Mixed-effects Modeling of the Influence of Midazolam on Propofol Pharmacokinetics

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INTRODUCTION

In clinical practice patients often receive midazolam to reduce preoperative anxiety, to ensure perioperative sedation during locoregional anesthesia or to strengthen the effect of intraoperative administered anaesthetics. The influence of midazolam on the pharmacodynamics of various anaesthetic agents has been described in detail(1-4). These studies show that midazolam increases the sedative levels induced by other hypnotic agents and often interacts synergistically at the γ-aminobutyric acid receptor type A.

Various studies describe the pharmaco*kinetic* interaction between anaesthetic agents and pharmacodynamic interactions.(5) In general, the interaction between anaesthetics leads to an increase in the blood or plasma drug concentration. Next to cytochrome P450 enzyme induction, hemodynamic alterations may be responsible for these pharmacokinetic interactions.

Midazolam is frequently used as preoperative sedative and accordingly is often present when intraoperatively hypnotics such as propofol are administered. Propofol is known as a high extraction ratio drug and its clearance may thus be susceptible to hemodynamic alterations when hepatic blood flow is affected. Previous studies already indicate that the pharmacokinetics of other anaesthetic agents than propofol are affected by hemodynamic alterations (6) and hypovolemia has been found to influence the pharmacokinetics of propofol itself.(7)

To our knowledge there are no data that describe whether, and to what degree, midazolam affects the pharmacokinetics of intraoperatively administered opioids or intravenous hypnotics like propofol. We hypothesized that midazolam affects the pharmacokinetics of propofol and that hemodynamic parameters indeed are involved. We therefore studied the influence of midazolam on the pharmacokinetics of propofol and measured hemodynamic parameters in a group of healthy volunteers.

METHODS

VOLUNTEERS AND STUDY PROTOCOL

After obtaining approval of the Medical Ethics Committee of the Leiden University Medical Centre and written informed consent, eight healthy male volunteers, aged 20-30 years, were studied to obtain 16 propofol concentration-time data sets in the absence and presence of midazolam. All volunteers were within 30% of ideal body weight, had no history of renal or hepatic disease and were not taking medication within 6 months prior, or during, the investigation. All volunteers denied smoking or consumption of more than 20 g of alcohol per day.

Before the investigation a blood sample was taken for screening of renal or hepatic disease. Volunteers were studied on two occasions using a randomized cross-over design. On one occasion (session A) the volunteers received a propofol bolus dose of 1 mg/kg in 1 min followed by an infusion of 2.5 $mg.kg^{-1}.h^{-1}$ (= 41.7 $\mu g\ kg^{-1}.min^{-1}$) for 59 min. On another occasion (session B) the volunteers received the same propofol infusion scheme as during session A, but now on top of a midazolam target controlled infusion (TCI) aimed at a target midazolam concentration (C_T) of 125 ng/ml that was started 15 min the propofol administration. The TCI midazolam was maintained constant in this session for up to 6 h after termination of the propofol infusion.

The two sessions were separated by a period of at least two weeks. The order of the two sessions was randomized, such that in half of the volunteers, the control session preceded the midazolam session and *vice versa*. Volunteers fasted from midnight of the night before the study until the last blood sample had been collected. During the administration of midazolam, the volunteers breathed 30% oxygen in air. When indicated, ventilation was assisted using a face mask to maintain the end-tidal CO_2 partial pressure below 50 mmHg. After termination of session A and B, the subjects were monitored for another 4 h and received a light meal before they were escorted to their home.

MATERIALS

The studies were performed in a designated room in the OR complex. An IV cannula was inserted into a large forearm vein for the infusion of propofol and midazolam and an arterial cannula was inserted in the contralateral radial artery for collection of blood samples and hemodynamic data. The electrocardiogram, respiratory rate, peripheral oxygen saturation, the Bispectral index and intra-arterial blood pressure were monitored continuously throughout the study. Furthermore, the cardiac output was determined using the pulse-contour methodology on the basis of the intra-arterial blood pressure curve with the LiDCOplus monitor (LiDCOgroup plc, London (8)). The LiDCO cardiac output measurement is comparably reliable to traditional thermodilution cardiac output measurement for up to 8 h after calibration (LidCO versus thermodilution: r = 0.86).(9) In the light of the described

reliability of the LiDCO and the invasiveness of pulmonary artery catheterisation, non-invasive cardiac output monitoring by the LiDCO offered the best option for hemodynamic monitoring in this study in volunteers. The LiDCO monitor was calibrated before each experiment. For this purpose, a lithium sensor was connected to the arterial cannula. Next, after 0.2 mmol lithium was injected intravenously, and the LiDCO monitor was calibrated on the basis of the non-invasive online determined arterial lithium concentration-time curve and the cardiac output calculated. Blood samples were drawn from the arterial cannula, after calibration of the LiDCO.

Heart rate, cardiac output, cardiac index, systemic vascular resistance, the systolic, mean and diastolic arterial blood pressure were all recorded online at every heart beat and saved for further analysis. All volunteers received an infusion of saline of 2 $ml.kg^{-1}.h^{-1}$ during each session.

Propofol was administered with a conventional infusion pump. A Psion pocket computer, provided with a 3-compartment pharmacokinetic parameter set of midazolam(10) was used to control an infusion pump for the target-controlled infusion of midazolam.

BLOOD SAMPLES AND ASSAYS

During session A, a blank blood sample (10 ml) was obtained. This sample was used for calibration purposes. Additional arterial blood samples (3 ml) for the determination of the blood propofol concentration, were taken at 1, 3, 5, 10, 20, 30, 45 and 60 min after the start of the propofol infusion, and at 3, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after termination of the propofol infusion. Blood samples were collected in syringes coated with potassium-oxalate for determination of the blood propofol concentration. These blood samples were stored at 4 ℃. Propofol assays were carried out within 12 weeks. Propofol concentrations in blood were measured by HPLC-fluorescence at 276 nm.(11) The intra- and inter-assay coefficients of variation were 4.3% and 3.7% for propofol in blood in the concentration range of 0.06 – 6.8 µg/mL.

During session B, in addition to the sample scheme in session A, every 60 min an additional arterial blood sample (3 ml) was taken for determination of the plasma midazolam concentration. These samples were centrifuged to obtain plasma which was subsequently stored at -20 ℃ until analysis. The concentration of midazolam in plasma was determined by reversed-phase high-performance liquid chromatography-UV detection at 216 nm (HPLC).(12) The intra- and inter-assay coefficients of variation were 2.2% and 2.0% for midazolam in plasma in the concentration range of 9.7-1120 ng/ml. Midazolam assays were conducted within 12 weeks. The assays of midazolam and propofol did not interfere as the fluorescence wavelengths of midazolam (217 nm) and propofol (276 nm) do not overlap. This allows a distinct and accurate estimation of the two drugs.

