Response Surface Modeling of the Propofol-Midazolam Interaction to Define the Optimal Concentration Combination that Assures Unconsciousness and Hemodynamic Stability.

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IMPLICATIONS STATEMENT

Sedative potency of midazolam ($EC_{50,M\ BIS}$ = 532 ng/ml) was 13.1 times that of propofol ($EC_{50,P\ BIS}$ = 6.98 µg/ml). At these equihypnotic concentrations, propofol depressed hemodynamics (MAP and CO) 3.1 times more compared to midazolam. Propofol and midazolam exhibit a synergistic interaction for sedative endpoints but an additive interaction for hemodynamic endpoints. The use of an optimal propofol-midazolam combination (C_P (ng/ml) = 4.688 * C_M (ng/ml)) assures sedation or unconsciousness in the presence of minimal hemodynamic depression.

INTRODUCTION

Benzodiazepines may well be the hypnotic agents most often used preoperatively to reduce anxiety in patients scheduled for surgical procedures. Intraoperatively, propofol is the intravenous hypnotic most often used to induce and maintain unconsciousness. As such, benzodiazepines like midazolam and intravenous hypnotics like propofol are often administered in combination to reduce anxiety preoperatively and induce unconsciousness perioperative and thus facilitate therapeutic or diagnostic procedures.[1]

The detailed study of the pharmacokinetic and pharmacodynamic interactions[2-5] of other anesthetic combinations has allowed for a selection of concentration- or dose-combinations that exert an optimal anesthetic effect in the presence of only minimal hemodynamic or respiratory side effects. In contrast, for the combination of midazolam and propofol that is used so often in anesthetic practice we noticed a lack of data that described both the pharmacokinetic and pharmacodynamic interaction between these agents.

Over the past years we described the *pharmacokinetic* interaction between propofol and midazolam. We found that propofol and midazolam affect each other's distribution and clearance such that in the presence of sedative concentrations of midazolam the blood propofol concentrations become elevated by 25%, while the same holds true for the plasma midazolam concentrations in the presence of propofol.[6;7]

The *pharmacodynamic* interaction between benzodiazepines and propofol has been described previously. These data show that midazolam strengthens the sedative properties of other hypnotic agents and interacts synergistically at the $GABA_A$-receptor.[8-10] However, due to the methodology and analysis of these studies no conclusions can be drawn for midazolam-propofol combinations other than those precisely studied and no selection is possible of the propofol-midazolam combination that assures unconsciousness in the presence of optimal hemodynamic stability.

We therefore studied the pharmacodynamic interaction between propofol and midazolam in healthy male volunteers. We hypothesized that midazolam would affect the pharmacodynamics of propofol and vise versa, both regarding the sedative effects as well as the hemodynamic effects. Our main objective for this study was to define the optimal propofol-midazolam combination that assures unconsciousness in the presence of minimal hemodynamic side effects.

METHODS

VOLUNTEERS AND STUDY DESIGN

The concentration-time-effect data used in this study were gathered during 2 studies evaluating the pharmacokinetic interaction between propofol and midazolam as described elsewhere.[6;7] In these studies, after obtaining approval of the Medical Ethics Committee of the Leiden University Medical Center and written informed consent, the propofol-midazolam interaction data of healthy male volunteers, aged 20-30 yr were studied. The volunteers were studied twice to obtain 8 midazolam concentration-time-effect data sets in the absence (M1) and 8 midazolam concentration-time-effect data sets in the presence of propofol (M2) next to 8 propofol concentration-time-effect data sets in the absence (P1) and 8 propofol concentration-time-effect data sets in the presence of midazolam (P2). The 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.

In studies M1 and M2 the influence of a constant target propofol concentration[11] of 0, 0.6 or 1 µg/ml, when given for 435 min, was studied on the pharmacokinetics and pharmacodynamics of midazolam in volunteers receiving a midazolam bolus dose of 0.035-0.05 mg/kg in 1 min followed by an infusion of 0.035-0.05 $mg.kg^{-1}.h^{-1}$ for 59 min.[7] In studies P1 and P2 the influence of a constant target midazolam concentration[12] of 0 or 125 ng/ml, when given for 435 min, was studied on the pharmacokinetics and pharmacodynamics of propofol in volunteers receiving a propofol bolus dose of 1 mg/kg in 1 min followed by an infusion of 2.5 $mg.kg^{-1}.h^{-1}$ for 59 min.[6] During the studies 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 6.5 kPa. After termination of study the subjects were monitored for another 4 h and received a light meal before they were escorted to their home.

Pharmacodynamic data

During the studies the volunteers remained on a hospital bed in an operating theatre. The ECG, heart rate (HR), respiratory rate, ET-CO_2 and SaO_2 were recorded continuously to assure adequate ventilation. Both sedative and hemodynamic end points were recorded.

The bispectral index ((BIS), BIS®, Aspect Medical Systems, Newton, MA) as determined over a 15 sec period and the Ramsay sedation score were recorded at 1, 3, 5, 10, 20, 30, 45 and 60 min after the start of the propofol or midazolam infusion and at 3, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after termination of the propofol or midazolam infusion, when blood was sampled for midazolam and propofol concentration determination. The Ramsay sedation score has the following levels: score 1, volunteer anxious and restless; score 2, volunteer cooperative, oriented, and tranquil; score 3, volunteer drowsy or asleep, responds easily to commands; score 4, volunteer asleep, brisk response to a light glabellar tap; score 5, volunteer asleep, sluggish response to a light glabellar tap; and score 6, volunteer asleep, no response to a light glabellar tap.[13]

The cardiac output (CO) and systemic vascular resistance (SVR) were determined using the pulse-contour methodology on the basis of the intra-arterial blood pressure curve with the LiDCOplus monitor (LiDCOgroup plc, London[14]). The LiDCO monitor was calibrated before each experiment. For this purpose, a lithium sensor was connected to the arterial cannula. Then, after 0.2 mmol lithium was injected intravenously, the LiDCO monitor was calibrated on the basis of the non-invasive online determined arterial lithium concentration-time curve and the cardiac output calculated. The LiDCO has been found reliable in cardiac output monitoring when compared with traditional thermodilution cardiac output monitoring for up to 8 h after calibration (LidCO versus thermodilution: $r = 0.86$) in relatively stable hemodynamic conditions like in this study.[15] The heart rate, cardiac output, systemic vascular resistance and the mean arterial blood pressure were all online recorded at every heart beat and saved for further analysis. Off-line, the arithmetic means of these hemodynamic parameters were calculated for the time periods before a blood sample was taken for blood propofol or plasma midazolam concentration determination and used in the analysis.

BLOOD SAMPLES AND ASSAYS

As described elsewhere[6;7] frequent arterial blood samples were taken for blood propofol and plasma midazolam concentration analysis. Propofol concentrations in blood were measured by HPLC-fluorescence at an excitation wavelength of 276 nm with emission wavelength of 310 nm.[16] 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. The concentration of midazolam in plasma was determined by reversed-phase high-performance liquid chromatography-UV detection at 216 nm (HPLC).[17] 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. Propofol assays were conducted within 12 weeks. The assays of midazolam and propofol did not interfere with each other due to the differences in detection. Midazolam is not detectable using fluorescence at the excitation wavelength of 276 nm with emission wavelength of 310 nm (the way propofol is detected). Vice versa propofol is detectable using UV at 217 nm (the way midazolam is detected) but is clearly separated in our hands using a C8 column and a mobile phase that consisted of methanol-buffer at a pH of 7,05.

DATA ANALYSIS

A population pharmacokinetic-pharmacodynamic analysis was performed on the Ramsay sedation score and bispectral index (BIS) as recorded at the time a blood sample was taken, and the mean values of MAP, heart rate, CO and SVR as calculated for the time period prior to the time a blood sample was taken, versus the arterial blood propofol and arterial plasma midazolam concentrations. The pharmacodynamic model used was based on receptor binding theory with extensions to account for interaction.[18-21]

In the analysis, the pharmacokinetic parameters of propofol and midazolam as determined in the previous 2 pharmacokinetic studies were used. Midazolam and MAP were used as covariates affecting the pharmacokinetics of propofol.[6] Propofol and heart rate were used as covariates affecting the pharmacokinetics of midazolam.[7] In the analysis of the pharmacodynamic effect of propofol and midazolam a k_{on} and a k_{off} were introduced to model the sometimes slow return to baseline of sedative and hemodynamic effects properly. The k_{on} and k_{off} incorporate k_{e0}, receptor binding kinetics as well as control system dynamics and indirect response dynamics. In the combined analysis k_{on}/k_{off} estimated from experiments with a primary drug were also used for estimation in experiments where this drug was the second drug in the background.

