacokinetic model used and the effect parameter studied.
References


