PK-PD modelling of the interaction of Propofol and Midazolam

Implementation and future perspectives

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CONTENT

Introduction

The Basic Equation; Pharmacokinetics, Pharmacodynamics and Training.

Basic research in anesthesia has given anaesthesiologist a new window of opportunity to further improve management of patients. The introduction of Target Controlled Infusion (TCI) has proven to be one of the key elements with which can (visually) help the anaesthesiologist understand the action-reaction chain of events when inducing and maintaining anesthesia. With increasing possibilities for the anaesthesiologist to incorporate pharmacokinetic principles in the operating theatre, one must seek new possibilities to incorporate all of this information into a practical tool. [1]

Even though basic research is not in the spotlights, it is essential for every day practice [2]. Knowledge of pharmacokinetic parameters of different drugs will give the anaesthesiologist the advantage of knowing how and when to differ in strategy. In current practice, intravenous drugs are commonly administered using standard dosing guidelines, an approach which ignores inter- and intra-individual variability in the dose-response relation. It has been proven that incorporating pharmacokinetic-dynamic information as an additional input to guide clinical anaesthesia can result in better patient care.[3]

This research will partially open the so-called “black box”. Understanding interactions between different drugs is the fundament for patient safety.

In this thesis we have studied hypnotic-hypnotic interaction. Medication given to patients to decreases preoperative stress interacts with induction of anesthesia, and although this is taken into consideration when inducing anesthesia, the interaction has never been studied. Knowledge of this interaction helps to redefine the induction dose needed for a safe and efficient induction with the least hemodynamic changes.

TCI can further improve safety for a wide range of patients. Incorporating Bispectral indexing (BIS) completes this equation. Not only a comprehensive understanding of the pharmacokinetic, but also the dynamic principles, of intravenous medication is needed to understand the hemodynamic alterations during induction and maintenance of anesthesia. BIS has developed into a basic tool in the operating theatre, which can visually help guide the anaesthesiologist in dosing the necessary medication needed for the operation, although a low BIS value itself is not a full guarantee for a deep anaesthesia [4]

With increasing number of patients who can benefit from the pharmacokinetic and dynamic interactions now being researched and published it is essential to dedicate more time in schooling residents in this field. It is therefore essential to optimize and broaden the training of residents in anesthesia in PK-PD. Increasing knowledge of PK-PD principles ensures increasing patient safety. [1]

In **chapter 1** we describe the optimization of opioid drug combinations. For every combination an optimal dose has been described and a TCI model has been developed. In this review we also give a comprehensive overview of the use of BIS monitoring.

In **chapter 2** we have studied the influence of midazolam on the pharmacokinetics of propofol. Volunteers were studied in a randomized crossover manner during two separate sessions with a minimum of two weeks between the two sessions. During the first session they were given a bolus of propofol of 1 $mg.kg^{-1}$, and an infusion of 2 $mg.kg^{-1}$, for 59 minutes. In the second session we have given midazolam with a target controlled infusion to reach a steady state and the same dosing scheme of propofol. Blood samples were drawn to measure midazolam and propofol levels. Additional hemodynamic measurements were recorded using the LiDCO® non invasive hemodynamic monitor and stored for later use. With these data we constructed a model for the pharmacokinetic influence of midazolam on propofol, with the use of additional parameters.

In **Chapter 3** we describe three case reports from our study. Volunteers were deeply sedated, resulting in low BIS values but were able to answer simple questions. Hypnotic – hypnotic interaction without the use of muscle relaxants can cause this phenomenon.

In **Chapter 4** we have studied the influence of propofol on the pharmacokinetics of midazolam. Volunteers were studied in a randomized crossover manner during two separate sessions with a minimum of two weeks between the two sessions In one session they were given midazolam in a bolus and a continuous infusion. In the second sessions they received an additional infusion with propofol guided by TCI. Blood samples were drawn to measure midazolam and propofol levels. Additional hemodynamic measurements were recorded using the LiDCO® non-invasive monitor and stored for later use. With these data we constructed a model for the pharmacokinetic influence of propofol on midazolam with the use of additional parameters.

In **Chapter 5** studies 1 and 2 are combined. All pharmacokinetic and pharmacodynamic measurements of studies 1 and 2 are combined to research the interaction of propofol and midazolam on hemodynamic endpoints. The combination of the two previous studies allows the researchers to define an optimal dosing scheme for induction and maintenance of anesthesia with as few as possible side effects. Three-dimensional surface modelling was used for the interaction of midazolam and propofol on different hemodynamic parameters.

In **Chapter 6** a comprehensive review is given regarding the current concepts in PK-PD with regards to the BIS, learning curve of residents and future perspective of PK-PD. New developments with respect to visual display of concentration time curves of anaesthetic agents for use in the operating theatre are described.

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Strategies to Optimise Propofol-Opioid Anaesthesia

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Introduction

Anaesthesia facilitates a wide variety of surgical procedures. Patients generally receive a combination of anaesthetic and analgesic agents to induce and maintain an adequate depth of anaesthesia and analgesia. In addition to anaesthesia and analgesia, muscle relaxation is provided using muscle relaxants, facilitating the surgical procedure. Next to the positive effects of anaesthetic agents in maintaining unconsciousness, analgesia and muscle relaxation, these agents potentially compromise the autonomic stability of the patient. Thorough knowledge of the pharmacokinetics and pharmacodynamics of these agents enables the anaesthesiologist to administer a combination that offers the most stable anaesthetic with the shortest possible induction and recovery times and optimal operating conditions with the least incidence of adverse effects.