The receptor occupancies of propofol (R_P) and midazolam (R_M) are governed by

$$dR_P/dt = k_{on,p} \cdot C_P \cdot (1 - Rp - Rm) - k_{off,p} \cdot R_P \qquad (1)$$

$dR_M/dt = k_{on,m} \cdot C_M \cdot (1 - Rm - Rp) - k_{off,m} \cdot R_M$, (2)

where $k_{on,p}$ = receptor binding rate of propofol, $k_{off,p}$ = receptor dissociation rate of propofol, $k_{on,m}$ = receptor binding rate of midazolam, $k_{off,m}$ = receptor dissociation rate of midazolam and C_P and C_M the blood propofol concentration and the plasma midazolam concentration, respectively, obtained using empirical Bayesian individualization of the pharmacokinetic models established earlier.[6;7]

We assume the effect of the drugs in combination is related to $E = R_P + R_M$ (cf. Ref.[22])

At steady-state this gives effect E as:

$$E = \frac{\frac{C_P}{C50_P} + \frac{C_M}{C50_M}}{1 + \frac{C_P}{C50_P} + \frac{C_M}{C50_M}} = \frac{UA + UB}{1 + UA + UB}, \quad (3)$$

where $C50_P$ and $C50_M$ are the blood propofol and plasma midazolam concentrations that correspond to 50% receptor occupancy and UA and UB are the normalized concentrations of propofol and midazolam.[19]

Then, groups of “drugs” of combinations of propofol and midazolam can be defined each having a unique ratio of UA and UB. Each “drug” will be defined in terms of Q,

$$Q = \frac{UB}{UA + AB} \quad (4)$$

Q ranges from 0 (only drug A) to 1 (only drug B). The “drug” concentration equals UA + UB. An $U_{50}(\theta)$ was incorporated according to Minto et al.[19] by dividing the k_{on} of both drugs by an interaction function I(Q).[20] This affects potency but, as desired, not k_{off}. For mutually non-exclusive drugs a term UA.UB should be added.[23] This term implies that the drugs have more effect than expected from additivity. The receptor binding equations (1) then do not incorporate the background drug (R_M in the first differential equation and R_P in the second) and the desired steady-state equation is obtained by using (see Appendix):

$E = R_P + R_M - R_P.R_M$ rather than $R_P + R_M$. (5)

An inhibitory Emax model was used to convert receptor binding to the effect parameter

(EP): $EP = E_{max}\,(1\text{-}E^{\gamma})$ (6)

So it was assumed that values of 0 could be approached for all these parameters. This makes *SVR = MAP/CO* always well-defined. It should be noted that the effect of γ as incorporated here is somewhat different from usual.[24] When the concentration of a drug equals k_{off}/k_{on} *and* $E = ½$, the effect parameter *EP* is not necessarily $E_{max}/2$. Therefore EC_{50} was calculated according to:

$$EC_{50} = \frac{k_{off}}{k_{on}} \cdot (½)^{1/\gamma} / (1 - (½)^{1/\gamma}) \quad (7)$$

For Ramsay score (RS), a proportional odds model was used,[25] where *RA+RB = 1* was related to score 3 and the receptor binding values for the remaining scores were parameters to be estimated (see Appendix for details). For plots of fits, the expected value was calculated.

For systemic vascular resistance often a triphasic response was observed in time (decrease, increase, decrease). A single concentration-effect relationship would not be able to adequately model this triphasic response. The interaction of propofol and midazolam on SVR was therefore modeled via the ratio of MAP and CO, with a conversion factor (to be estimated) to account for the residual error and conversion from mmHg/L/min (woods units) to absolute resistance units; dynes.sec^{-1}.cm^5 Response surfaces were constructed even though concentrations were known only on, or near, about four lines (varying concentrations of the primary drugs with zero or approximately fixed concentrations of the secondary drug, from the two complementary PK studies; propofol had two secondary targets, and there was also some variability in the attained concentrations).

The sedative and hemodynamic responses to the exclusive, and suboptimal, use of propofol or midazolam given as single agents were determined using the equation:

$$E = E_{\max} \cdot \left[1 - \left(\frac{C_{P,M}}{\frac{k_{off\,P,M}}{k_{on\,P,M}} + C_{P,M}} \right)^{\gamma} \right], \quad (8)$$

where E_{max} = the maximum sedative or hemodynamic effect, $k_{off,P,M}$ = receptor dissociation rate of propofol or midazolam, $k_{on,P,M}$ = receptor binding rate of propofol or midazolam, γ = the steepness of the concentration-response relation and $C_{P,M}$ = the concentration of propofol or midazolam. The sedative and hemodynamic responses to the optimal combination of propofol and midazolam were determined using the equation:

$$E = E_{\max} \cdot \left[1 - \left(\frac{\left(\frac{C_P}{C50_P} + \frac{C_M}{C50_M} \right) \Big/ I(Q)}{1 + \left(\frac{C_P}{C50_P} + \frac{C_M}{C50_M} \right) \Big/ I(Q)} \right)^{\gamma} \right] \quad (9),$$

with

$$C50_{P,M} = \frac{k_{off\,P,M}}{k_{on\,P,M}}, \quad (10)$$

where I(Q) = 1 for additive interactions and I(Q) < 1 for synergistic interactions.

Statistical analysis

Data analysis was performed using NONMEM (version VI 1.2) (Nonlinear Mixed-Effects Modeling; Icon Development Solutions, Ellicott City, Maryland, USA, 1989-2010). A probability level of < 0.01 was considered significant in hypothesis testing (nonlinearity, synergism, ω^2). Lognormal interindividual error (ω^2) except E_{max} additive; additive intra-interindividual error (σ^2) except for Ramsay score for which the maximum likelihood method was used.[25]

Results.

All volunteers completed the study without adverse events. During one session on the influence of propofol on the pharmacokinetics and pharmacodynamics of midazolam, hemodynamic data were lost due a storage malfunction of the LidCO. The mean ± SD age, weight and length of the male volunteers were 24.1 ± 4.6 yr, 80.2 ± 9.9 kg and 185 ± 5.7 cm. Propofol pharmacokinetics and pharmacodynamics were studied in the presence of a constant measured arterial midazolam concentration that ranged from 0 – 334 ng/ml. Midazolam pharmacokinetics and pharmacodynamics were studied in the presence of a constant measured arterial blood propofol concentration that ranged from 0 – 1.5 µg/ml. During the 32 sessions a total of 940 arterial blood samples were taken for plasma midazolam and blood propofol concentration determinations.

Figure 1 shows a typical example (mean measured arterial plasma midazolam concentration of 289 ng/ml) of the sedative (Ramsay sedation score and BIS) and hemodynamic variables (MAP, HR, CO and SVR) in the presence of a combination of propofol and midazolam in a single volunteer. In the presence of a constant mean measured arterial plasma midazolam concentration of midazolam (C_M: 289 ng/ml) the bolus and 1 h infusion of propofol induced an increase in this typical volunteer in the Ramsey score up to 6, parallel to a reduction in BIS from 98 to 31. Simultaneously, the MAP dropped from 77 to 54 mmHg, heart rate decreased from 78-61 min^{-1}, cardiac output decreased from 6.6 – 4.5 L/min and SVR decreased from 1150-590 $dyn.s^{-1}.cm^{-5}$. Termination of the 1 h propofol infusion in the presence of a continuing background infusion of midazolam at a mean measured arterial plasma concentration of 289 ng/ml then resulted in a partial recovery of consciousness characterized by a decrease in the Ramsay score from 6 to 3 parallel to an increase in the BIS from about 35 to up to 75. The declining measured arterial blood propofol concentration furthermore was associated with a partial return of MAP to pre-induction levels, a continued reduced heart rate and cardiac output and a rise in SVR up to and above pre-induction values.

The interaction between propofol and midazolam was successfully modeled for sedative and hemodynamic endpoints. Table 1 and 2 display the pharmacodynamic parameter estimates for the interaction between propofol and midazolam with regard to the sedative and hemodynamic end points. Figure 2 displays the measured versus predicted values for BIS, the Ramsay sedation score, MAP, HR, CO and SVR. Figures 3 and 4 display the response surfaces and iso-effect curves for the interaction between propofol and midazolam with respect to the Ramsay sedation score and BIS. For both sedative end points the interaction was found synergistic that could be explained by mutually nonexclusive drug binding or via an interaction function I(Q), respectively.

Figures 5, 6, 7 and 8 display the response surfaces and iso-effect curves for the interaction between propofol and midazolam on the hemodynamic parameters MAP, heart rate, cardiac output and SVR. For none of the hemodynamic parameters synergism or mutually exclusiveness could be identified. The γ was greater than 1 for all hemodynamic parameters except for cardiac output.

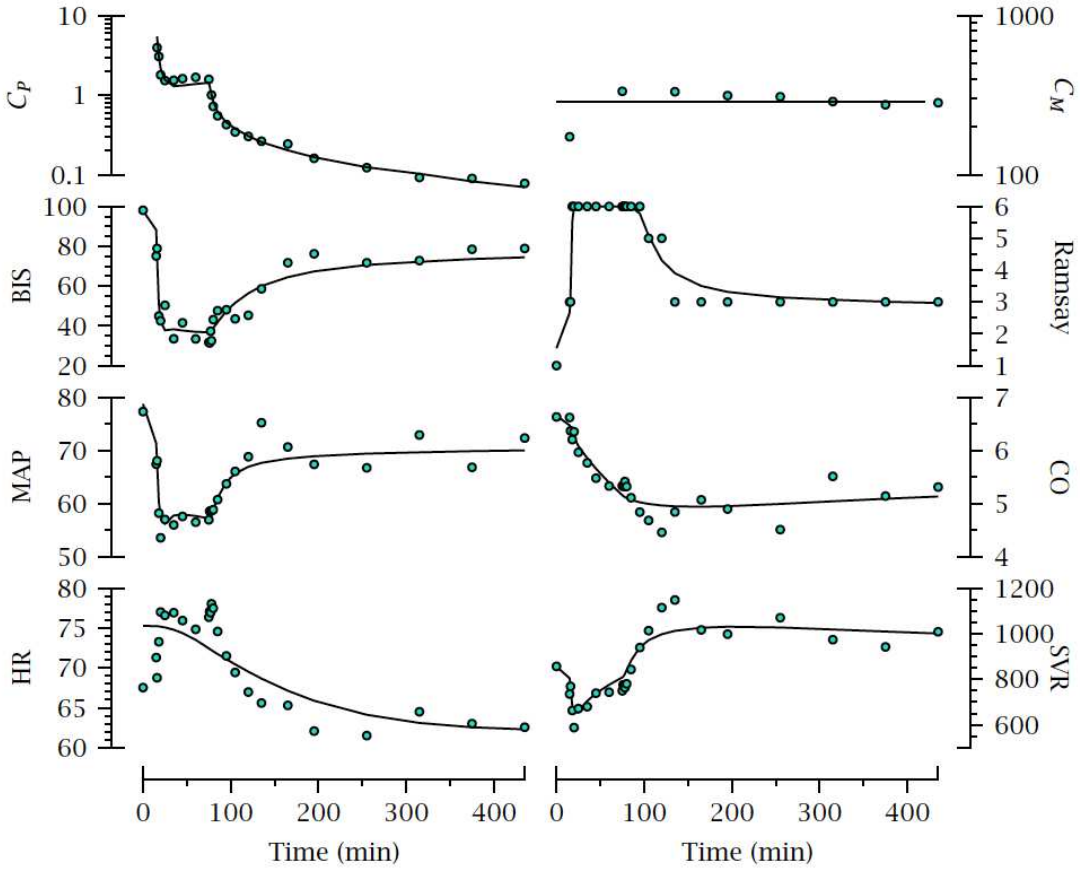

Figure 1.

