Early Phase Pharmacokinetics of Propofol in Humans: the Role of the Lung Explored by Recirculatory Modeling

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Introduction

The pharmacology of the induction of anesthesia is still poorly understood and often roughly described using compartmental modeling. The inability to describe and predict the plasma concentration of a drug like propofol during induction of anesthesia may lead to under- or overdosing in various patient groups, leading to insufficient anesthetic effect or undesired side effects and is a problem that has been recognized in the anesthetic field.1

In contrast to compartmental modeling, the early disposition of induction agents may be better described using physiological based modeling techniques like recirculatory modeling, as is described in chapter 2 of this thesis. Unfortunately, for intravenous anesthetics data on this type of modeling are still scarce. Within the short timeframe of the induction of anesthesia the importance of cardiac output as driving force of drug distribution is generally accepted, while the role of the lung as a modulator of the peaks and troughs in blood drug concentration is still poorly understood. This is especially the case for the disposition of anesthetic agents in humans.

The role of the lung as a pharmacological entity that modulates drug disposition, biotransformation and elimination can be studied in vivo by inclusion of the lung as a separate compartment within the central blood compartment.2 The central blood compartment includes the intravascular volume of the heart and the lungs combined, as well as that of the central arteries. Ideally, the characteristics of such a compartment are best studied when the drug concentrations (and metabolites) are measured in the volumes before, after and from the compartment itself.

The fast-acting intravenous hypnotic agent propofol is known to be primarily cleared and metabolized in the liver, but is also known to undergo renal metabolism and excretion.3-5 The lungs play a significant role in the uptake of propofol, but so far, discrepancy6-8 remains on the significance of metabolism of propofol in, or excretion from, the lungs. Because propofol is a volatile and highly lipophilic agent, diffusion into the alveoli after disposition in the pulmonary tissues is likely. This assumption has proven realistic9-13, now that propofol is detected in the expired air, although the actual expired propofol concentration still remains difficult to quantify.

The scarcity of recirculatory data on propofol in humans and the uncertainty of the role of the lung in its pharmacokinetics has led us to study the early-phase
pharmacokinetics of propofol in healthy patients during induction of anesthesia. The aim of this study was 3-fold:

1. To describe the early-phase pharmacokinetics of propofol in humans.
2. To determine the role of the lung in the clearance and distribution of propofol.
3. To compare the predictive accuracy of a recirculatory pharmacokinetic model for propofol with compartmental models from the literature, which are used in daily practice to predict the blood propofol concentration during induction of anesthesia.

Methods

Patients
The study was performed after approval of the Medical Ethics Committee of the Leiden University Medical Centre and written informed consent. Ten patients, ASA status I or II scheduled for elective surgery were included in the study. Exclusion criteria included a BMI>30, a medical history of severe cardiovascular, respiratory, renal, hepatic, neurological or psychiatric disease, use of anti-hypertensive or anti-arrhythmic medication, pregnancy or lactation and a history of hypersensitivity to ICG.

Procedures
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 intra-arterial blood pressure measurement and cardiac output monitoring through arterial pulse contour analysis with the LiDCO (LiDCO plus, LiDCO Ltd, Cambridge, UK). At every heart beat the arterial systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure, heart rate, cardiac output and stroke volume were gathered, provided the arterial cannula was not used for blood sampling. Peripheral oxygen saturation and pulse rate was measured using a finger probe. A second finger probe was applied for the transcutaneous measurement of ICG (DDG 2001, Nihon Kohden, Japan). Sedative data were gathered using the bispectral index score (BIS) (A-2000, Aspect Medical Systems, USA); the raw and processed electroencephalogram (EEG) data were transferred to a laptop computer every second. ECG monitoring was applied as well. Control blood samples were taken for the construction of reference aliquots and
determination of the hemoglobin level and sodium content, needed for the calibration of the LiDCO and DDG monitor. The LiDCO monitor was calibrated before each experiment by intravenous administration of 0.2 mmol lithium. The LiDCO monitor calibration was based on the non-invasive online determined arterial lithium concentration-time curve and the cardiac output calculated. The LiDCO has been studied and found acceptably reliable in cardiac output monitoring, when compared with traditional thermodilution cardiac output monitoring for up to 8 h after calibration (LidCO versus thermodilution: \( r = 0.86 \)).\textsuperscript{14,15}