In contrast to the past practice of administering anaesthesia on the basis of knowledge of the needs of the population, modern anaesthesia focuses on the individual needs of the patient. To focus the administration of intravenous anaesthetics on the individual needs of the patient, the anaesthesiologist has three strategic tools.

The first and most important tool is the pharmacological knowledge that has been gathered over the past 20-30 years. From this body of knowledge, the anaesthesiologist may take data that allows him or her to adjust the administration of the various anaesthetic agents to the specific need of the individual patient. In this way, each individual patient may experience rapid induction, stable maintenance and rapid recovery from anaesthesia without serious adverse effects.

The second tool to optimize intravenous anaesthesia is the application of state-of-the-art intravenous drug administration techniques. Until recently, intravenous anaesthetic agents were administered either as a bolus doses or by manually controlled infusion pumps, but now target-controlled infusion is the state of the art and is increasingly gaining interest from the clinical anaesthesiologist. Target controlled infusion offers significant advantages over conventional administration methods for intravenous agents and thereby allows for further optimization and individualization of intravenous anaesthesia.

The third and last tool to optimize intravenous anaesthesia is the use of the most recent CNS monitoring techniques. The past 20-30 years saw an intense search for a reliable parameter to track the depth of anaesthesia. So far, monitoring the depth of anaesthesia is still a utopia. However, with respect to the monitoring of the level of (un)consciousness, considerable progress has been made. This has resulted in the clinical introduction of the bispectral index

monitoring (BIS). The bispectral index, a mathematical derivative of the electroencephalogram (EEG), closely correlates with the state of the unconsciousness and the concentration of various anaesthetic agents. As such, it may be used to guide the administration of intravenous agents and may thus lead to a more controlled anaesthesia that again is better tailored to the individual needs of the patient.

This manuscript describes the current status of the application of these three strategic tools to optimize the administration of propofol-opioid anaesthesia.

1. Pharmacokinetic-Pharmacodynamic Knowledge

In everyday clinical practice, anaesthesiologists are faced with dose-effect relationships of both opioids and intravenous anaesthetic agents that exhibit a wide interindividual variability.

This interindividual dose-effect variability of anaesthetic agents is caused by both pharmacokinetic and pharmacodynamic differences between patients. The pharmacokinetic variability is in the order op 70%. With a propofol infusion rate of 10 mg/kg/h, blood propofol concentrations may vary between patients between 3 and 5 mg/L. Differences in cardiac output, hepatic perfusion, protein binding and enzyme activity are responsible for these interindividual pharmacokinetic differences.[1-6]

The pharmacodynamic variability is much larger, in the order of 300-400%. During induction of anaesthesia with a target-controlled infusion of propofol, some patients already lose consciousness at a target of 1mg/L, whereas others need 4-5 mg/L to experience the same effect. Factors that are responsible for this huge pharmacodynamic interindividual variability still remain obscure, but genetic differences in receptor pharmacology may play an important role. [4]

Next to the pharmacokinetic and pharmacodynamic variability of single agents, the administration of two or more agents together gives rise to pharmacokinetic and pharmacodynamic interactions. Anaesthesiologists combine anaesthetic agents on a daily basis because the provision of anaesthesia on the basis of a single agent is associated with significant adverse effects compromising hemodynamic and/ or respiratory function, affecting operating conditions, and/or postponing postoperative recovery. Because of the small therapeutic window, a detailed characterization of anaesthetic agents and their interactions is required to allow a proper selection of the various intravenous agents and their combinations, and to obtain an optimal therapeutic pharmacological effect in the absence of significant adverse effects.

In this section we describe the pharmacology of propofol and the four most uses opioids (fentanyl, remifentanil, alfentanil and sufentanil) when given as sole agents and when given in combination. Finally, the optimal concentration combinations of propofol with the various opioids are defined for various endpoints.[7,8]

1.1 Pharmacology of propofol

Propofol, a lipophilic agent, has a fast onset and short duration of action due to a rapid penetration through the blood-brain barrier and distribution to and from the CNS followed by redistribution to inactive tissue depots such as muscle and fat. [9] Propofol pharmacokinetics are best described on the basis of a three compartment model (table I). The short effect-site equilibration half-life and the small central compartment are responsible for its time peak effect of only two minutes. The larger volumes of distribution, combined with a clearance that equals hepatic perfusion, are associated with a context sensitive half-time that only increases from about 20 to about 30 minutes with infusion durations increasing from 2 to 8 hours. Consequently, propofol is very well suited for continuous infusion techniques. Its high clearance and redistribution, even after prolonged infusion, allow for a rapid return to consciousness even after many hours of anaesthesia. Propofol as a single agent for anaesthesia, without opioid pre-treatment, causes loss of consciousness in 50% of the patients (EC_{50}) at a blood concentration of 3.4 mg/L. Propofol may be used as a monoanaesthetic agent during surgery. Then blood concentrations in excess of 10-12 mg/L are required to suppress responses evoked by surgical stimulation. [10-12]