The influence of propofol (given as a propofol bolus dose of 1 mg/kg in 1 min followed by an infusion of 2.5 $mg.kg^{-1}.h^{-1}$ for 59 min) and midazolam (given as midazolam target controlled infusion with Ct = 125 ng/ml; mean measured arterial plasma midazolam concentration = 289 ng/ml) on Ramsay score, BIS, mean arterial pressure (MAP), heart rate (HR), cardiac output (CO) and systemic vascular resistance (SVR) in a typical patient. The dots indicate the raw data, the lines indicate the predicted effect on the basis of the final pharmacokinetic-pharmacodynamic models.

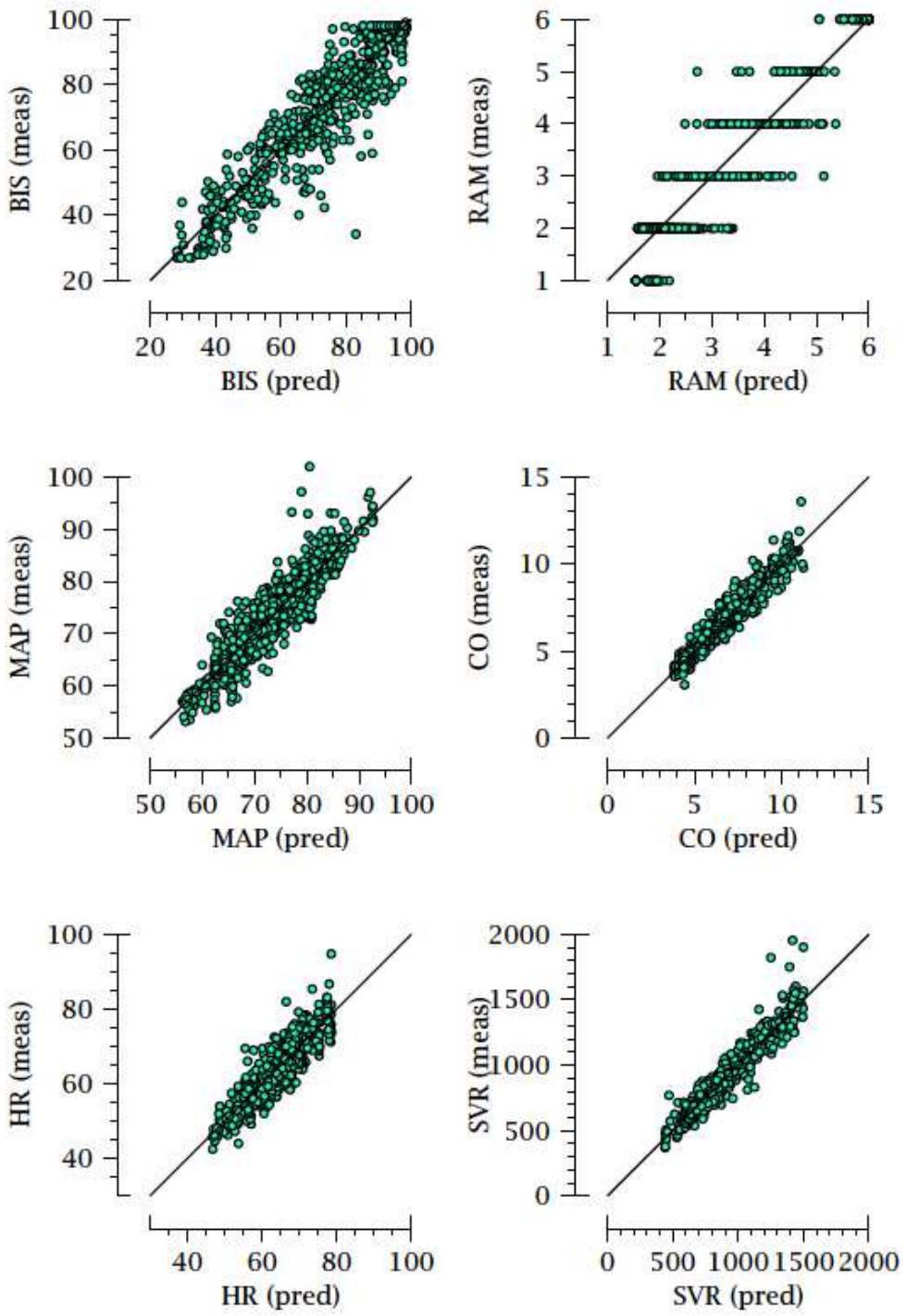

Figure 2.

The measured versus individual predicted sedative and hemodynamic values for BIS, Ramsay sore, mean arterial pressure (MAP in mmHg), heart rate (HR in beats.min^{-1}), cardiac output (CO in L.min^{-1}) and systemic vascular resistance (SVR in dyne.sec^{-1}. cm^{-5}). The straight line indicates Y = X.

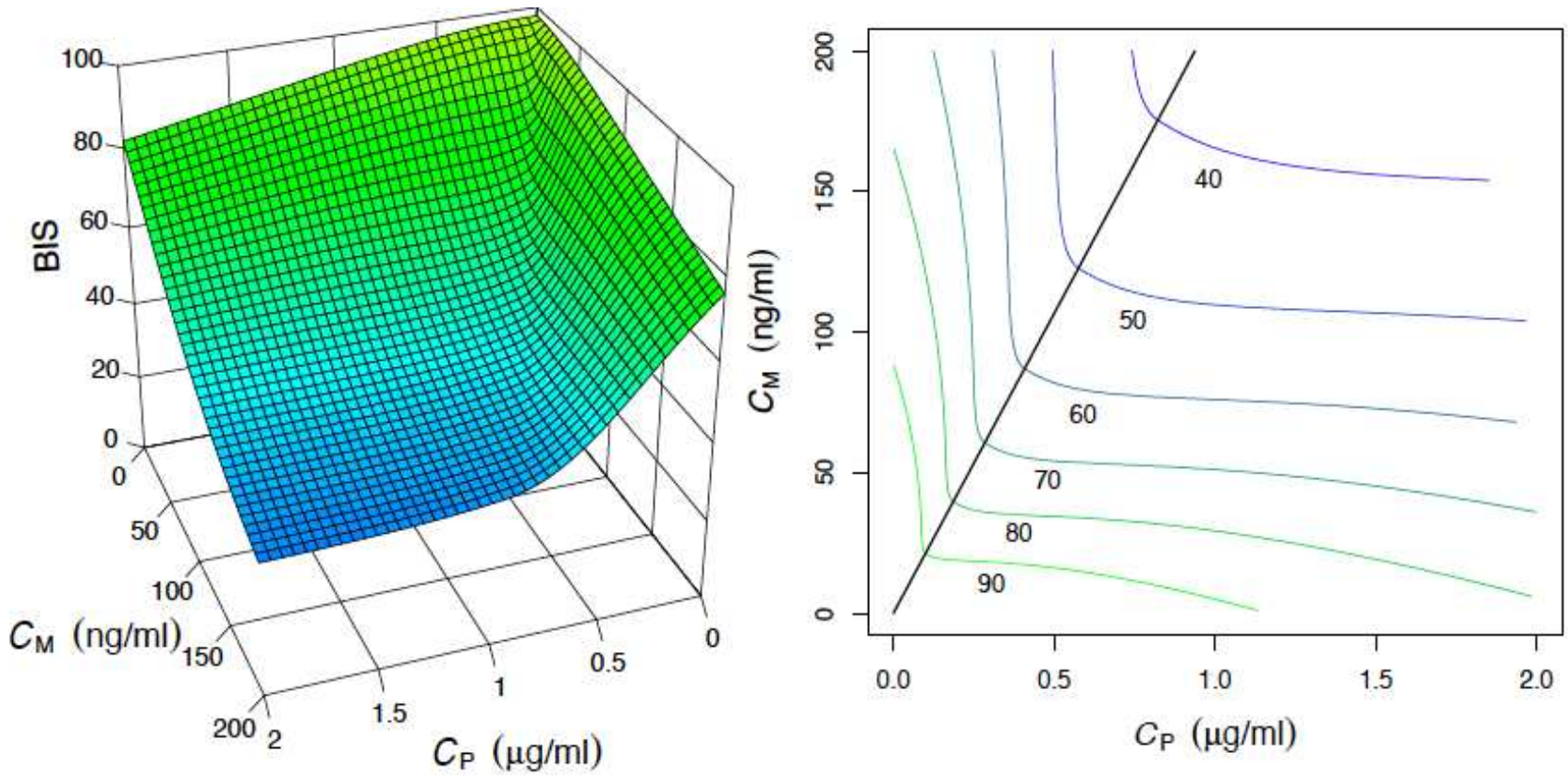

Figure 3.