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% \( \text{O}_2 \), each session started with the rapid intravenous administration of propofol 3 mg kg\(^{-1} \), mixed with 10 mg of ICG (Infracyanine\textsuperscript{®}, Laboratoire SERB, France). 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 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 100, 110, 120, 130, 140, and 150 sec. Due to the construction of the sampling device, no mixing in the tubing could occur, as has been described before\textsuperscript{16} (Figure 1). Five more blood samples were drawn manually at 3, 4, 5, 7.5 and 10 min after administration of the ICG bolus dose. During manual sampling, a waste sample was drawn first. The blood samples were collected in heparinized glass tubes and processed immediately.

**Measurements of ICG and propofol in blood**

The concentrations of ICG and propofol were determined in series in heparin whole blood using High Performance Liquid Chromatography (HPLC) (Separations analytical instruments, Hendrik-Ido-Ambacht, The Netherlands; column: Ultrasphere ODS 4.6 x 7.5 cm 244254, Beckman Coulter, Mijdrecht, The Netherlands) with ultraviolet and fluorescence detection for respectively ICG and propofol. Thymol was used as the internal standard for both compounds and was measured by fluorescence detection. For each patient a calibration curve was constructed, using the patients own blood prior to injection of ICG and propofol. The blood was deproteinized with acetonitril and the supernatance was injected on the HPLC. The fluorescence settings were as follows; excitation at a wavelength of 275 nm and the emission wavelength at 310 nm with a gain of 10 to measure propofol. ICG was measured at
785 nm, its peak in the spectrum, on the PDA 100. Both ICG and its degradation product were identified by this diode array (Photodiode detector PDA 100, Dionex, Amsterdam, The Netherlands). The detection limit of the whole blood assay for ICG was at 0.2 mg.L\(^{-1}\) and at 0.5 mg.L\(^{-1}\) for propofol. The coefficient of variation was less than 8 % over the range from 0.5 to 10.45 mg.L\(^{-1}\) for ICG and less than 4 % in the range of 1 to 90 mg.L\(^{-1}\) for propofol.

![Schematic representation of the syringepump](image)

**Figure 1** Schematic representation of the syringepump, in which the tubing and stopcock construction is represented. Since the volume that is aspirated by the syringe equals the volume in the tubing, no mixing of the blood samples can occur.

**Data collection and processing**

BIS and raw EEG data were transferred to a laptop and imported into a spreadsheet program (Excel 2000, Microsoft Corporation, Seattle, U.S.A.). The same applied for the hemodynamic data derived from the LiDCO monitor, including arterial blood pressure and cardiac output, as well as for arterial blood ICG-concentrations, to undergo further analysis.
Pharmacokinetic modeling

A recirculatory model, in analogy to the model described for determination of lung uptake and pulmonary clearance of propofol in sheep\textsuperscript{17} and explained in chapter 2 of this thesis, was constructed using the indicator ICG to estimate the intravascular compartment. The model for ICG contained a central part, consisting of two parallel pathways, modeled by n tanks-in-series (Figure 1). To account for the delay observed between injection of the bolus ICG and the detection of any amount of ICG, a lag-time was incorporated into the model as an extra delay element: $T_{\text{lag}}$. Cardiac output was calculated by dividing the administered ICG dose by the area under the first pass concentration-time curve ($A_1 + A_2$; see below). The shape of the first pass concentration-time curve, including all data before evidence of ICG recirculation, was described by the sum of two Erlang functions, each representing the convolution of $n$ 1-compartment models connected in series\textsuperscript{18}

$$C(t) = A_1 \frac{k_1 n_1 t^{n_1-1}}{(n_1 - 1)!} + A_2 \frac{k_2 n_2 t^{n_2-1}}{(n_2 - 1)!}$$

where $n_1$ and $n_2$ are the number of compartments in series in the central delay elements; $k_1$ and $k_2$ are the rate constants between the compartments in series; $n_1/k_1$ and $n_2/k_2$ are the mean transit times of the central delay elements; $A_1$ and $A_2$ are the areas under the first pass concentration-time curves. The two Erlang functions were fitted to the data using the solver function in Excel (Microsoft Corporation, Seattle, U.S.A.), whereby data were uniformly weighted. The lag-time and parameters simulating the first-pass curve ($T_{\text{lag}}, V_{C(f+s)}$ and $MTT_{C(f+s)}$) were then transferred to the SAAM program (SAAM II, version 1.1.1, SAAM Institute, University of Washington, USA) to further analyze the peripheral part of the systemic circulation, including recirculation. This part consisted of two parallel pathways as well, defined by their respective volumes ($V_{ND(f+s)}$) and clearances ($Cl_{ND(f+s)}$). Combined with the elimination clearance $Cl_{EL}$ the summed clearances equaled the cardiac output.