Propofol dosage schemes should be adjusted for age and sex. Schnider et al. [13] described the relation ship between dose, age and blood concentrations for loss of consciousness in healthy non –premedicated volunteers. In this study, the EC_{50} for loss of consciousness was 2.4, 1.8 and 1.3 mg/L in volunteers aged 25, 50 and 75 years, respectively[13]. Children require a higher induction dose as result of a larger central compartment, [14] whereas elderly patients require a lower induction dose as a result of smaller central compartment and a reduced clearance. [15,16] As well as the relatively larger central compartment in children, the clearance is increased to a lesser extent. The application of target-controlled infusions of propofol in children using adult pharmacokinetic parameter sets will therefore cause a divergence of the blood concentration from the desired target concentration. Elderly female patients need a higher dosage of propofol compared with males because of a higher clearance rate. [17]

Cytochrome P450 (CYP) 2B6 is predominantly involved in the oxidation of propofol, [18] whereas part of the propofol hydroxylase activity is mediated by CYP2C9 in human liver, especially in lower substrate concentrations. Moreover, propofol is metabolized by additional isoforms such as CYP2A6, 2C8, 2C18, 2C19 and 1A2, especially when substrate concentrations are high. This low specificity of CYP isoforms may contribute to low pharmacokinetic interindividual variability of propofol (70%) and to the low level of metabolic drug interactions observed with propofol. [19]

Table I. Pharmacokinetic and pharmacodynamic parameters of propofol and the opioids. Various pharmacokinetic parameter sets are available in the literature for all of these agents, but population pharmacokinetic data are available only for propofol, remifentanil and alfentanil. These population pharmacokinetic parameter sets may therefore be best applicable in a population that varies greatly in age, weight and gender.

Parameter and unit	Propofol(20)[a]	Fentanyl[21]	Remifentanil[22]	Alfentanil[23]	Sufentanil[24]
V_1 (L)	4.27	8.9	4.98	8.9	14.3
V_2 (L)	24.0	50.3	9.01	13.8	63.1
V_3 (L)	238	295.5	6.54	12.1	261.6
CL_1 (L/min)	0.68	0.63	2.46	0.36	0.92
CL_2 (L/min)	1.60	4.83	1.69	0.93	1.55
CL_3 (L/min)	0.836	2.23	0.065	0.15	0.33
t½,keO (min)	2.40	4.70	0.90	1.10	5.87
EC50 (µg/L)	3400[b]	1.1[c]	4.7[c]	90[c]	0.14[c]

a Model estimation for patient 40 years, 180 cm and 80 kg.

b For loss of consciousness

c Optimal EC_{50} in the presence of propofol

Cl_1 = elimination clearance; **Cl_2** = rapid distribution clearance; **Cl_3** = slow distribution clearance; **EC_{50}** = 50% effective concentration for loss of consciousness (propofol) or adequate analgesia (opioids); **t½keO** = effect site equilibration half-time; **V_1** = volume of central compartment; **V_2** = volume of rapidly equilibrating peripheral compartment; **V_3** = volume of slow equilibrating peripheral compartment.

Propofol inhibits CYP 2A1 (phenacetin *O*-de-ethylation), CYP2C9 (tolbutamide 4'-hydroxylation), CYP2D6 (dextromethorphan *O*-demethylathion) and CYP3A4 (testosterone 6β-hydroxylation) activities with 50% inhibitory concentrations (IC_{50}) of 40, 49, 213 and 32 µmol/L, respectively. [25]

Propofol induces a marked loss of sympathetic tone in healthy volunteers. Cardiac and sympathetic baroslopes are significantly reduced with propofol, especially in response to hypotension, suggesting that propofol induced hypotension may be mediated by an inhibition of the sympathetic nervous system and impairment of baroreflex regulatory mechanisms. [26] Loss of vascular tone in arteries, as a result of a reduced Ca^{2+} influx, may also contribute to the hypotension following induction with propofol. [27] Reduction of cardiac muscle contraction is a result of reduced free systolic Ca^{2+} concentration in myocardial cells (28) resulting in a negative inotropic state of the cardiac muscle by propofol. Especially in elderly patients, this may contribute to propofol induced hypotension, giving rise to the need for adjusted induction schemes for propofol in the elderly. Propofol, even at low doses, depresses the ventilatory response to acute hypoxic incidents. The depression of the acute hypoxic response results from an exclusive effect within the central chemoreflex loop at the central chemoreceptor. [29,30]

These adverse effects of propofol may lead to severe haemodynamic and respiratory depression, especially in patients with a more fragile homeostatic balance such as elderly and those with cardiovascular and respiratory diseases. This furthermore stresses the importance of individualisation of anaesthetic drug administration.

1.2. Pharmacology of Opioids

The pharmacology of the four most commonly used opioids, fentanyl, alfentanil, remifentanil and sufentanil, has been studied extensively. The opioids differ in their pharmacokinetics but, by acting at similar receptor sites, exhibit comparable pharmacodynamics. Table I gives an overview of representative pharmacokinetic parameters of the four opioids. The effect site equilibration half time ($t_{½,keO}$) is fastest for alfentanil and remifentanil. (Table I) The context sensitive half time of the four opioids gives an indication of the suitability of these agents to be given by prolonged infusion.

Remifentanil has the most rapid pharmacokinetics of the four opioids. It has the shortest time to peak effect as a result of its small central compartment and short $t_{½,keO}$. As a result of its high rate of clearance of tissue esterases, remifentanil the shortest context-sensitive half-time of only a few minutes even after continuous infusion for many hours or days. The measured context-sensitive half-time of remifentanil after a 3 hour infusion was 3 minutes, with an offset of respiratory depressant effect of about 5 minutes, whereas the measured context-sensitive half-time of alfentanil was 47 minutes with an offset of about 54 minutes. [31] Increasing the infusion duration hardly increases the time to a 50% reduction in the blood remifentanil concentration after termination of the infusion. This is caused by the fact that remifentanil reaches steady state very rapidly and thus becomes context-insensitive. Alfentanil an sufentanil become context-insensitive after a few hours of infusion (figure 1), whereas in the clinical situation fentanyl does not reach this state. Consequently, remifentanil is generally administered by continuous infusion.