Left panel. Response surface of the interaction between propofol and midazolam on BIS. The parameter estimates determining the shape of the surface are displayed in table 2 and were determined using equation 3.

Right panel. Iso-effect curves for the influence of propofol and midazolam on BIS expressing a synergistic interaction. The bold line displays the propofol and midazolam concentration combination with the strongest interaction (= the optimal concentration combination).

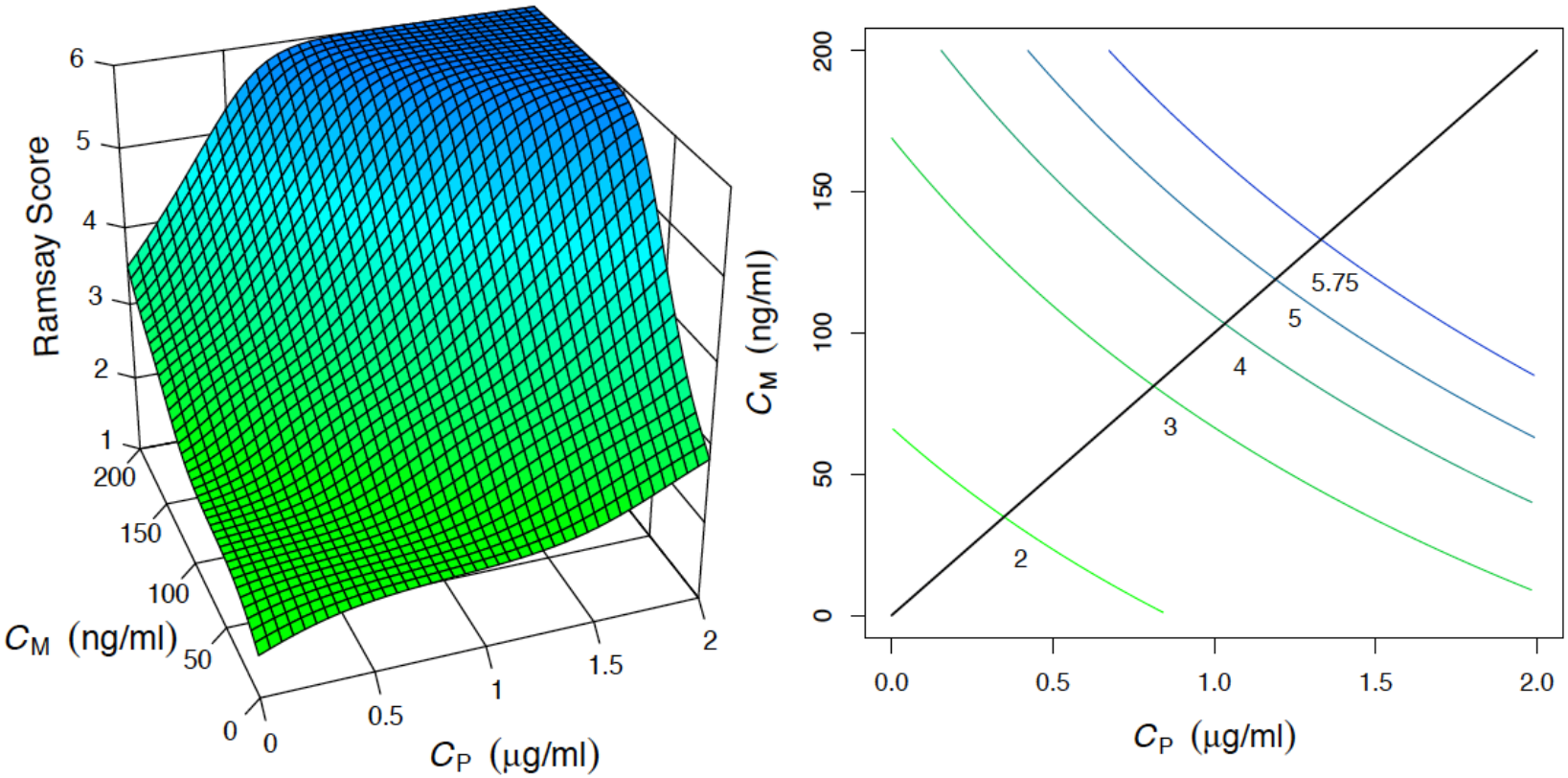

Figure 4.

Left panel. Response surface of the interaction between propofol and midazolam on Ramsay sedation score. The parameter estimates determining the shape of the surface are displayed in table 2 and were determined using equation 12-13 (Appendix).

Right panel. Iso-effect curves for the influence of propofol and midazolam on the Ramsey sedation score expressing a slight synergistic interaction. The bold line displays the propofol and midazolam concentration combination with the strongest interaction (= the optimal concentration combination**).**

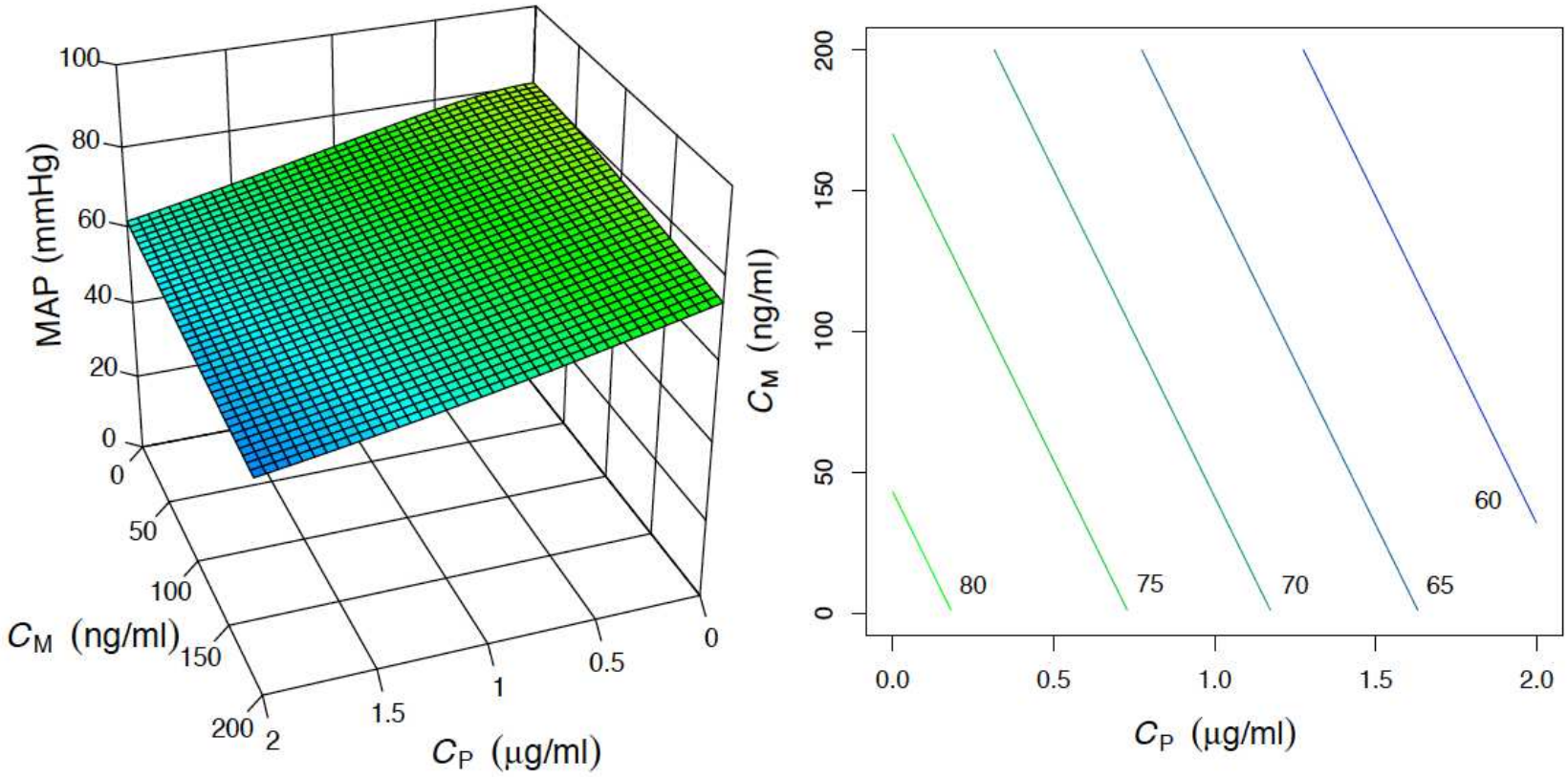

Figure 5.

Left panel. Response surface of the interaction between propofol and midazolam on mean arterial pressure (MAP). The parameter estimates determining the shape of the surface are displayed in table 2 and were determined using equation 2.

Right panel. Iso-effect curves for the influence of propofol and midazolam on mean arterial pressure expressing an additive interaction.