STATISTICAL ANALYSIS

A first exploratory analysis of differences in mean arterial pressure, heart rate, cardiac output, systemic vascular resistance and stroke volume between sessions 1 and 2 was done with the Wilcoxon signed rank test (SPSS version 12.5 for Windows). A probability level < 0.05 was considered significant. The goal of this analysis was to limit the number of hemodynamic variables to be tested as covariate in the population pharmacokinetic analysis which was performed using NONMEM (version VI 1.2). Population pharmacokinetic parameters were estimated using the first-order conditional estimation method with η-ε interaction for a 3-compartment model (ADVAN11). A proportional error model was used with variance σ^2 of the intraindividual variability terms (ε). The interindividual variability of each model parameter was specified using a log-normal variance model:

$$\Phi_i(t) = \Phi_{TV,i}(t).e^{\eta_i}$$ with

$$\Phi_{TV,i}(t) = \Theta i.e^{\sum_{j=1}^{m} \alpha j.(COVji(t)-(MD\,\mathrm{cov}\,j))}$$

Where Φ_i is the population value and $\Phi_{TV}\ i(t)$ is the typical value with fixed effects taken into account of the pharmacokinetic parameter in individual *i* at time *t*. η_i is the Bayesian estimate of the normally distributed random variable η (with mean zero and variance ω^2) in the individual *i* (which is estimated by NONMEM), *m* is the number of covariates considered, α_j is the value of a coefficient parameter describing the dependence of the pharmacokinetic parameter on covariate *j*, and *MD*cov$_j$ is the median of the covariate *j* in the population. *MD*cov$_j$ is the median of 16 observations (8 volunteers times 2 sessions), except for the midazolam concentration (only session B).

Coefficients of variation (CV%) were calculated as 100 times the square root of the variance ω^2 of η and, parameter distributions being asymmetric, are only approximately the coefficients of variation as usually defined.

PHARMACOKINETIC DATA ANALYSIS AND INCLUSION OF COVARIATES

A pharmacokinetic parameter set was determined on the basis of the blood propofol concentration-time data alone (without covariates) of the 16 sessions. Three compartment models were fitted to the data (number of components based on literature and experiment design) with parameters V_1-V_3 and Cl_1-Cl_3 (central volume of distribution [V_1], shallow peripheral volume of distribution [V_2], deep peripheral volume of distribution [V_3], elimination clearance [Cl_1], rapid distribution clearance [Cl_2], and slow distribution clearance [Cl_3]).

2. To determine the influence of midazolam on the 6 propofol pharmacokinetic parameters, all 64 possible combinations for the covariate midazolam were evaluated (64 = 2^6, 2 referring to presence or absence of the covariate, 6 referring to the 6 possible pharmacokinetic parameters). Midazolam was treated as a time-independent covariate. The model with the lowest Akaike's Information Criteria (AIC) value was considered best.(13)
3. The hemodynamic parameters that differed significantly between sessions A and B were evaluated as potential covariates to further improve the predictability of the propofol pharmacokinetic parameter set. The arithmetic means of these hemodynamic parameters prior to each measured plasma midazolam concentration were calculated. These data then were treated as time-dependent variables in the analysis. For each hemodynamic parameter another 64 analysis runs were performed on the basis of the pharmacokinetic parameter set of propofol with midazolam as covariate included. Again, the combination with the lowest AIC was considered best.
4. To assess the accuracy of the model, we calculated the weighted residual (WR) and the absolute weighted residual (AWR) for each sample.

$$WR_{ij} = \frac{C_{meas,ij} - C_{pred,j}}{C_{pred,j}} \qquad AWR_{ij} = \frac{|C_{meas,ij} - C_{pred,j}|}{C_{pred,j}}$$

In which $C_{meas,ij}$ is the *j*th measured concentration of the *i*th individual, and the $C_{pred,j}$ denotes the corresponding population predicted values. The median values of the weighted residuals (MDWR) and the absolute weighted residuals (MDAWR) were used as overall measures of goodness of fit.

Computer Simulations

The clinical consequences of the influence of midazolam on propofol pharmacokinetics were explored by computer simulation using TIVAtrainer[1] with the final propofol pharmacokinetic parameter with midazolam and mean arterial pressure as covariates in a 74 kg male.

Three computer simulations were performed. 1) A computer simulation exploring the influence of the plasma midazolam concentration (0 or 225 ng/ml) on the propofol

*available at: www.eurosiva.org. Accessed September 16, 2008

concentration-time profile in the presence of a mean arterial pressure of 78 and 68 mmHg. This most closely resembles the actual study conditions. 2) We then performed 2 simulations to distinguish between the effects of midazolam and mean arterial pressure on the propofol concentration-time relationship. For this purpose we first explored the influence of midazolam (0 and 225 ng/ml) on the propofol concentration-time profile in the presence of a stable mean arterial pressure of 74 mmHg. Next a computer simulation was performed to explore the influence of mean arterial pressure (50, 75 and 100 mmHg) on the propofol concentration-time profile in the absence of midazolam. 3) Finally, a computer simulation evaluated the influence of midazolam on the 50% (i.e., the context sensitive half-time) and the 80% decrement time of propofol. For this purpose we used the final propofol pharmacokinetic data set in the presence of a plasma midazolam concentration of 0 or 225 ng/ml with a mean arterial pressure of 78 and 68 mmHg (Table 3).

Data are presented as mean (SD) unless stated otherwise.

RESULTS

All volunteers completed the study without adverse events. The mean ± SD age, weight and height of the volunteers were 21.8 ± 1.8 years, 73.6 ± 9.7 kg and 182.1 ± 6.0 cm. The midazolam TCI system administered 13.1 ± 2.1 mg of midazolam in the first hour of infusion and administered another 6-8 mg to maintain the target concentration of 125 ng/ml.(10) The mean total midazolam dose given was 49.25 ± 5.32 mg. The plasma midazolam concentration (mean ± SD: 224.8 ± 41.6 ng/ml) proved sufficiently stable in all volunteers (Figure 1). None of the volunteers experienced significant respiratory depression and the end-tidal partial CO_2 pressure never exceeded 50 mmHg.

During the 16 study sessions a total of 470 blood samples were collected for both midazolam and propofol concentration determination. Of these, 368 were used for blood propofol concentration determination and analysis of the propofol pharmacokinetics. An exploratory analysis of the hemodynamic data showed that in the presence of midazolam MAP and stroke volume were significantly lower while heart rate was significantly more rapid compared with the controls when propofol was given as sole agent (table 1).