Remifentanil is eliminated from the blood through hydrolysis by blood and tissue esterases. The metabolites formed do not contribute to the total effect of remifentanil. [32] In patients with liver disease, even severe, the elimination half-life is not different from healthy volunteers, [33] but with renal failure the main metabolite of remifentanil is excreted more slowly, may accumulate and reach active concentrations. [34] The other opioids are metabolised through the CYP enzyme system and clearance can not exceed hepatic perfusion. Due to differences in redistribution and clearance, the context-sensitive half time increases in the order sufentanil<alfentanil<<fentanyl (figure 1). Similarly, due to differences in effect site equilibration and initial distribution, the time to peak effect after a bolus increases in the order remifentanil<alfentanil<fentanyl<sufentanil (figure 2). Consequently, fentanyl, sufentanil and alfentanil are given predominantly by bolus administration, with fentanyl being the least suitable for use in continuous infusion techniques

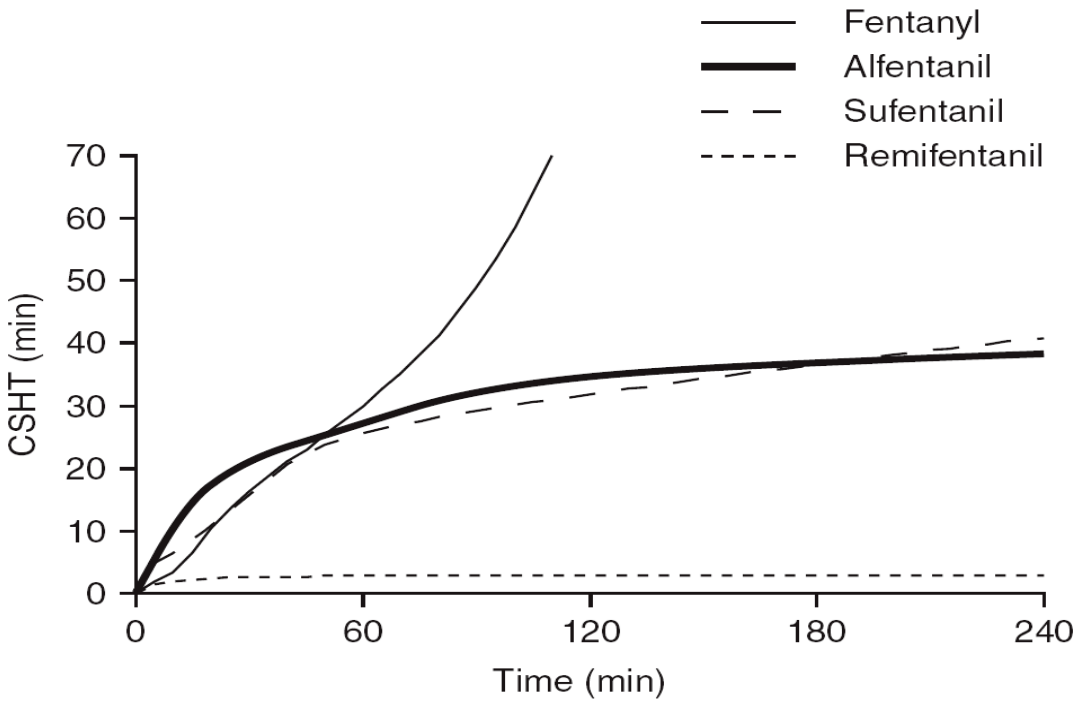

Figure 1: Context-sensitive Half-times (CSHT; the time required after termination of an infusion for the blood concentration to drop by 50%) for the opioids fentanyl, alfentanil, sufentanil and remifentanil.