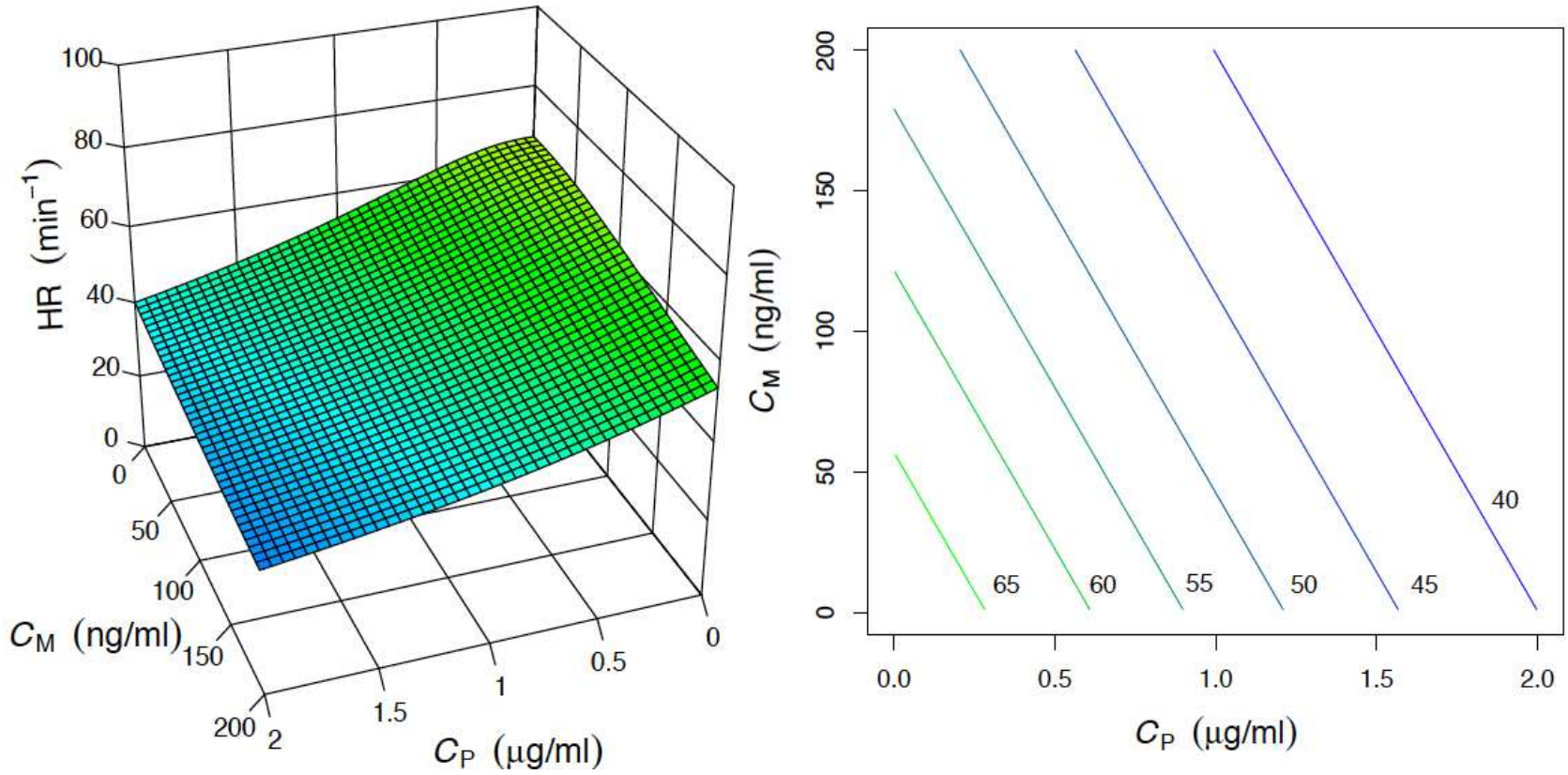

Figure 6.

Left panel. Response surface of the interaction between propofol and midazolam on heart rate (HR). The parameter estimates determining the shape of the surface are displayed in table 2 and were determined using equation 2.

Right panel. Iso-effect curves for the influence of propofol and midazolam on heart rate expressing an additive interaction.

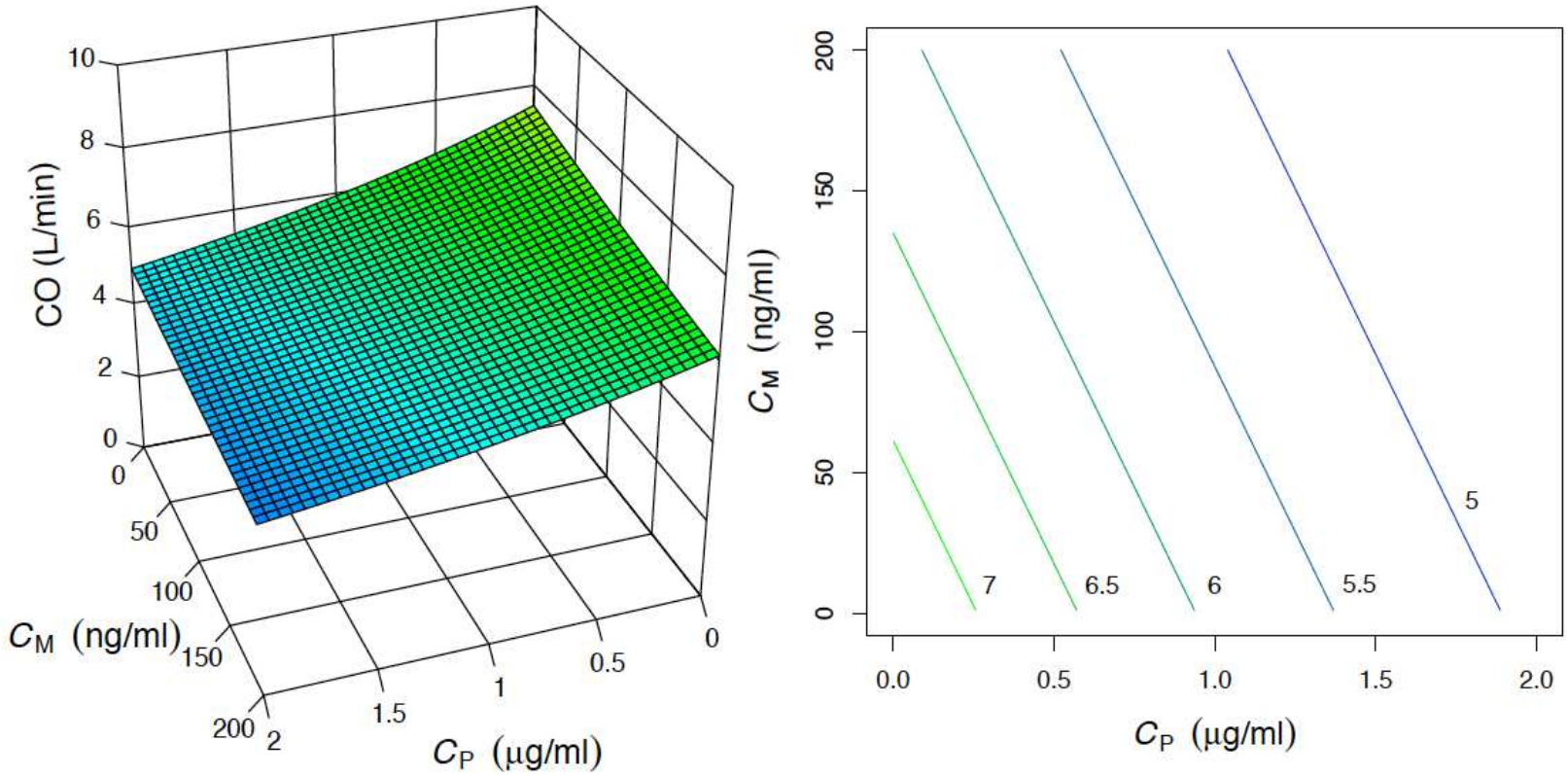

Figure 7.

Left panel. Response surface of the interaction between propofol and midazolam on cardiac output (CO). The parameter estimates determining the shape of the surface are displayed in table 2 and were determined using equation 2.

Right panel. Iso-effect curves for the influence of propofol and midazolam on CO expressing an additive interaction.