The model for propofol was constructed in a similar way, meaning that the data before recirculation of ICG were fitted by two Erlang-functions. The lag-time was fixed from the ICG data. Then, the parameters were transferred to the SAAM program. For the model of propofol a single tissue compartment was added, in analogy to drug modeling described by Henthorn et al.\textsuperscript{19}, since only a short period after recirculation was studied (Figure 2). The ratio between the peripheral systemic circulation pathways (ND-f and ND-s) was kept identical to
this ratio determined for ICG. Lung retention at first-pass was determined as described before.20,21

**Comparison to other pharmacokinetic datasets**

For comparison of the accuracy of the pharmacokinetic parameters found in this study in relation to the pharmacokinetic parameter sets reported in literature, the 2 parameter sets were selected that are clinically used in the target controlled infusion (TCI) systems for propofol and are commercially available. These are the parameter set described by Marsh23, which is incorporated in the Diprifuor® system (AstraZeneca), and the parameter set described by Schnider24, which is incorporated in the Orchestra Base Primea® system (Fresenius Kabi ltd). For both pharmacokinetic parameter sets the predicted plasma concentration-time curve of propofol was simulated, based on the administration of an instantaneous bolus of 201.3 mg of propofol to a woman of 42 years of age, weighing 67 kg, and with a length of 1.72 m (our average patient with the average dose administered). Simulation was performed using the Tivatrainer© (F.H.M. Engbers, LUMC, Leiden, the Netherlands).

![Diagram](image)

**Figure 2** Intravascular part of the recirculatory model, used to fit the ICG data. The model consists of a delay element representing the venous lag time (T\textsubscript{lag}), two parallel central pathways represented by a varying number of tanks-in-series (a fast V\textsubscript{C-f} and slow V\textsubscript{C-s}) and two parallel non-distributive peripheral compartments (a fast V\textsubscript{ND-f} and slow V\textsubscript{ND-s}). Cl\textsubscript{EL} is the elimination clearance.
Statistical analysis

Descriptive statistics were generated by the SPSS statistical package (SPSS, version 17). Parameters were tested for normality using the Kolmogorov-Smirnov test. Any parameter that was not normally distributed was tested for normal distribution after log transformation. If the log transformed parameters proved to be normally distributed, the mean and standard error of the mean (SEM) were thereafter transformed back using the following equations: mean = e^{\mu+\sigma^2/2n} and SEM = \sqrt{(e^{\sigma^2/n}-1)e^{2\mu+\sigma^2/n}}. Linear regression analysis was performed using the same statistical package. Statistical significance was assumed at p<0.05. Data are described as mean ± SD, unless reported 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) seconds (median and range) after the intravenous administration of propofol. All patients had to be ventilated by mask. With again decreasing blood propofol concentrations and sedative levels, BIS reached a mean of 72 before the data collection was terminated. Data collection was terminated after sufficient data was gathered to allow recirculatory modeling of propofol pharmacokinetics but before return to consciousness. After termination of the study, anesthesia was 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. All blood samples were analyzed within 12 weeks.

The mean peak arterial plasma ICG and peak arterial blood propofol concentration occurred at 18 and 21 sec past administration, respectively, reflecting the equally rapid distribution of ICG and propofol. Examination of the propofol-concentration time data revealed that the peak arterial blood propofol concentration, with an average of 88 ± 17 µg.ml⁻¹, profoundly exceeded that generally considered sufficient for surgical anesthesia (EC₅₀ for loss of consciousness 3.4 µg.ml⁻¹)²⁵, reflecting the poor initial mixing of propofol in the
vascular compartment. The pharmacokinetic parameters of ICG are displayed in Table 1. The cardiac output in these healthy volunteers was close to 7 L.min\(^{-1}\), equivalent to the sum of clearances of ICG. Furthermore, ICG elimination clearance was 1.19 L.min\(^{-1}\), smaller but close to the assumed hepatic blood flow of 1.35 L.min\(^{-1}\), reflecting the sole elimination of ICG through hepatic elimination.