The propofol concentrations in the presence of a mean midazolam concentration of 224.8 ± 41.6 ng/ml were on average 25.1 ± 13.3 % higher compared to when propofol was given as sole agent (Figure 2).

The population pharmacokinetic analysis of the propofol concentration-time data revealed that a 3-compartment model best fitted the data. First the pharmacokinetics of propofol were determined without consideration of any covariate (first column Table 2). When midazolam was introduced as covariate the AIC decreased significantly (second column Table 2). Midazolam was a significant covariate on Cl_1, Cl_2 and Cl_3 of propofol such that a plasma midazolam concentration of 225 ng/ml reduced Cl_1 from 1.94 to 1.61 L/min, Cl_2 from 2.86 to 1.52 L/min. and Cl_3 from 0.95 to 0.73 L/min.

In addition to midazolam, the hemodynamic parameters that significantly differed between sessions were tested to determine if any of these additional hemodynamic parameters could further clarify still existent variability in the propofol concentration-time data. Of the studied hemodynamic parameters, MAP resulted in the most significant decrease in AIC thus contributing most to improve the propofol pharmacokinetic model that already included midazolam as covariate, (third column Table 2). The propofol pharmacokinetic parameters that were influenced by MAP were V_1, V_2 and Cl_3 (Table 2). In accordance with this model a decrease in mean arterial pressure is associated with an increase in the blood propofol concentration when the propofol dosage scheme is left unchanged. Figure 3 gives an overview of the optimization process of the analysis. Inclusion of midazolam and mean arterial pressure in the final model resulted in the lowest AIC and the narrowest window for MDWR and MDAWR. Figures 4 and 5 display the individual estimates of the various

pharmacokinetic parameters that were significantly affected by midazolam and mean arterial pressure, respectively.

Table 1. Median hemodynamic parameters obtained during the 420 min study period in session A (no midazolam) and session B (in the presence of midazolam). Data were compared using the Wilcoxon signed rank test**.**

Parameter	Session A median (range)	Session B median (range)	Difference (%)	P-Value
HR (beats/min)	61.8 (49.3-85.4)	64.7 (46.3-94.7)	+ 3.5	< 0.001
MAP (mmHg)	78.3 (63.3-101.9)	68.4 (53.5-97.1)	- 12.5	< 0.001
SVR ($dyn.sec^{-1}.cm^{-5}$)	909.2 (611.8-1751.0)	830.3 (368.6-1444.8)	- 4.4	0.12
SV (ml/beat)	107.7 (55.9-132.9)	91.1 (63.1-148.5)	- 9.4	< 0.001
CO (L/min)	6.6 (4.0-9.0)	5.5 (3.5-13.6)	- 4.0	0.15

HR = heart rate; MAP = mean arterial pressure; SVR = systemic vascular resistance; SV = stroke volume; CO = cardiac output.

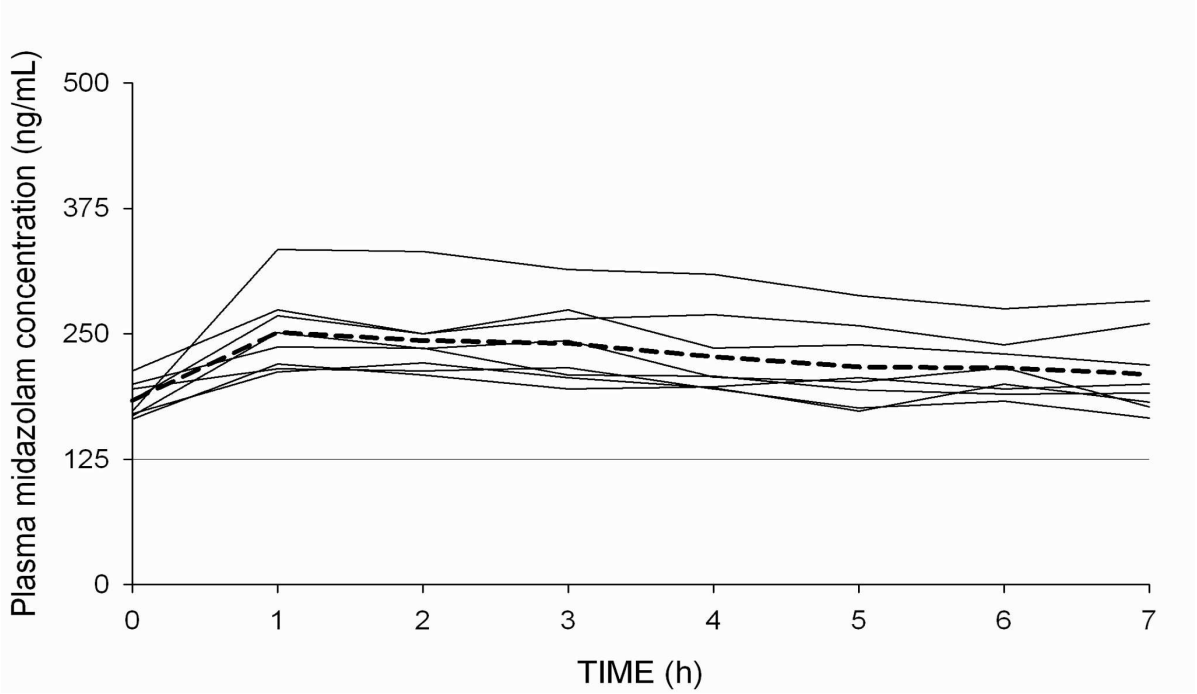

Figure1. Plasma Midazolam Concentration-time data of the individual subjects during session B when midazolam was given at a constant target midazolam of 125 ng/mL.