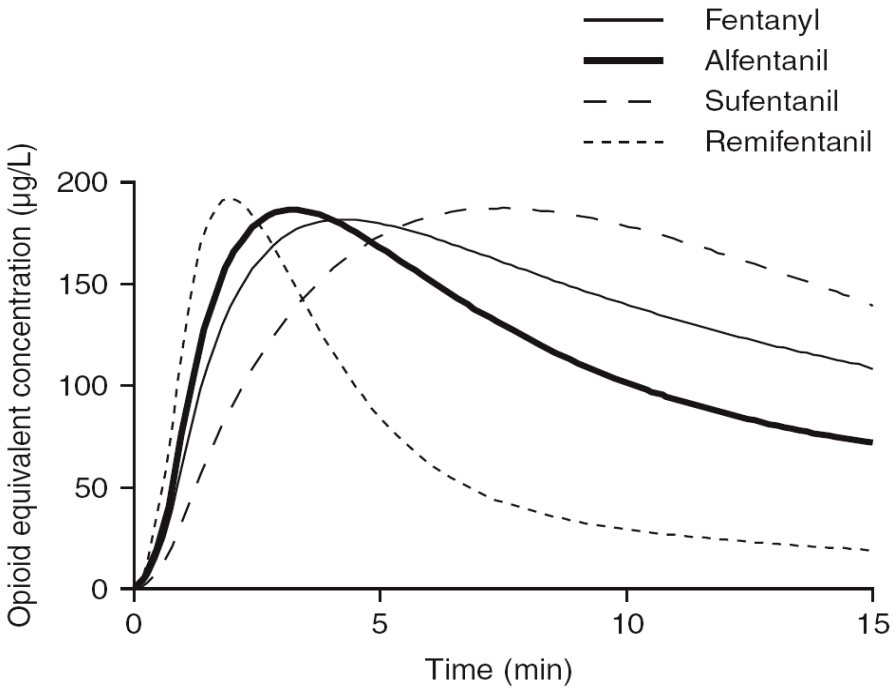

Figure 2: Computer simulations using the pharmacokinetic parameters as described in table I to determine the time to peak effect for the four opioids when given as equipotent bolus in 15 seconds.

Age and lean body mass significantly influence opioid distribution and clearance. With increasing age from 20 to 80 years, $t_{½keO}$ increases by approximately 50%; effect site equilibration is thus considerable slower in the elderly. [35] Lean body mass is also a significant covariate in the distribution of remifentanil. In both young and elderly obese patients, remifentanil dosage should be based on lean body mass rather than total body mass. [22,36]

Pharmacodynamically, opioids are very much alike; they all produce physiological changes consistent with potent μ opioid receptor agonist activity, including analgesia and sedation. The adverse effect profile (like that of other drugs in this class) includes ventilatory depression, nausea, vomiting, muscular rigidity, bradycardia and pruritis. [37] The potency ratio between the opioids, although showing some variation throughout the literature, is such that 1 μg/L of fentanyl is approximately equipotent to 0.1 μg/L of sufentanil, 70 μg/L alfentanil and 2 μg/L remifentanil. This is not only for the major desired effect, analgesia, but also for the adverse effects such as respiratory depression.

1.3 Pharmacokinetic interactions between Propofol and Opioids

The first suggestion of pharmacokinetic interactions between propofol and the various opioids go back to 1993 when Schütller and Ihmsen [16], revealed, on the basis of a mixed effects modelling population pharmacokinetic analysis, that fentanyl and alfentanil both decreased the volume of the central compartment and the clearance of propofol. More recently, Pavlin et al. [38] showed that in the presence of alfentanil at plasma concentrations of 40 µg/L, with patients still breathing spontaneously, blood propofol concentrations were increased by 20%. Furthermore, Matot et al. [39] showed that the first pass pulmonary uptake reduced from 60-40% after pretreatment with fentanyl. A reduced first-pass uptake of propofol may indeed increase the initial blood propofol concentration after bolus dose administration.

Conversely, both Gepts et al. [40] and Pavlin et al.[38] reported increased alfentanil concentrations in the presence of propofol. This may be the result of inhibition by propofol of the oxidative metabolism of alfentanil by CYP, which so far has only been described *in vitro*. [41,42] Also, sufentanil metabolism appears to be inhibited in the presence of propofol. Other sedative agents that interfere with the metabolism of opioids are midazolam and dexmedetomidine, which have been shown to inhibit the metabolism of alfentanil and eltanolone (pregnanolone). [41,43]

Recently, two pure pharmacokinetic interaction studies have shed more light on interactions between propofol and opioids. In the presence of a constant blood propofol concentration of 1.5 mg/L, the pharmacokinetics of alfentanil were significantly altered.[44] Propofol increased mean plasma alfentanil concentrations by approximately 15%. Propofol decreased the elimination clearance (Cl_1) of alfentanil by 15%, rapid distribution clearance (CL_2) by 68%, slow distribution clearance (CL_3) by 51% and lag-time by 62%. Mean arterial pressure and systemic vascular resistance were significantly lower in the presence of propofol, suggesting that the hemodynamic changes induced by propofol may be the cause of the pharmacokinetic interaction. This pharmacokinetic interaction was furthermore expressed by the prolonged context-sensitive half-time of alfentanil during combined infusion with propofol. Propofol increased the context sensitive half time of alfentanil by 10-15% on average for durations of infusion from 6-240 minutes, at which time alfentanil reaches a steady state and decay becomes context insensitive.

Similarly, in the presence of alfentanil, propofol concentrations also increase. Alfentanil reduces the metabolic clearance of propofol and increases the slow distribution volume. Next to alfentanil, heart rate also proved a significant covariate on the mixed effects analysis of the pharmacokinetics of propofol in this study. Tachycardia reduced the blood propofol concentrations because of increased hepatic blood perfusion, whereas in the presence of

bradycardia blood propofol concentrations tended to be elevated. The authors conclude that propofol has a flow limited clearance; all processes that influence liver blood flow might influence blood propofol concentration. Tachycardia induced by perioperative stress or fever, or bradycardia induced by β-adrenoreceptor agonists or co administered opioids, may, through changes in cardiac output, significantly affect dose-concentration relationship for propofol, thereby affecting its dose-effect relationship.[45]

In conclusion, it becomes increasingly evident that propofol and the opioids affect each other's distribution and elimination. Further studies are necessary to evaluate the precise mechanisms that cause these pharmacokinetic interactions.