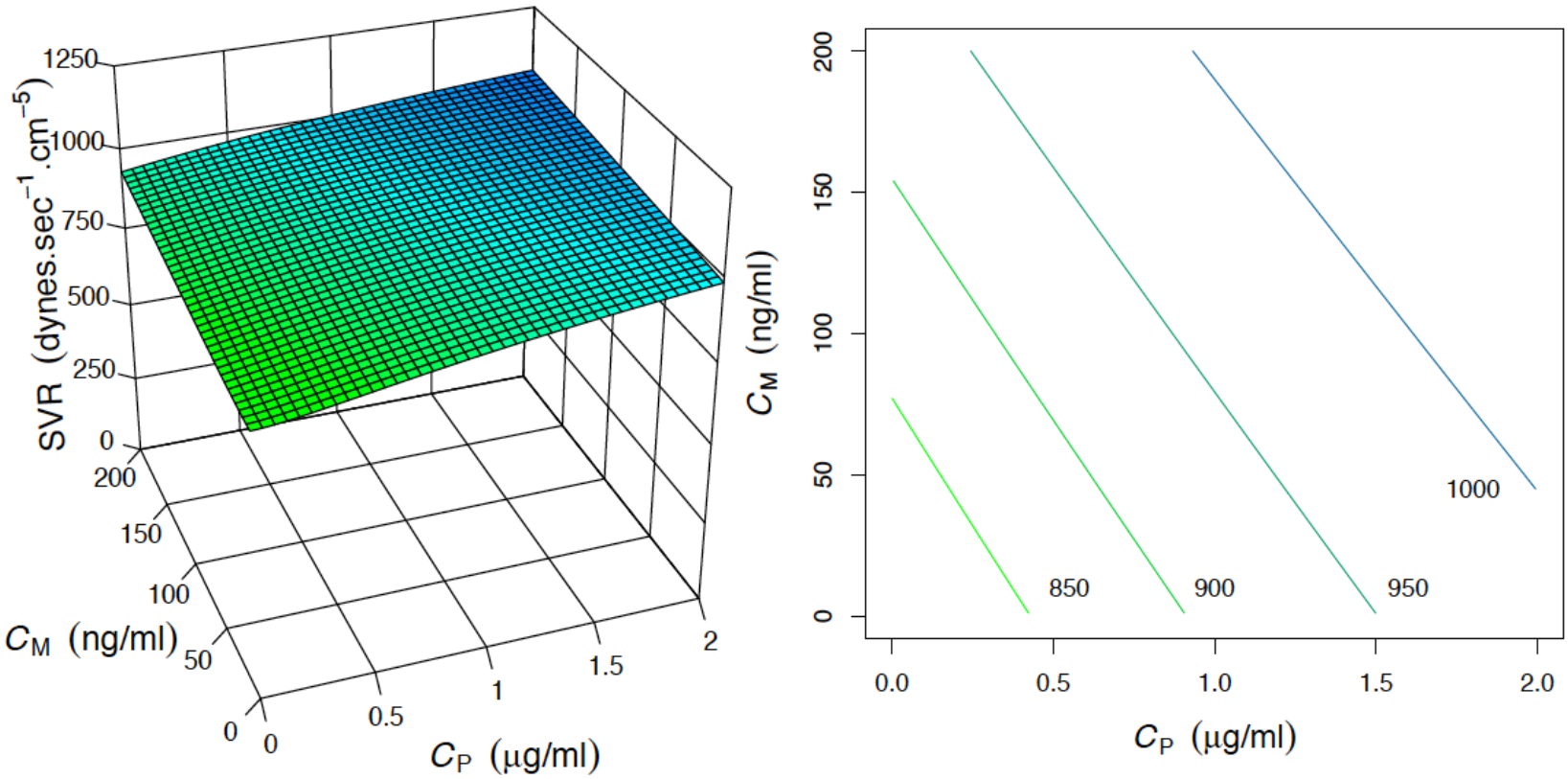

Figure 8.

Left panel. Response surface of the interaction between propofol and midazolam on systemic vascular resistance (SVR). The parameter estimates determining the shape of the surface are displayed in table 2 and were determined using equation 2.

Right panel. Iso-effect curves for the influence of propofol and midazolam on SVR expressing an additive interaction.

DISCUSSION.

This study describes the successful modeling of the pharmacodynamic interaction between propofol and midazolam for sedative and hemodynamic end points. We used measured arterial blood propofol and measured arterial plasma midazolam concentrations to define the population pharmacokinetics of propofol and midazolam in volunteers.[6;7] On the basis of these pharmacokinetic parameter sets we determined empirical Bayesian individualized propofol and midazolam concentrations and used these in the pharmacodynamic analysis of the sedative and hemodynamic effects of propofol and midazolam and their combination. Propofol and midazolam potentiate each other for sedative end points and display an additive interaction regarding their hemodynamic depressant effects.

The pharmacodynamic parameters described in Table 1 and 2 confirm those previously reported for midazolam and propofol when given as sole agent. Kazama et al. reported for propofol an $EC50_{BIS}$ of 5.6-7.7 µg/ml compared to 6.98 µg/ml in this study.[26] Similarly, the $EC50_{MAP}$ of propofol in our study (2.82 µg/ml) closely corresponds to that reported previously (2.1-4.6 µg/ml) and confirms that propofol induces hemodynamic depression already at concentrations associated with only light sedation.[26] For midazolam, when given as single agent, the concentration-response relationship for the influence on sedation parameters like e.g. the Ramsay sedation score also closely correspond with those described previously.[25] Barr et al. described for midazolam an $EC50_{Ramsey=2}$ and $EC50_{Ramsey=6}$ of 68 and 375 ng/ml. This closely matches the corresponding midazolam EC50's at Ramsey = 2 and Ramsay = 6 of 75 and 365 ng/ml found in our study.[27] In line with previous studies the effect site equilibration of both propofol and midazolam with regard to the hemodynamic effects is significantly slower compared to that for the sedative effects.[26] Please notice that the lower the concentration has been with respect to k_{on}/k_{off}, the more comparable k_{off} *and* k_{e0} are. At higher concentrations the nonlinearity of the receptor kinetics equation becomes significant. Still, the dissociation half-lives for hemodynamic effects for both propofol and midazolam are longer than we had expected (1-2 h) and exceed those previously described.[26] The methodology of our study that lacks multiple rapid changes in the drug concentrations as well as the nonlinearity in the receptor kinetics at higher concentrations probably both are responsible for this discrepancy with data from the literature.

Table 1. Pharmacodynamic parameter estimates and standard errors (SE) for sedative end points.

	Estimate	SE	ω^2	SE
Ramsay score				
$k_{on,P}$	0.0216	0.00397	0.234	0.119
$k_{off,P}$	0.0569	0.00927	0.109	0.0566
$k_{on,M}$	0.000438	0.0000654	0.0795	0.0440
$k_{off,M}$	0.0892	0.0147	0.194	0.0527
γ	11.8	1.21		
v_1	0.686	0.0440		
v_2	0.330	0.0415		
v_4	0.210	0.0542		
v_5	0.167	0.0393		
Bispectral Index Score				
$k_{on,P}$	0.0484	0.0108	-	
$k_{off,P}$	0.136	0.0249	0.156	0.0823
$k_{on,M}$	0.000216	0.0000536	0.288	0.0954
$k_{off,M}$	0.0462	0.00746	-	
Emax	97.9	0.482	0.806	0.435
γ	2.05	0.296		
Imax	0.325	0.0390		
Qmax	0.737	0.0432		
σ^2	51.5	5.49		
$EC50_P$ (μg/ml)	6.98			
$EC50_M$ (ng/ml)	532			

k_{on} = rate constant determining onset of effect, k_{off} = rate constant determining offset of effect, v_{1-5} = parameters of proportional odds model (see Appendix), γ = a shape factor, ω^2 = between-subject variability, Emax = maximum effect, σ^2 = within-subject variability, Imax = maximum interaction, Qmax = is the maximum value of Q when maximum interaction occurs (see equation 3), $EC50_P$ = blood propofol concentration that assures 50% of the maximum effect, $EC50_M$ = plasma midazolam concentration that assures 50% of the maximum effect (decrease in BIS or rise in Ramsay score).

Our results confirm, for the concentrations of the agents used in this study, that propofol and midazolam interact in a synergistic manner with respect to their effect on BIS and Ramsay sedation score.[8;28] This may suggest, again, that the sedative effects of midazolam and propofol may not be propagated through a similar site of action.[23] Synergism with regard to this end point also has been described between hypnotics and other intravenous agents like barbiturates or opioids. This, in contrast to the interaction of propofol and midazolam with ketamine that appears additive to infra-additive. Only very few studies describe the interaction between anesthetics with respect to their side effects like hemodynamic or respiratory depression. Hardly any data are available that describe therapeutic and side effects of a combination of anesthetic agents in one study and thus allow for the determination of optimal concentration combinations of 2 agents that exert a certain therapeutic effect in the presence of the least possible side effects. We were able for various combinations of propofol and midazolam to describe the interaction for both the therapeutic effect (sedation and hypnosis) and an important side effect (depression of MAP and CO).

Table 2. Pharmacodynamic parameter estimates and standard errors (SE) for hemodynamic end points.

	Estimate	SE	ω^2	SE
Mean arterial pressure				
$k_{on,P}$	0.0180	0.00608	0.194	0.0781
$k_{off,P}$	0.0401	0.00690	0.358	0.160
$k_{on,M}$	0.000232	0.0000979	0.119	0.137
$k_{off,M}$	0.120	0.0406	0.432	0.359
Emax	80.6	1.06	29.3	8.23
γ	1.91	0.434		
σ^2	12.4	1.75		
$EC50_P$ (µg/ml)	2.82			
$EC50_M$ (ng/ml)	654			
Heart rate				
$k_{on,P}$	0.00300	0.00115	0.966	0.315
$k_{off,P}$	0.00221	0.000522	0.0362	0.0602
$k_{on,M}$	0.0000343	0.0000141	0.812	0.345
$k_{off,M}$	0.00501	0.000788	0.0748	0.0668
Emax	66.6	1.10	34.2	8.21
γ	2.93	1.03		
σ^2	130	1.16		
$EC50_P$ (µg/ml)	2.76			
$EC50_M$ (ng/ml)	547			
Cardiac Output				
$k_{on,P}$	0.00145	0.000361	0.715	0.302
$k_{off,P}$	0.00553	0.00128	0.239	0.152
$k_{on,M}$	0.00000788	0.00000293	1.90	0.805
$k_{off,M}$	0.00706	0.00176	0.334	0.216
Emax	7.48	0.308	2.94	0.649
γ	1 (Fixed)			
σ^2	0.234	0.0280		
$EC50_P$ (µg/ml)	3.81			
$EC50_M$ (ng/ml)	896			

k_{on} = rate constant determining onset of effect, k_{off} = rate constant determining offset of effect, γ = a shape factor, ω^2 = between-subject variability, Emax = maximum effect, σ^2 = within-subject variability, $EC50_P$ = blood propofol concentration that assures 50% of the maximum effect, $EC50_M$ = plasma midazolam concentration that assures 50% of the maximum effect (decrease in MAP, HR or CO).