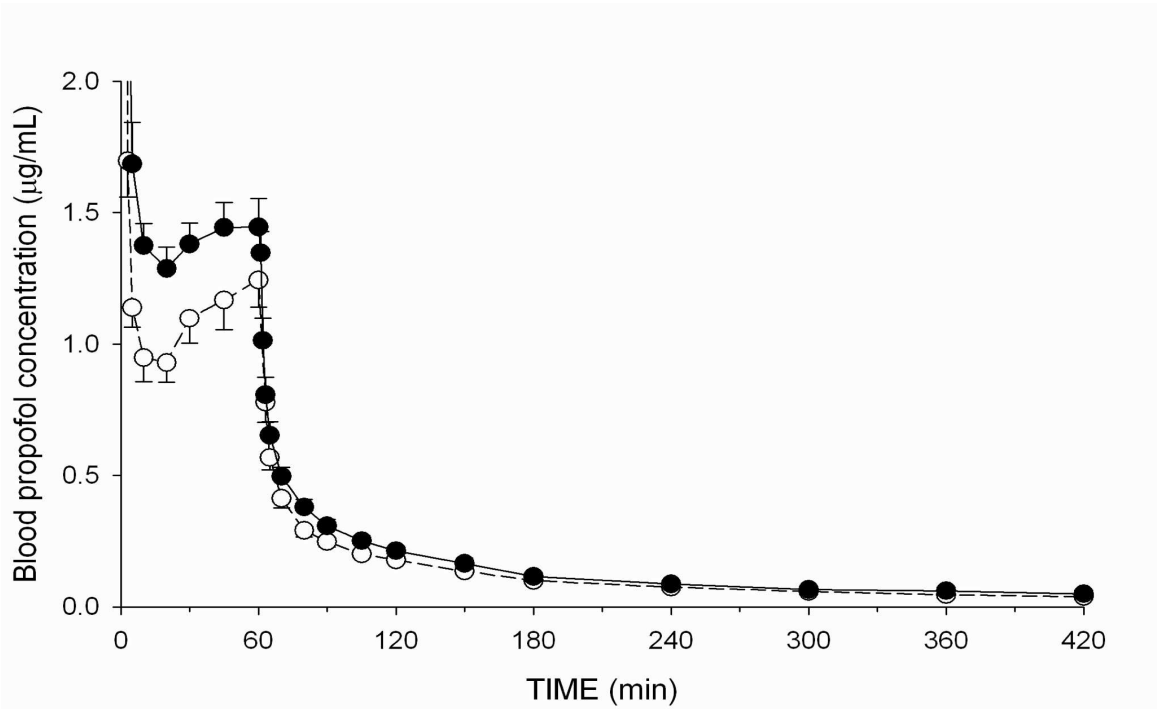

Figure 2. Mean (SE) blood propofol concentration-time curves in the volunteers in the presence (continuous line, closed circles) or absence (discontinuous lines, open circles) of a target-controlled infusion of midazolam with a target concentration of 125 ng/ml

Table 2. population Pharmacokinetic Models of Propofol

	No Covariates			Midazolam			Midazolam + MAP		
Parameter	Value	%CV	SE	Value	%CV	SE	Value	%CV	SE
V_1 (L)	4.87	30	0.67	4.90	32	0.44	5.29	30	0.51
V_2 (L)	26.4	-	1.77	26.9	-	1.67	29.9	-	1.96
V_3 (L)	137	18	9.86	139	18	9.79	144	21	11.3
Cl_1 (L/min)	1.76	15	0.07	1.75	12	0.06	1.77	12	0.06
Cl_2 (L/min)	2.13	31	0.25	2.11	16	0.18	2.09	27	0.21
Cl_3 (L/min)	0.84	22	0.56	0.83	16	0.04	0.85	18	0.05
Covariates									
α_{MID,V_1}									
α_{MID,V_2}									
α_{MID,V_3}									
α_{MID,Cl_1}				$-8.20*10^{-4}$		$3.19*10^{-4}$	$-8.18*10^{-4}$		$3.21*10^{-4}$
α_{MID,Cl_2}				$-2.74*10^{-3}$		$7.82*10^{-4}$	$-2.80*10^{-3}$		$8.81*10^{-4}$
α_{MID,Cl_3}				$-1.42*10^{-3}$		$4.88*10^{-4}$	$-5.23*10^{-4}$		$5.54*10^{-4}$
α_{MAP,V_1}							$-2.46*10^{-2}$		$8.61*10^{-3}$
α_{MAP,V_2}							$1.07*10^{-2}$		$4.68*10^{-3}$
α_{MAP,V_3}									
α_{MAP,Cl_1}									
α_{MAP,Cl_2}									
α_{MAP,Cl_3}							$1.40*10^{-2}$		$7.88*10^{-3}$
Performance measures									
-2*LL*	-1433.74			-1461.12			-1484.59		
AIC	-1409.74			-1431.12			-1448.59		
MDWR (%)	-1.34			-1.23			-1.42		
MDAWR(%)	16.4			15.9			15.7		
σ^2	0.0192			0.0191			0.0168		

Parameters V_1, V_2…. Cl_3 are the parameters of an individual with median covariate values. The median covariate values are 112.375 ng/ml for midazolam and 74.017 mmHg for mean arterial pressure. For example: $Cl_1 = 1.77 * e^{(-0.000818*(C_{MID} - 112.375))}$

MAP = mean arterial pressure (mmHg); V_1 = central volume of distribution; V_2 = rapidly equilibrating peripheral volume of distribution; V_3 = slowly equilibrating peripheral volume of distribution; Cl_1 = elimination clearance; Cl_2 = rapid distribution clearance; Cl_3= slow distribution clearance ; *CV* = coefficient of variation (CV V_2 : - = not estimable); *SE;* standard error of estimate; α = measure of covariate importance (when omitted, the covariate is not significant); *MID* = concentration of midazolam; –2*LL* = –2 x log likelihood; AIC = -2LL + 2P, where P is the number of nonfixed parameters*; AIC* is the Akaike's information-theoretic criterion[10]; *MDWR* = median weighted residual; *MDAWR* = median absolute weighted residual; σ^2 = relative residual error.