1.4 Pharmacodynamic interactions between propofol and opioids.

1.4.1 Terminology

Bovill[46] reviewed the methodology of the study of drug interactions in anaesthesia and described four methods of interaction analysis: fractional analysis, isobolographic analysis, the method of Plummer and Short and the parallel line assay. The response surface modelling technique described recently by Minto et al.[47] is the latest branch of the pharmacodynamic modelling tree. Each of these modelling techniques uses more or less the same terminology. In general, four classes of drug interactions can be defined as follows.[48,49]

Zero interaction is said to occur when the effect of the combination of two drugs is exactly the sum of the individual agents. This is more often referred as an additive interaction. This occurs when two agents do not really interact but simply provide their action next to one another without influence. Inhalational anaesthetic agents generally exhibit an additive interaction.

When the effect of the combination is greater than expected, as based on the concentration-effect relationships of the individual agents, the interaction is said to be synergistic. Supra-additivity or potentiation are often used as synonyms for synergism. One then needs relatively less of the combination obtain a certain effect compared to when the agents are given alone.

An infra-additive interaction is said to occur when the effect of the combination is less than the sum of the effects of the individual agents. One needs relatively more of the combination to obtain a certain effect to when the agents are give alone.

Lastly, antagonism is the situation where the effect of the combination is less than that of one of the constituents. For example, the combined effect of alfentanil and nalaxone is less than that of alfentanil alone.

1.4.2 Interactions is practice

Combinations of propofol (0.1-1 mg/L) and fentanyl (40µg/L) have enhanced the sedative and analgesic properties. Although propofol has no analgesic properties, it can be used as a monoanaesthetic agent at blood concentrations exceeding 10-12 mg/L in the absence of opioids. Furthermore, propofol offsets the emetic effects of alfentanil (EC_{50} 0.5 mg/L), whereas alfentanil induced pruritis persists.(38) With these concentrations, ventilation is only moderately affected. Resting minute ventilation decreases by approximately 25%, in the presence of a somewhat smaller reduction in CO_2 production of approximately 15%, resulting in a moderate increase (41-46 mmHg) in the end-tidal partial pressure of CO_2.

Both fentanyl and alfentanil have been shown to decrease propofol requirements for induction of anaesthesia in a synergistic manner.[10,50] A fentanyl concentration of 3 µg/L and a plasma alfentanil concentration of 122 µg/L both reduce the blood propofol EC_{50} for loss of consciousness by 40%. Although alfentanil reduces propofol requirements, the reduced dosage requirements of propofol do not assure a more haemodynamically stable induction of anaesthesia in American Society Anaesthesiology (ASA) status classification 1-2 patients, because alfentanil potentiates the haemodynamically depressant effects of propofol to a similar degree as it potentiates the its sedative effects. The interaction between fentanyl and propofol is also a source of hemodynamic changes. Billard et al.[51] have shown that the mean decrease in systolic pressure after induction with propofol alone was 28 mm Hg, but 53 mmHg in the presence of fentanyl 2µg/kg. Hemodynamic changes post-intubation were not different with increasing doses of propofol.[51]

Intraoperative, propofol is also potentiated by opioids.[8,12] Propofol concentrations required to blunt motor responses to skin incision in 50% of the patients ($EC_{50,INC}$) diminished greatly with plasma fentanyl concentrations increasing from 0 to 3µg/L.[10] Higher plasma fentanyl concentrations, did not further reduce the $EC_{50,INC}$ of propofol, demonstrating a ceiling effect for propofol dosage reduction by fentanyl. Intraoperatively, with a 5-fold increase in the propofol concentration from 2-10 mg/L, alfentanil requirements were reduced by over 10-fold in female patients undergoing gynaecological surgery.[8,12] For both alfentanil and fentanyl, the magnitude of the interaction with propofol increases with the strength of the stimulus (the concavity of the isobole for loss of eyelash reflex or loss of consciousness < skin incision < intra-abdominal surgery). Lastly, alfentanil has been shown to affect the propofol concentrations at which patients awake postoperatively. In the presence of still significant alfentanil concentrations of 150µg/L, the blood propofol concentration had to decrease to 0.5-1 mg/L before patients regained consciousness, whereas with plasma concentrations of alfentanil below 50 µg/L patients awoke at blood propofol concentrations of 2-3 mg/L.[8] For remifentanil and propofol, the interaction for intraoperative endpoints and awakening run parallel to those between alfentanil and propofol. In general, one may conclude that propofol concentrations at which patients regain consciousness are affected by the degree of painful stimulation postoperatively and the opioid concentration. The extend of reduction in propofol EC_{50} for intraoperative anaesthetic stability is similar for alfentanil and remifentanil, with a potency ratio of alfentanil to remifentanil of 35:1.[8,12]

By computer simulation, based on both pharmacokinetic and pharmacodynamic interaction data, the optimal propofol-alfentanil concentration combination has been defined that assures both adequate anaesthesia and the most rapid possible recovery in 50% of