**Recirculatory modeling**

The concentration-time data for ICG were modeled by the classic recirculatory model for the central circulation as discussed in chapter 2 of this thesis, with the addition of a venous lag time (\(T_{lag}\)) to correct for the delay of the drug transfer from the venous injection point to the right atrium. The parameters determined for ICG are represented in table 1. All parameters were distributed normally or lognormally. Parameters that were transformed back from logtransformation were \(V_{ND-s}\), \(V_{SS}\), \(MTT_C\) and \(MTT_{ND-f}\). The model for the central compartment is represented in figure 2.

For the modeling of the propofol concentration-time data, the recirculatory model that provided the best fit was selected following visual inspection and application of the Akaike criterion. The resulting recirculatory model consisted of two parallel tanks-in-series representing the central compartment including the lungs. The propofol concentration-time data before recirculation of propofol was observed, were analyzed separately using Erlang functions. This procedure is similar as is described for the modeling of the central compartment for ICG. The cardiac output and venous lag time were fixed according to the ICG model for each patient. No elimination from the pulmonary compartment could be determined. As a consequence, the pulmonary volume acted as a distribution volume and was determined as the difference in volumes of the central compartments determined for ICG and propofol. The peripheral part of the model consists of two parallel non-distributive pathways, a slow (ND-s) and a fast one (ND-f), defined by their volumes and clearances, and is completed by a peripheral distributive tissue compartment as can be seen in figure 3.

The non-distributive compartments represent the part of the intravascular compartment outside the thorax and may represent vascular beds like the great vessels and the splanchnic vascular bed. The ratio between the fast and the slow intravascular pathway was kept equal for the ICG and the propofol model. The parameters for the recirculatory propofol model are presented in table 1 as well. All parameters were distributed normally or lognormally (\(Cl_{ND-f}\)). The
parameter $\text{Cl}_{\text{ND-f}}$ was transformed back after logtransformation. The individual fits for the ICG and propofol concentration-time curves for the 10 patients show that the predicted ICG and propofol concentrations very closely correspond to those actually measured (Figure 4). Linear regression analysis showed good correlation between the measured and predicted blood propofol concentrations ($R^2 = 0.959; p<0.001$, Figure 5).

![Figure 3](image.png)

**Figure 3** Representation of the recirculatory model used to fit the propofol concentration data. The intravascular compartment as described for ICG in figure 1 is extended with a peripheral tissue compartment $V_T$. The ratio between the flows ($\text{Cl}_{\text{ND-f}}$ and $\text{Cl}_{\text{ND-s}}$) to the non-distributive compartments $V_{\text{ND-f}}$ and $V_{\text{ND-s}}$ is kept equal to that determined for ICG. The total of all clearances equals the cardiac output.

The propofol concentrations predicted by the pharmacokinetic models as described by Marsh$^{23}$ and Schnider$^{24}$, based on the simulated administration of a bolus propofol dose, are represented in figure 6. Plasma concentrations were simulated for the average bolus administered to a female patient with the average characteristics from our study population. The simulated plasma concentration curves are plotted against all plasma concentrations determined in our study. The curve constructed from the recirculatory pharmacokinetic parameters in our study is represented by the solid line in figure 6. The peak
blood propofol concentrations detected in our study by rapid sampling were almost 10 times higher as predicted by the Marsh model and twice as high as predicted by the Schnider model.

Table 1 Pharmacokinetic parameters found for the ICG and propofol model, stating volumes (V) in L, clearances (Cl) in L.min^-1 and mean transit times (MTT) in min for the central (C), non-distributive fast (ND-f), non-distributive slow (ND-s), tissue (T) and pulmonary (P) compartment, as well as the steady state volume (V SS) and the elimination clearance (Cl EL) and cumulative clearance (ΣCl), which equals the cardiac output. T lag represents the venous lag time. At the bottom row the lung retention in represented in %. Parameters are stated as mean with their standard error of the mean (SEM).