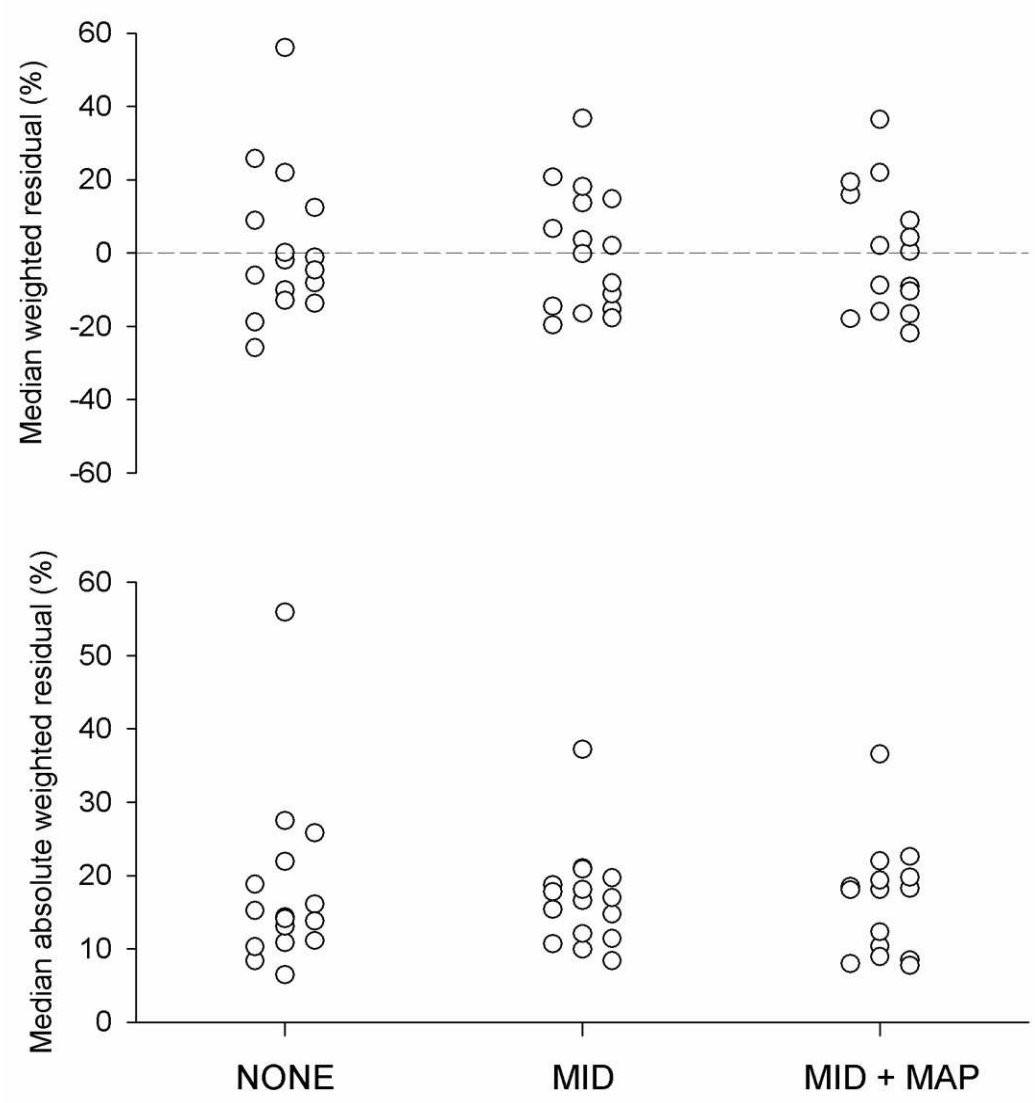

Figure 3. Population median weighted residuals (MDWR) and median absolute weighted residuals (MDAWR) (lower panel) determined for the pharmacokinetic models displayed in Table 2.

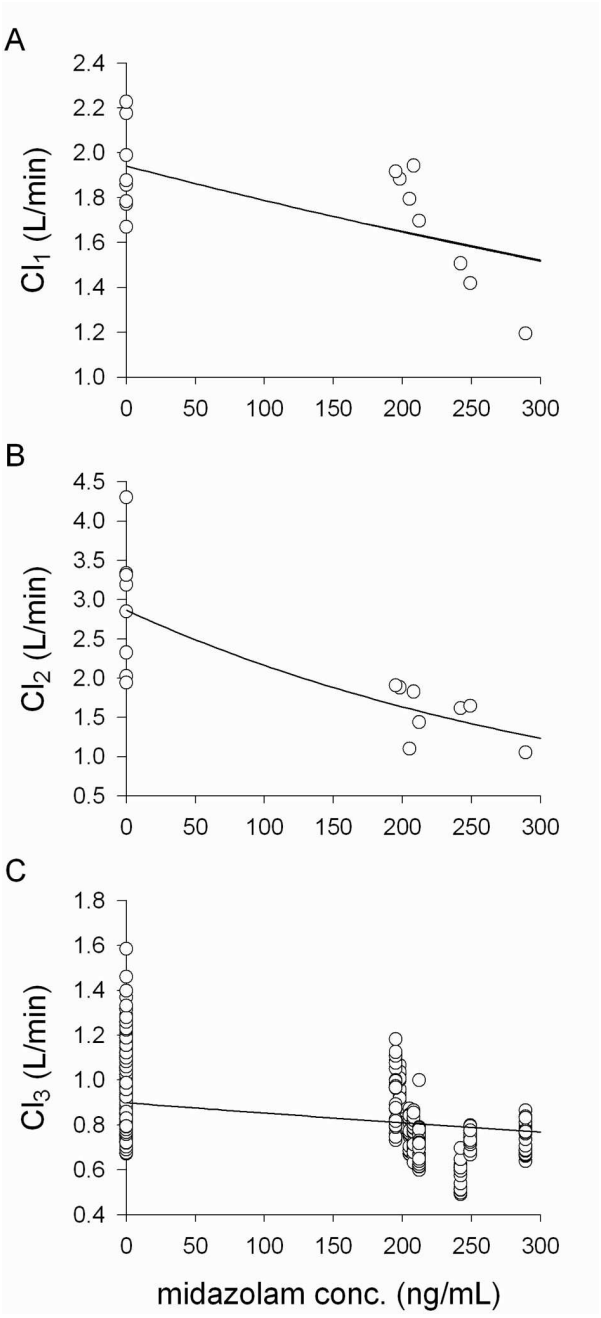

Figure 4. Individual estimates of (A) the elimination clearance (CL_1), (B) rapid distribution clearance (CL_2) and (C) slow distribution clearance (CL_3), obtained from the model without covariates as function of the plasma midazolam concentration. The regression line results from the NONMEM analysis.