patients.[8] This optimal propofol-alfentanil concentration combination has been determined to be a blood propofol concentration of 3.5 mg/L in the presence of 85 µg/L alfentanil. After termination of a 5-hour target controlled infusion with these concentrations, 50% of the patients will regain consciousness after 16 minutes. With higher propofol concentrations the postoperative surplus of propofol will postpone recovery, whereas in the presence of lower propofol concentrations the higher intraoperative alfentanil concentrations will delay recovery. With the use of pharmacokinetic-pharmacodynamic computer simulation, this optimal propofol concentration is affected by both the choice of the opioid as well as the infusion duration. The steeper the decay in the opioid concentration relative to the decay in the propofol concentration, the more the optimal propofol-opioid concentration shifts to a lower propofol and a higher opioid concentration. As a consequence, the optimal propofol concentration is much lower when it is combined with remifentanil compared when it is combined with fentanyl, sufentanil or alfentanil. For example, the optimal propofol concentration (EC_{95} for no response to surgical stimuli) when combined with fentanyl is in the order of 5 mg/L, whereas the optimal propofol concentration when combined with remifentanil is 2.5 mg/L.[8] The exact optima of these propofol-opioid concentrations are defined on the basis of steepness of the concentration decay of propofol relative to those of the opioids, as well on the position of the interaction curves associated with a 50 or 95% probability of no response to a surgical stimulus, relative to the position of the interaction curve associated with a 50% probability of return of consciousness postoperatively. Consequently, the optimal propofol concentration decreases in the presence of various opioids in the order of fentanyl > alfentanil > sufentanil >> remifentanil (with the order of alfentanil and sufentanil changing after approximately 180 minutes (see figure 1)). The duration of infusion is the second factor influencing the decay of the two agents and thereby the optimal propofol-opioid concentrations. However, with increasing duration of infusion the optimal effect-site concentrations change only marginally.

Although the concept of the context-sensitive half-time has improved our understanding of the clinical implications of the pharmacokinetics of anaesthetic agents much more than has the elimination half-life, one should keep in mind that concentrations not always need to decrease by 50% to achieve return of consciousness or spontaneous breathing. It is clear that at suboptimal concentrations (not associated with adequate anaesthesia and the most rapid possible recovery), as often will occur in clinical practice due to the interindividual variability in pharmacokinetics, recovery is much more postponed after propofol-fentanyl anaesthesia than when propofol is combined with alfentanil, sufentanil or remifentanil. It is also clear that the optimum for the propofol-remifentanil combination is less important than for the other propofol-opioid combinations, because even at suboptimal propofol-remifentanil

concentrations recovery, even after prolonged infusion, is still rapid. To avoid a delayed return to consciousness, these data suggest that intraoperative responses may be best counteracted by additional propofol in combination with fentanyl, alfentanil or sufentanil and by additional remifentanil during propofol remifentanil anaesthesia.

Furthermore, when spontaneous breathing is desired, lower (than optimal) effect-site opioid concentrations (e.g. effect-site alfentanil concentrations, < 50 µg/L) in the presence of corresponding higher (than optimal) effect-site propofol concentrations should be given. In contrast, in the cardiovascular compromised patient, haemodynamic function may become less depressed in the presence of higher (than optimal) effect-site opioid and correspondingly lower (than optimal) effect-site propofol concentrations. In spontaneously breathing patients and cardiovascular compromised patients, suboptimal (with respect to speed of recovery) propofol-opioid concentrations thus are indicated intraoperatively at the expense of a prolonged recovery.

From the optimal propofol-opioid concentrations, optimal propofol and opioid infusion schemes have been derived that assure adequate anesthesia and the most rapid return of consciousness after termination of the infusion when propofol is combined with one of the opioids fentanyl, alfentanil, sufentanil or remifentanil (table II). These infusion schemes should be used as guidelines and adjustments must be made to the meet the individual needs in anticipation of factors such as age, sex, and stimulus intensity related to the type of surgery.

1.5 Can We Benefit From Drug Interactions?

For various clinical endpoints one may now evaluate, on the basis of existing pharmacokinetic-dynamic interactions data, if it is possible to benefit clinically from the interactions between propofol and the various opioids.

1. Is it possible to increase the speed of induction on the basis of propofol-opioid interactions? Two factors govern speed of induction with a single agent. These are the speed of administration and time to peak effect. Time to peak effect is determined by the initial distribution of a drug (V_1, K_{12}, and K_{13} with a three compartment model) and the equilibration rate between blood and effect site (k_{e0}). It is possible to improve speed of induction using propofol opioid combinations, simply because in the presence of high opioid concentrations

Table II. Infusion schemes of propofol and opioids required to maintain effect site concentrations of these agents, when given in combination, with ±15% of the effect-site concentrations that are associated with a 50% and 95% probability of no response to surgical stimuli (EC50 and EC95) and the most rapid return of consciousness after termination of the infusions. These optimal infusion schemes have been derived from data in female patients undergoing lower abdominal surgery. They should be uses as guidelines and be adjusted to the individual needs of the patients. (vuyk et al. (8))

	Alfentanil	**Fentanyl**	**Sufentanil**	**Remifentanil**
Opioid				
EC50-EC95 (µg/L)	90-130	1.1-1.6	0.14-0.20	4.7-80
Bolus (µg/kg in 30 sec)	25-35	3	0.15-0.25	1.5-2
Infusion 1 (µg/kg/h)	50-75 x 30 min	1.5-2.5 x 30 min	0.15-0.22 thereafter	13-22 x 20 min
Infusion 2 (µg/kg/h)	30-42.5 thereafter	1.3-2 x 150 min		11.5-19 thereafter
Infusion 3 (µg/kg/h)		0.7-1.4 thereafter		
Propofol				
EC50-EC95 (mg/L)	3.2-4.4	3.4-5.4	3.3-4.5	2.5-2.8
Bolus (mg/kg in 30 sec)	2.0-2.8	2.0-3.0	2.0-2.8	1.5
Infusion 1 (mg/kg/h)	9-12 x 40 min	9-15 x 40 min	9-12 x 40 min	7-8 x 40 min
Infusion 2 (mg/kg/h)	7-10 x 150 min	7-12 x 150 min	7-10 x 150 min	6-6.5 x 150 min
Infusion 3 (mg/kg/h)	6.5-8 thereafter	6.5-11 thereafter	6.5-8 thereafter	5-6 thereafter