Optimal dosing.

The main goal of this study was to define the optimal concentration combination that assures sedation in the presence of minimal hemodynamic depression. From the analysis of BIS an asymmetric synergism was found with $C_{50,P}$ = 0.136/0.0484 = 2.81 and $C_{50,M}$ = 0.0462/0.000216 = 213.9, the optimal C_P = 0.263/0.737 * 2.81/213.9 * C_M = 0.004688 * C_M. Because the interaction between propofol and midazolam for hemodynamic end points was found additive, this ratio (C_P (ng/ml) = 4.688 * C_M (ng/ml)) also defines the optimal concentration combinations of propofol and midazolam that assure the desired sedative effect in the presence of the smallest possible hemodynamic depression (Table 3).

Table 3. Hemodynamic and sedative response to optimal and suboptimal combinations of propofol and midazolam associated with BIS scores between 40 – 90 as obtained from the pharmacodynamic models described in tables 1 and 2.

BIS	C_P(μg.ml^{-1})	C_M (ng.ml^{-1})	Ramsay	MAP (mmHg)	HR (min^{-1})	CO (L.min^{-1})	SVR (dynes.sec^{-1}.cm^{-5})
97	0	0	1.55	80.6	66.6	7.48	796.3
90	1.16	0	2.06	70.2	50.8	5.73	904.6
90	0	88.6	2.06	78.6	62.8	6.81	852.8
90	0.10	21.2	1.87	80.0	65.8	7.13	829.4
80	2.18	0	2.99	59.6	38.3	4.76	925.3
80	0	165.7	2.96	75.2	56.2	6.31	880.5
80	0.19	39.7	1.98	78.8	63.7	6.84	850.6
70	0.28	60.6	2.06	77.0	60.4	6.55	868.8
60	0.41	87.0	2.45	74.5	56.0	6.21	885.7
50	0.58	122.8	3.38	70.8	50.3	5.81	901.2
40	0.82	175.4	5.62	65.6	43.3	5.30	914.8

From Table 3 the benefit of the use of optimal concentration combinations of propofol and midazolam on hemodynamic function becomes clear. A BIS of 80 may be reached with propofol alone at a blood concentration of 2.18 μg/ml, with midazolam as sole agent at a plasma concentration of 165.7 ng/ml, or with a combination of propofol and midazolam (C_P:

0.19 µg/ml and C_M: 39.7 ng/ml). In these healthy volunteers, mono-propofol sedation to a BIS of 80 was associated with a decrease in MAP and CO of 26% and 36% respectively, mono-midazolam sedation was associated with a decrease of 7% and 16 % in these hemodynamic parameters whereas the propofol-midazolam combination only induced a 2% and 9% decrease in MAP and CO at this same sedative level of a BIS of 80. Furthermore, from table 1 the potency ratio between propofol and midazolam can be determined for their effect on BIS. Based on the respective EC_{50}'s, midazolam is 13.1 times more potent than propofol in its capacity to reduce BIS. Please note that this is very close to the potency ratio described by Billard et al., who found, with a widely different methodology, that propofol at 3.4 µg/ml equally reduced BIS as midazolam at 303 ng/ml (potency ratio: 1: 11.22).[29]

Next to their sedative capacities both agents exhibit hemodynamic depressant effects. Purely based on the respective EC_{50}'s for reduction of MAP and CO, midazolam is 4.3 times more potent than propofol (Table 2). Please note that this comparison only is meaningful when the hemodynamic depressant effects of propofol and midazolam are examined at concentrations that exhibit a similar sedative effect. In this perspective, at equisedative concentrations the hemodynamic depressant effect of propofol on CO and MAP is 3.1 times greater than midazolam (= 13.1/4.3).

Computer simulation.

The impact of the PK-PD interaction between propofol and midazolam becomes clear in the clinical scenario displayed in figure 9. In the LUMC premedication in the majority of ASA 1-2 patients is with oral midazolam 15 mg, 30-90 min preoperatively. The concentration-time profile of midazolam 15 mg PO is comparable to that of a 5-7.5 mg intravenous bolus dose given over 15 min, taking in consideration intestinal and hepatic first pass metabolism.[30] On the basis of the pharmacokinetics of midazolam as described[7] intravenous midazolam 7.5 mg in 15 min results in a peak plasma concentration of 250 ng/ml at 15 min, that decreases to 94 ng/ml at 40 min and 43 ng/ml at 120 min post administration. According to the pharmacodynamic model these plasma midazolam concentrations (still in disequilibrium with the effect site) are associated with BIS scores of 87, 86 and 95 and reductions in mean arterial pressure of 7%, 4% and 1% at 15 min, 40 min and 120 min after midazolam administration, respectively. Thirty min after midazolam premedication, in the operating room unconsciousness may be induced to a BIS of 50 with propofol. In the absence of midazolam a propofol concentration of 6.8 µg/ml would be needed to assure this BIS level (BIS = 50), inducing a reduction in MAP of over 40%, exceeding the boundaries of this study. In the presence of midazolam (C_M: 94 ng/ml) the required propofol concentration only is 1.24 µg/ml and the reduction in MAP then only is 10% (see Table 3). Please note that the optimal

propofol-midazolam combination to assure BIS = 50 exists at higher midazolam and lower propofol concentrations (C_M: 122.8 ng/ml with C_P: 0.58 µg/ml).

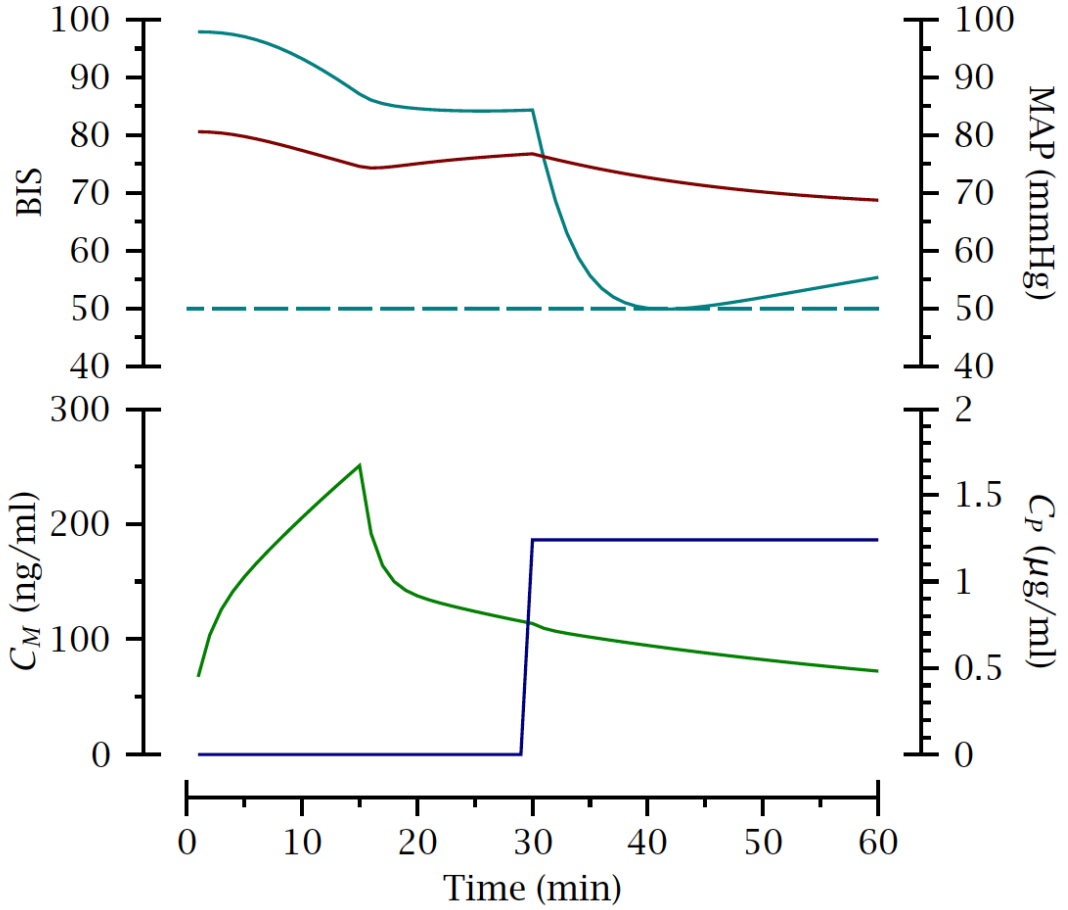

Figure 9. Computer simulation of the hemodynamic consequences of a clinical scenario with midazolam premedication of 15 mg per os (~ 7.5 mg IV) 30 min prior to propofol induction aimed at reaching a BIS of 50.

Figure 10 offers an insight in the complex interplay of the pharmacokinetic and pharmacodynamic interaction between propofol and midazolam on BIS, MAP and return to consciousness (time for BIS to return from BIS=50 (unconsciousness) to BIS=75 (eye opening)) after termination of propofol-midazolam infusions of various durations.