<table>
<thead>
<tr>
<th>parameter</th>
<th>ICG mean</th>
<th>ICG SEM</th>
<th>propofol mean</th>
<th>propofol SEM</th>
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<tr>
<td>VC</td>
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<td>0.07</td>
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<td>0.18</td>
<td>0.22</td>
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<td>VP</td>
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<td>0.11</td>
</tr>
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<td>VT</td>
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<td></td>
<td>9.90</td>
<td>1.39</td>
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<td>VSS</td>
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<td>12.71</td>
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<tr>
<td>Cl EL</td>
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<td>Lung retention(%)</td>
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<td>2.06</td>
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</table>
Figure 4 Individual fits of the blood concentration data of Indocyanine Green (●) and propofol (Δ) in each patient. On the horizontal axis the time in min, on the vertical left axis the ICG concentration and on the right vertical axis the propofol concentration in µg.ml⁻¹.
Figure 5  Correlation of the measured versus predicted data for propofol. The regression formula is prop predicted = -424.7 + (1.112 * prop measured). The $R^2$ equals 0.959; $p<0.001$. The line in the graph is the line of equality ($y=x$).

**Discussion**

We studied the recirculatory pharmacokinetics of propofol with the aims to:

1. Closely evaluate the early-phase concentration-time relationship of propofol during induction of anesthesia.
2. To determine the role of the lung in the clearance and distribution of propofol.
3. To compare the predictive accuracy of a recirculatory propofol pharmacokinetic model with compartmental models from the literature.

We conclude that propofol, after bolus administration, exhibits blood concentrations that profoundly exceed those related to the hypnotic effect reflecting its poor initial mixing. We conclude that propofol shows no clinical relevant clearance from the lung. Lastly, we demonstrate that compartmental models, now widely used in anesthetic practice in target controlled infusion...
pumps, significantly underestimate the actual blood propofol concentration in the first minutes after induction of anesthesia.

**Figure 6** Simulations of the concentration-time curves of propofol after administration of an intravenous bolus of 201 mg to a female of 42 yrs, weight 67 kg and height 1.72 m (averages in our study population) based on different pharmacokinetic models. The open circles represent all propofol blood samples in our study. The dotted curve is a simulation based on pharmacokinetics from the Marsh\(^23\) model; the propofol concentrations are underestimated in the peak and overestimated in the elimination phase. The striped curve is a simulation based on the pharmacokinetic model by Schnider\(^24\), which performs better, but still underestimates peak concentrations and those in the elimination phase. The solid line represents the simulation based on our average pharmacokinetic parameters from the recirculatory model.

**This recirculatory model compared to existing model.**

So far, the only recirculatory pharmacokinetic model for propofol in humans available was that by Upton et al.\(^{26}\), who gathered data from various sources to describe and model the distribution and elimination of propofol. Although we acknowledge the uniqueness of this model, various assumptions and estimates were necessary to develop this model that was accomplished after combining the data of many authors. In particular, not all parameters were determined
based on the available data but some parameters had to be estimated based on “known physiology”. In addition to the uncertainty involved with combining data from various sources, also the results presented by Upton, though very worthy form a physiological point of view, offer little clues to be implemented directly and associated to the clinical dose-concentration-effect relationship of propofol. Because, apart from Upton et al., only animal data were available on the recirculatory pharmacokinetics of propofol we studied the recirculatory pharmacokinetics in humans.

**Modeling of the pulmonary compartment**

The role of the lungs in the early phase of mixing and distribution of propofol into deeper tissue compartments remained yet not fully understood. Consensus exists in that the liver is the main organ of biotransformation and elimination of propofol, partly due to its high extraction ratio of up to 0.9. However, during the anhepatic phase in liver transplantations, extrahepatic clearance of propofol has been demonstrated. Also total body clearance exceeds the hepatic blood flow. To explore the role of the lung, recirculatory modeling of our data for propofol was initiated in analogy to the model described by Kuipers et al.\textsuperscript{17} regarding the propofol recirculatory pharmacokinetics in sheep. In the sheep model pulmonary uptake was modeled by a distribution compartment placed in series with the tanks-in-series. For the description of lung uptake in our patients the addition of a distribution compartment, either parallel or in series, did not result in an adequate description of the concentration time curves for propofol. Yet, these curves of propofol and ICG were different, indicating a delay of propofol in the lungs. Pulmonary elimination could not be discerned from distribution or central elimination. Therefore a model for propofol was constructed in which pulmonary distribution was described by tanks-in-series only (Figure 1) to indicate a delay in the appearance of drug molecules at the effluent side of the organ. This delay is inhomogeneous compared to a fixed delay (expressed in sec). The pulmonary volume was determined as the difference between the combined volumes of the fast and slow central compartments for ICG and propofol.\textsuperscript{19} Also the mean transit times for ICG and propofol through the central compartment differed.