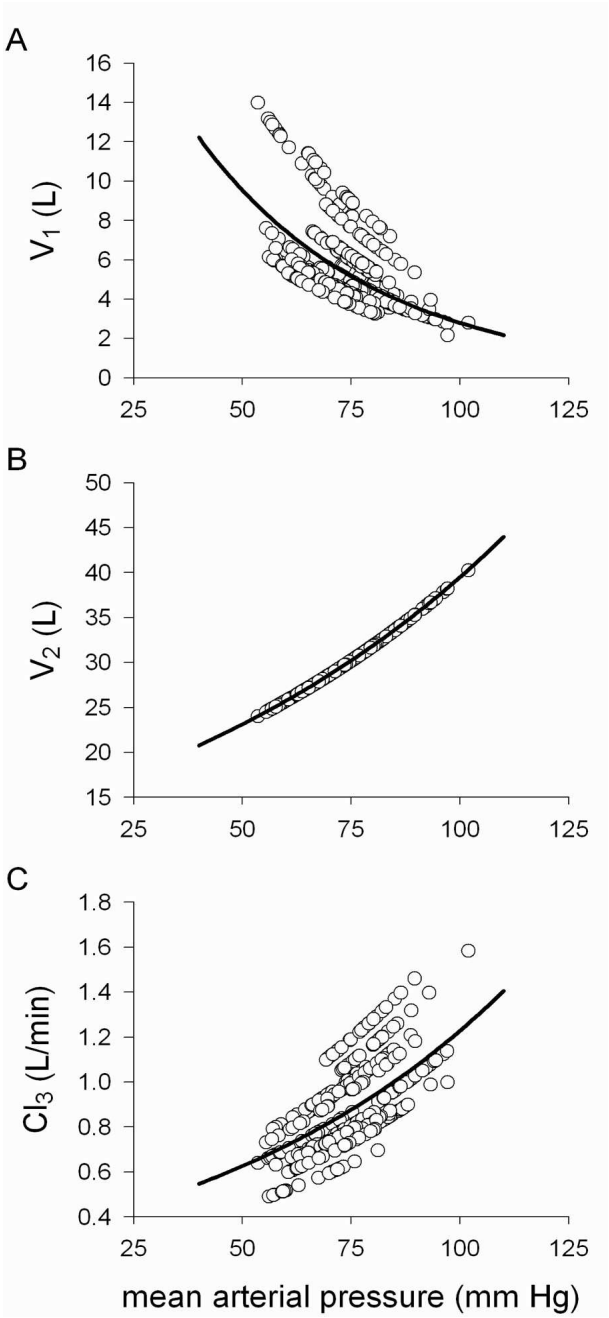

Figure 5. Individual estimates of (A) the central volume of distribution (V_1), (B) rapidly equilibrating peripheral volume of distribution (V_2), and (C) slow distribution clearance (CL_3), obtained from the model without covariates as function of the MAP. The regression line results from the NONMEM analysis.

COMPUTER SIMULATIONS

With the use of the final pharmacokinetic parameter set obtained from NONMEM (Table 3) we performed three computer simulations to reveal the influence of alterations in midazolam and mean arterial pressure on the blood propofol concentrations. (1). In Figure 6 the influence of midazolam in the presence of a slight reduction of mean arterial pressure (resembling the clinical conditions during the study) is clearly visible. In the presence of a plasma midazolam concentration the blood propofol concentration is elevated, particularly during infusion. Furthermore, the blood propofol concentration appears to decrease more rapidly in the presence of midazolam. (2). In figure 7 the separate influences of midazolam and mean arterial pressure are made clear. Both covariates induce an increase in the blood propofol concentration. Using the same dosing strategy as in the study, alteration of the mean arterial pressure from 50 to 100 mmHg in steps of 25 mmHg leads to a marked decrease in the simulated blood propofol concentration (Figure 7B). (3). Finally, we studied the alterations in 50% (the context-sensitive half-life) and 80% decrement time using the final pharmacokinetic parameter data set. Figure 8 shows that the context-sensitive half-time of propofol in the presence and absence of midazolam in these young male volunteers, remains relatively short for up to a 4 hours infusion. Both the 50% and 80% decrement times of propofol are reduced in the presence of midazolam.

Finally, we calculated that when a propofol infusion is given in the presence of midazolam, the propofol bolus dose needs to be reduced by 25% and the infusion rate by 20% to obtain similar plasma propofol concentrations compared to a condition in which propofol is given as a sole agent.

Midazolam (ng/mL)	MAP (mm Hg)	V_1 (L)	V_2 (L)	V_3 (L)	Cl_1 (L/min)	Cl_2 (L/min)	Cl_3 (L/min)
0	78	4.80	31.20	144.00	1.94	2.86	0.95
225	68	6.13	28.04	144.00	1.61	1.52	0.73
0	50	9.55	23.12	144.00	1.94	2.86	0.64
0	75	5.16	30.22	144.00	1.94	2.86	0.91
0	100	2.97	39.48	144.00	1.94	2.86	1.29

Table 3. The pharmacokinetic parameters of propofol (based on the final pharmacokinetic parameter set with midazolam and mean arterial pressure as covariates) for various midazolam and mean arterial pressure values as used in the computer simulations.

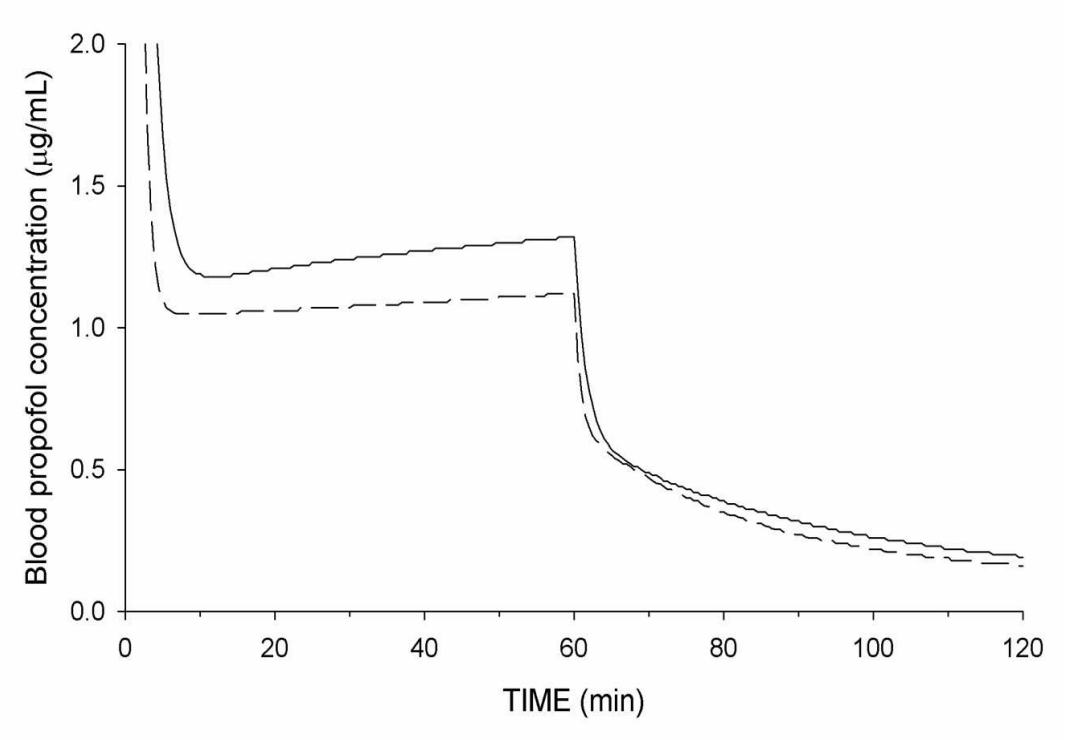

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Figure 6. Computer simulation of the influence of midazolam at a concentration of 0 (discontinuous line) and 225 ng/mL (continuous line) on the propofol concentration-time relationship with a propofol infusion scheme as used in this study (1mg/kg in 1 min followed by a 2.5 mg/kg/hr infusion for 59 minutes) using the final propofol pharmacokinetic data set with a mean arterial blood pressure of 78 and 68 mm Hg, respectively.