In the absence of midazolam (e.g. in the absence of premedication or co-induction), or in the presence of very low midazolam concentrations below 50 ng/ml, represented at the far left corner of figure 10, relatively high propofol concentrations (between 4-6 µg/ml) are required to assure a BIS of 50. At these simulated propofol concentrations hemodynamic depression is eminent and maximal (a MAP decrease down to 40-50% of the control) but even after prolonged infusion return to consciousness (return to a BIS = 75) is rapid (e.g. BIS increases from 50 to 75 within 15 min even after 360 min infusion). The speed of recovery at this

propofol-midazolam combination is predominantly driven by the rapid pharmacokinetics of propofol.

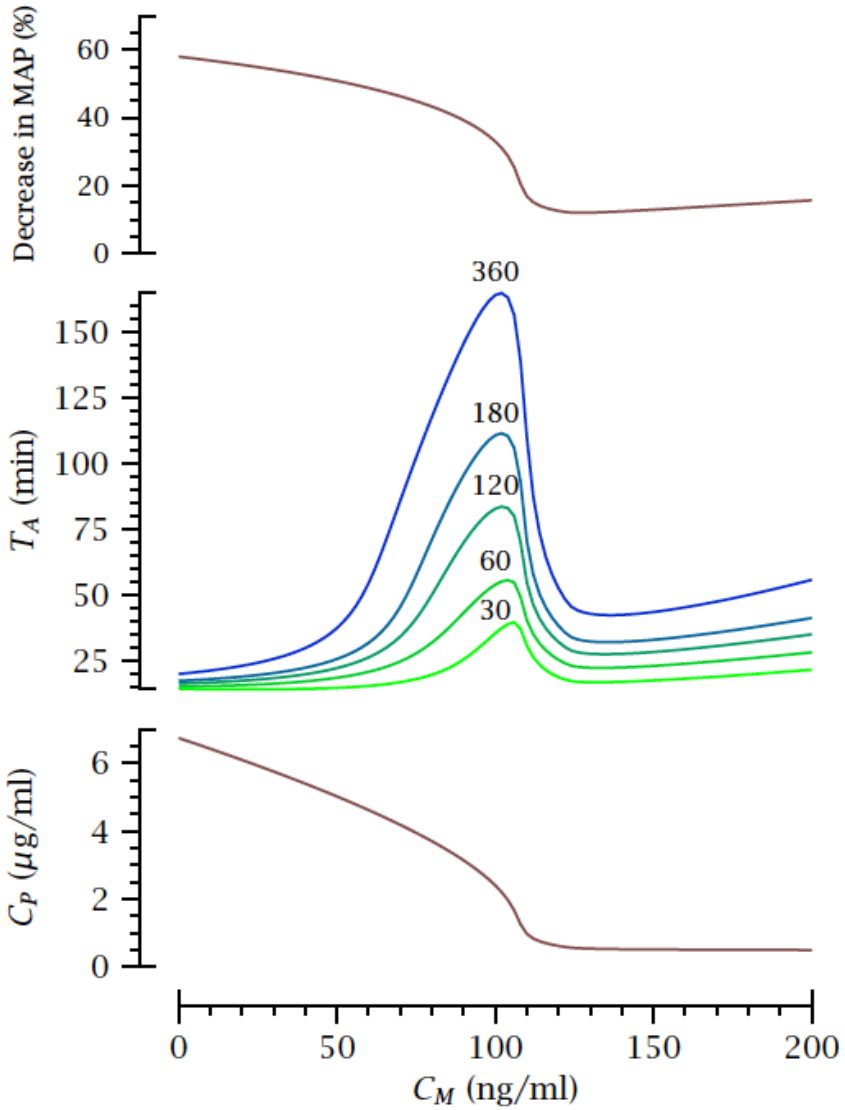

Figure 10. Computer simulation of the complex interplay of the pharmacokinetic and pharmacodynamic interaction between propofol and midazolam on BIS, MAP and return to consciousness (time for BIS to return from BIS = 50 (~unconsciousness) to BIS = 75 (~eye opening) after termination of propofol-midazolam infusions lasting 30-360 min. The lower panel displays the propofol and midazolam effect site concentrations associated with a BIS of 50. The intermediate panel displays the times required for the BIS to increase from 50 (~unconsciousness) to 75 (~eye opening) after termination of various durations of propofol-midazolam infusions aimed to maintain a BIS of 50. The upper panel displays the decrease in MAP from control as associated with the propofol-midazolam effect site concentrations required to maintain a BIS of 50.

With an increasing effect site midazolam concentration present (moving from left to right in figure 10), less propofol is needed to assure a BIS of 50, a smaller decrease in MAP is the result, but now return to consciousness is significantly postponed. At midazolam effect site concentrations of 50-100 ng/ml, midazolam does improve hemodynamic stability but does not reduce propofol requirements enough (at BIS = 50, see right panel figure 3) at these suboptimal midazolam-propofol concentration combinations, to prevent a significant delay in awakening. The sluggishness of recovery at this propofol-midazolam combination is driven by the slower pharmacokinetics of midazolam and the suboptimal pharmacodynamic interaction of the propofol-midazolam combination.

With midazolam effect site concentrations exceeding 100 ng/ml, midazolam now does reduce propofol requirements for BIS = 50 significantly. As a result, hemodynamic stability improves (MAP only decreases 10-15%) and due to the optimal use of the combination the speed of recovery, though longer than when propofol is given as sole agent, is acceptable (e.g. BIS rises from 50 to 75 within 40 min after 360 min of combined propofol-midazolam infusion). The speed of recovery at this propofol-midazolam combination is driven by the optimal pharmacokinetic-pharmacodynamic interaction of the propofol-midazolam combination.

The clinical lessons to be learned from figure 10 are the following. When rapid postoperative awakening is required and hemodynamic depression is thought not an important issue propofol anesthesia should be given without midazolam. This is what most of us offer our patients on a daily basis. We counteract the concurrent hemodynamic depression with fluid loading and/or the administration of α- and ß-sympathicomimetic agents. In cardiovascular compromised patients, such as in most patients for CABG surgery or patients with cardiac ischemia for noncardiac surgery, hemodynamic depression is potentially harmful, undesirable and avoidable. Intermediate midazolam (C_M: 110-150 ng/ml)-low propofol (C_P: 0.5 – 1 µg/ml) anesthesia may then offer unconsciousness, hemodynamic stability and an acceptable time to awakening. A lower midazolam dose may offer some anxiety reduction preoperatively (and this may account for other benzodiazepines as well) but may not reduce propofol requirements enough to be beneficial from a hemodynamic point of view, intraoperatively.

Summary.

We studied the pharmacokinetic-pharmacodynamic interaction between propofol and midazolam on various sedative and hemodynamic end points. The sedative potency of midazolam ($EC_{50,M\ BIS}$ = 532 ng/ml) is 13.1 times that of propofol ($EC_{50,P\ BIS}$ = 6.98 µg/ml) and at these equihypnotic concentrations, propofol depresses hemodynamics (MAP and CO) 3.1 times more compared to midazolam. Propofol and midazolam exhibit a synergistic interaction for sedative endpoints but an additive interaction for hemodynamic endpoints. The use of an optimal propofol-midazolam combination (C_P = 4.688 * C_M) assures sedation and unconsciousness in the presence of minimal hemodynamic depression.

Appendix

In the analyses of the pharmacodynamic data a term $R_{PM} = R_P + R_M - R_P \cdot R_M$ was used, because in steady-state $R_P = U_P / (1 + Up)$ and $R_M = U_M / (1 + U_M)$ (where U_P and U_M as defined before), so

$$R_P + R_M - R_P \cdot R_M = \frac{U_P}{1+U_P} + \frac{U_M}{1+U_M} - \frac{U_P}{1+U_P} \cdot \frac{U_M}{1+U_M} = \frac{U_P + U_M + U_P \cdot U_M}{1+U_P+U_M+U_P \cdot U_M} \qquad (11)$$

which has been derived to hold for mutually non-exclusive drugs.

For BIS, the drug interaction was better described using Minto's approach with an interaction function $I(Q)$; for the hemodynamic effect measures, using the term $R_P \cdot R_M$ resulted in higher values of the objective function; but for the Ramsay scores the above interaction function R_{PM} resulted in the lowest value of the objective function.

For the Ramsay scores, a proportional odds model was used. The values of R_{PM} range between 0 and 1; for the proportional odds model this was transformed to 0 and ∞ by using $z = R_{PM} /(1-R_{PM})$. Usually the logit transform is used (so log (z)), but this would result in a probability of 1 for the lowest Ramsay score, which was at odds with the observed data. Therefore, the probability of observing a Ramsay score less than or equal to k was written as:

$$P\{RS \leq k\} = \frac{1}{1 + e^{(\gamma \cdot (Z - Z_k))}} . \qquad (12)$$

For $k = 3$, z_k was set to one, because then $P\{RS \leq 3\} = P\{RS > 3\} = 0.5$ if $z = 1$, so when $R_{PM} = 0.5$, which is the case if either $C_P = k_{off,P}/k_{on,P}$ and $C_M = 0$, or $C_M = k_{off,M}/k_{on,M}$ and $C_P = 0$. This is a logical choice, and it keeps the rate constants identifiable. The remaining z_k were defined relative to z_3, via $z_2 = z_3 - v_2$, $z_1 = z_2 - v_1$, $z_4 = z_3 + v_4$, and $z_5 = z_4 + v_5$, where the v_k were parameters to be estimated. The probability of observing a Ramsay score k is now given by $P\{RS = k\} = P\{RS \leq k + 1\} - \{RS \leq k\}$, and $P\{RS = 6\} = 1 - \{RS \leq 5\}$. Finally, the expected value (for plots of fits) was calculated as

$$E\{RS\} = \sum_{k=1}^{6} k \cdot P\{RS = k\} . \qquad (13)$$

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