The pulmonary first-pass uptake of propofol in our patients of 25.7 ± 6.5% is in agreement with the 28% reported earlier by He et al.\textsuperscript{27}, however small compared to other intravenous drugs used in anesthesia, such as fentanyl, sufentanil or other basic amines.\textsuperscript{28} Despite the fact that propofol is highly lipophilic, the first pass lung uptake is relatively low. To be retained in the lungs, the drug in the lung tissue must be bound or otherwise hindered in the back
release to the blood. One mechanism that may be involved in this, is that the drug is ionized. This mechanism probably plays a significant role for basic amines, in which cellular depots possibly play a role.\textsuperscript{29,30} Despite the fact that propofol is highly lipophilic, its pKa of 11 makes it more ionized than the basic amines, resulting in less retention in the lungs. That propofol can penetrate in due time in deeper compartments has been shown by Grossherr and co-workers, who could detect propofol in epithelial line fluid.\textsuperscript{31}

Propofol lung uptake has been described in cats\textsuperscript{32}, sheep\textsuperscript{17} and goats and pigs.\textsuperscript{33} Pulmonary uptake and more importantly clearance is disputed in humans.\textsuperscript{6,27,34} The lungs have been viewed as a possible site of clearance because propofol is detectable in exhaled air.\textsuperscript{9-11,13} Yet, the quantities exhaled by the lungs are expressed in parts per billion that are detected by very sensitive equipment. These quantities multiplied by the exhaled minute volume embody a very small amount compared to the quantities delivered by the venous blood through the cardiac output. In mechanically ventilated patients undergoing cardiac surgery, Grossherr and coworkers\textsuperscript{12} measured 2.8 and 22.5 ppb in exhaled air while the concurrent blood concentrations were 0.3 and 3.3 µg/ml. From these and our data we conclude that propofol clearance by exhaling air is clinically insignificant. We assume that propofol is bound to the vascular tissues (endothelial lining) but that propofol does not transfer to “deep” compartments in the lungs. This would explain that a distribution compartment cannot be fitted and that propofol is better described using a dispersion model (tanks-in-series). We suspect that other sites of extrahepatic clearance are more important than the lungs and especially the kidneys are good candidates. Renal excretion of propofol and its metabolites has been demonstrated with a high renal extraction ratio of 0.6 to 0.7\textsuperscript{3,4}, leading to a renal clearance of almost up to 30% of the total body clearance.

**This recirculatory model compared to compartmental models**

The comparison of the predicted propofol concentrations based on the recirculatory pharmacokinetic model, with those predicted as based on the compartmental models by Marsh and Schnider, revealed a significant underestimation of the peak concentrations and an overestimation of the plasma concentration around the time of recirculation by compartmental models, as seen in figure 6. The fact that standard compartmental models poorly predict early-phase kinetics has been recognized before.\textsuperscript{19,35} Recently, an adaptation of a compartmental model by inclusion of a lag time and transit elements was introduced by Masui et al.\textsuperscript{36} Although this model performed better than the ones tested here, underestimation of the peak concentration
remained. These misrepresentations may have clinical implications indeed. Underestimation of the propofol blood concentration may result in unnecessary overdosing of propofol and aggravated hemodynamic depression when propofol is administered by TCI based on compartmental pharmacokinetic models. On the other hand can an overestimation of the propofol blood concentration lead to insufficient sedation and increase the chance of awareness of the patient.

In conclusion, we successfully described the pharmacokinetics of propofol by recirculatory modeling. After bolus administration, propofol exhibits blood concentrations that greatly exceed those related to hypnotic effect, reflecting its poor initial mixing. We conclude that propofol shows no clinical relevant clearance from the lung. Lastly, we demonstrated that compartmental models, now widely used in anesthetic practice in target controlled infusion pumps, significantly underestimate the actual blood propofol concentration in the first minutes after induction of anesthesia.

References