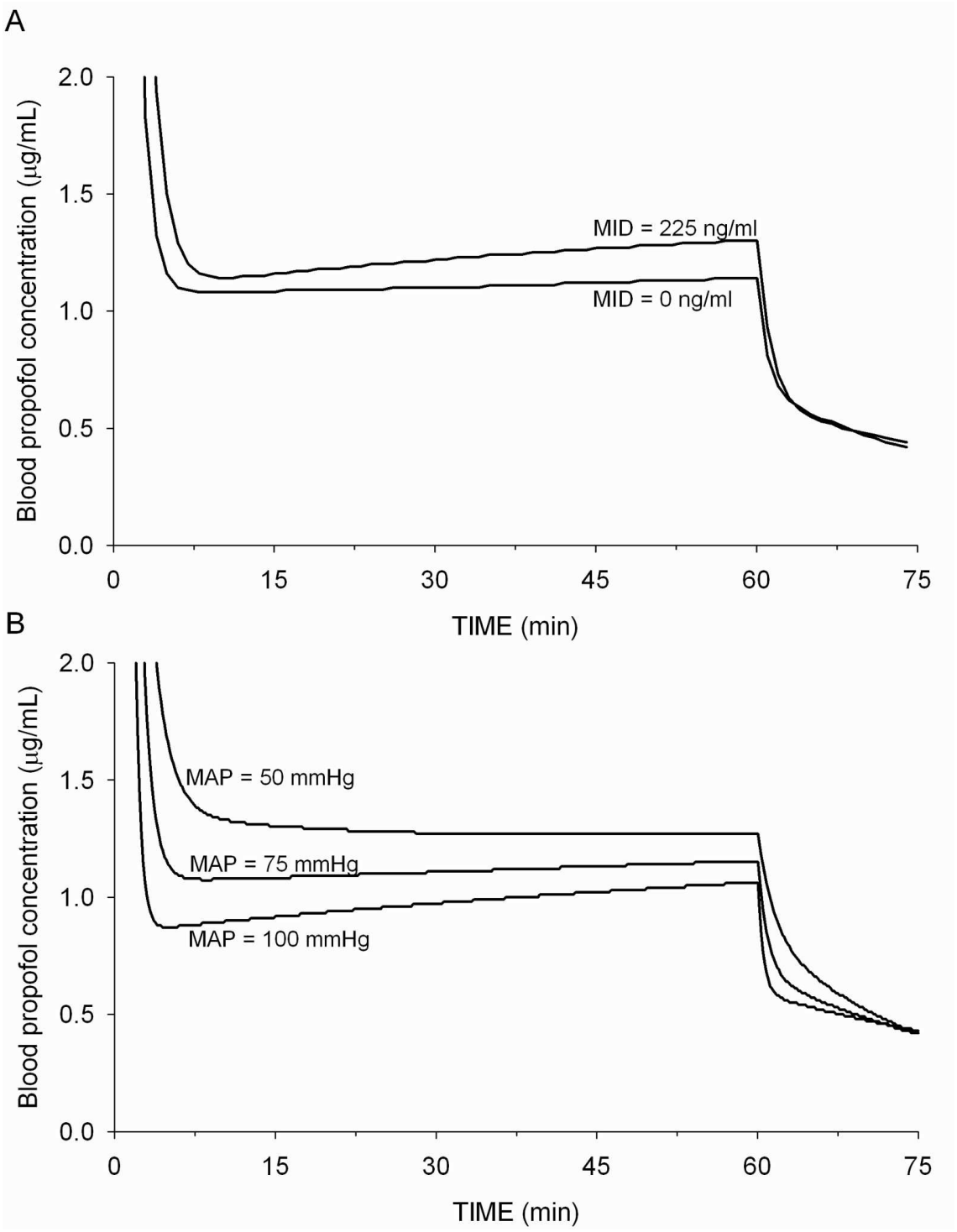

Figure 7. (A) the concentration-time profile of a simulated propofol infusion scheme (1 mg/kg in 1 min followed by 2.5 $mg.kg^{-1}.h^{-1}$ for 59 min) in the presence of a plasma midazolam concentration of 0 and 225 ng/mL at a stable MAP of 74 mm Hg.

(B) the concentration-time profile of a simulated propofol infusion scheme (1 mg/kg in 1 min followed by 2.5 $mg.kg^{-1}.h^{-1}$ for 59 min) in the presence of a MAP of 50, 75 and 100 mm Hg in the absence of midazolam.

DISCUSSION

We examined the influence of midazolam on the pharmacokinetics of propofol. The results of the study confirm our hypothesis that midazolam alters propofol's pharmacokinetics, causing a 25% increase in blood propofol concentration, and further that hemodynamics are involved such that a reduction in mean arterial pressure is associated with an increase in the blood propofol concentration.

INTERACTION MECHANISMS AND PHARMACOKINETIC MODEL PARAMETERS.

We observed a marked decrease in the metabolic and rapid and slow distribution clearances of propofol in the presence of midazolam. The decrease in propofol metabolism may be either an effect of midazolam on enzymatic function or the result of a reduction in hepatic perfusion. Tanaka et al. showed that midazolam did not affect the enzyme activity associated with propofol clearance in human liver microsomes in an in vitro study.(14) An effect of midazolam on propofol metabolism through enzyme inhibition therefore seems unlikely. Furthermore, the high extraction ratio of propofol of 0.79-0.92(15) suggests that the clearance of propofol may not be affected by enzyme inhibition but rather be susceptible to changes in hepatic perfusion. The relationship between hepatosplanchnic blood flow and propofol pharmacokinetics has been described previously in detail. In various studies changes in the metabolic clearance of propofol were closely related to hepatic blood flow. (16-18) Leslie et al. even suggested that propofol itself reduced liver blood flow and may thus impair its own clearance. (16) In our study, the addition of midazolam resulted in a significant decrease in the mean arterial pressure and stroke volume and a tendency for a reduced cardiac output (table 1). From these data and the referred manuscripts we therefore conclude that the changes in the pharmacokinetics of propofol induced by midazolam are the result of these hemodynamic alterations.

The influence of hemodynamics on propofol pharmacokinetics is furthermore stressed by our finding that next to the inclusion of midazolam mean arterial pressure as covariate further improved the propofol pharmacokinetic model (Figure 5). The clinical consequences of changes in mean arterial pressure on the propofol dose-concentration relationship was further explored using computer simulations. Figure 7B shows that a decrease in mean arterial pressure is associated with an increase in the blood propofol concentration while propofol dosing remained unchanged. This is in accordance with the work by Egan and colleagues (19,20) on the influence of hemodynamic shock on the pharmacokinetics of various anesthetic agents including propofol. In these studies a reduction in cardiac output and mean arterial pressure was evident in animals after blood loss. In the presence of a reduced cardiac output and mean arterial pressure the blood propofol concentrations were significantly elevated with an unchanged propofol dosing regimen. The population

pharmacokinetic analysis of the Egan study revealed that in the presence of these hemodynamic perturbations the elimination clearance as well as the rapid and slow distribution clearances of propofol was reduced in a similar fashion as we observed in our study. From the above we do not conclude that midazolam infusion resembles a state of hemorrhagic shock but rather that hemodynamic alterations induced by the combined infusion of propofol and midazolam significantly affect the propofol dose-concentration relationship such that a reduction in blood pressure, as sign of a reduction of blood flow, is associated with an increase in the blood propofol concentration when the propofol dose regimen is not altered. This is in analogy with the pharmacokinetic interactions between other anesthetic agents and/or opioids that also appear to be driven,(21-23) at least in part, by hemodynamic alterations.

The fact that the measured plasma midazolam concentrations significantly exceeded the predicted (Figure 1) may be, at least to some extent, the result of a pharmacokinetic interaction between midazolam and propofol in which propofol may have induced a rise in the plasma midazolam concentration. The difference in the characteristics between our study population (healthy volunteers, no surgery) and those in whom Zomorodi et al.(10) defined the pharmacokinetics of midazolam (patients after CABG surgery) may also have contributed to the significant midazolam measured-predicted difference. Further studies are needed to evaluate whether propofol indeed affects the pharmacokinetics of midazolam to this degree.

We explored the influence of midazolam on the 50% and 80% decrement times of propofol. Intuitively, one might expect, because propofol concentrations are elevated in the presence of midazolam, that the context-sensitive half-time (= 50% decrement time) of propofol would be prolonged in the presence of midazolam. However, this was not the case. In contrast, Figure 8 shows that in the presence of midazolam the context-sensitive half-time of propofol is reduced, as is the 80% decrement time. This counterintuitive observation has a simple explanation. According to the findings in this study, less propofol is required to reach and maintain a given propofol concentration in the presence of midazolam than when propofol is given alone. Consequently, upon the termination of the propofol infusion, the plasma concentration will drop faster compared to a condition in which the peripheral stores contain more propofol, as occurs when propofol is given as sole agent. The data in figures 2 and 6 showing that the difference in plasma propofol concentration between the two study groups is reduced upon termination of the infusion is in agreement with a reduced decrement propofol time when propofol is combined with midazolam. This counterintuitive pharmacokinetic behavior of propofol closely resembles the examples described by Shafer and Stanski (on Duzitol)(24) as well as that described by Schnider et al. (25) (on propofol in the elderly). We further like to stress the importance of computer simulation as an offline tool

in the exploration of the concentration-time relationship of new agents, or old agents in a new environment.

The findings on the pharmacokinetics of propofol in the presence of midazolam may be advantageous as it indicates that in the presence of midazolam propofol concentrations are elevated but also decrease more rapidly after termination of the propofol infusion than when propofol is given as sole agent. The clinical consequences, though, remain yet unsure.

In conclusion, we studied the influence of midazolam on propofol pharmacokinetics. Midazolam causes an increase in the blood propofol concentrations through a reduction in Cl_1, Cl_2 and Cl_3 of propofol. Mean arterial pressure additionally affects the pharmacokinetics of propofol such that a reduction in mean arterial blood pressure is associated with an increase in the blood propofol concentration.

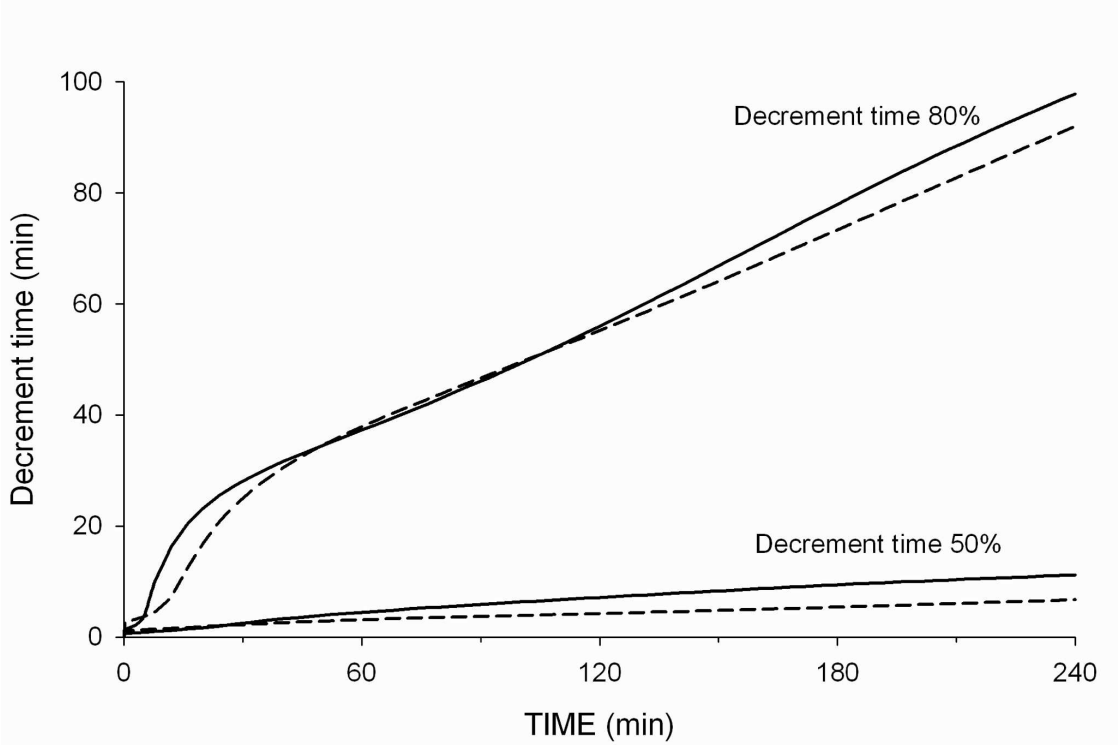

Figure 8. Context sensitive half time (CSHT = 50% decrement time) and 80% decrement time of propofol in the absence (continuous line) and in the presence of a plasma midazolam concentration of 225 ng/mL (discontinuous line) using the final propofol pharmacokinetic parameter set with a MAP of 78 and 68 mm Hg respectively (Table 3).

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