lower effect-site propofol concentrations are needed for loss of consciousness and these are reached more rapidly. Because the time to peak effect differs for propofol and the various opioids, the timing of the opioid bolus relative to that of propofol is critical in this respect. Times to peak effect for propofol, remifentanil, alfentanil, fentanyl and sufentanil are 2, 1.2, 2.3, 4.3 and 7.5 minutes, respectively (figure 2). To benefit most from the ability opioids to reduce anesthetic requirements, sufentanil should be given well in advance of propofol, more so than remifentanil or alfentanil.

2. Is it possible to increase the hemodynamic stability of the induction or maintenance of anaesthesia on the basis of the current knowledge of propofol-opioid interactions? Opioids reduce the anaesthetic dose requirements for induction of anaesthesia. In theory, this may lead to an improved hemodynamic profile of the induction of anaesthesia. However in ASA 1-2 patients this dose reduction does not leas to a more stable induction of anaesthesia. [12] In elderly patients or patients with cardiovascular instability, high opioid/low propofol anaesthesia may be associated with increased hemodynamic stability during induction of anaesthesia. However, not data are yet available to support this supposition.

3. Is it possible to decrease the time to awakening postoperatively on the basis of propofol-opioid interactions? With the use of optimal propofol-opioid concentrations, it is clearly possible to optimize intravenous, anaesthetic drug delivery. The propofol and opioid infusion regimens described in table II can be used as guidelines and will allow adequate anesthesia associated with a rapid recovery after termination of the propofol and opioid infusions. [8] In general, propofol-remifentanil anesthesia is associated with the most rapid return of consciousness after any infusion duration compared with fentanyl, alfentanil or sufentanil. Another benefit of remifentanil is that even at suboptimal high concentrations, return of consciousness is only marginally postponed.

4. What are the optimal propofol-opioid concentrations for anesthesia that allow spontaneous respiration? So far, no clinical relevant data regarding propofol-opioid interactions for spontaneous respiration have been described. Bouillon et al. [52] described for a single agent, alfentanil, the clinical profile in this respect. The EC_{50} for adequate ventilation during normocapnia is 60 µg/L. With higher plasma alfentanil concentrations, the arterial pressure of CO_2 has to increase considerable to maintain adequate ventilation. Similarly, for propofol is has been shown that with increasing concentrations the responses to both hypercapnia and hypoxia are diminished.[30] This means that in the presence of propofol hypoxia will be deeper and hypercapnia more severe before a ventilatory response will be evoked by these stimulants. Because no interaction data exist, and nor are data available regarding the effect of nociception on propofol-opioid respiratory depression, optimal propofol-opioid concentrations that assure adequate anesthesia and adequate respiration cannot yet be defined.

5. Lastly, the level of postoperative pain a patient experiences is not only influenced by the type of surgery but also by the propofol-opioid concentrations used intraoperatively. When propofol is given at high concentrations, intraoperative opioid needs are low. At the end of

surgery, when the propofol infusion is discontinued, the opioid concentration may appear to be insufficient for adequate postoperative analgesia. To prevent this from happening, in anticipation, intraoperative low opioid concentrations may be avoided or intravenous morphine may be administered well in advance of skin closure.

2. State-of-the-art Administration Techniques

Target-controlled infusion as used in modern anaesthetic practice refers to the use of an infusion pump with an integrated pharmacokinetic dataset. With this technique, the user does not set an infusion rate but rather sets the desired blood concentration, i.e. the so-called target-concentration. The computer then uses the incorporated pharmacokinetic dataset to calculate the infusion rate required to reach and maintain the desired blood concentration. Next, the computer triggers the infusion pump to actually administer the infusion rate calculated. The pump will initially at a high infusion rate, thus giving a loading dose. In addition, the pump will repeatedly calculate the running rate required to maintain a constant blood concentration. After the initial loading dose, the calculated maintenance infusion rate decreases logarithmically to maintain a constant blood concentration. The logarithmic decrease in infusion rate is the result of the gradual saturation of the various pharmacokinetic compartments. When a lower target is set, the computer will stop the infusion of the drug until, as a result of clearance and redistribution, the desired concentration is reached.

The development of computer-controlled infusion systems date back to 1983 when Schüttler et al. [(53)] described the use of a computer to perform the 'bolus elimination and transfer' infusion scheme with a system called CATIA (computer assisted total intravenous anesthesia). Many other systems followed, including that of Alvis et al. [(54)] who compared target-controlled infusion-controlled anesthesia with that from a manual administration scheme. This has led to the introduction of the clinically available target-controlled infusion pump registered for the administration of propofol, the Diprifusor®. The Diprifusor® is provided with prefilled propofol syringes containing either 10 or 20 mg/mL of propofol. The prefilled syringes are equipped with a passive magnetic device that serves as a recognition tag for the target-controlled infusion device to indentify the drug and the solution of the drug in the syringe. Two important features of the Diprifusor® are the display of the predicted effect-site concentration and the prediction of the time to reach a lower blood concentration. With this last feature, anaesthesiologist now is capable of predicting the time to recovery in patient irrespective of the infusion duration.

The accuracy in the prediction of the actual blood concentration [(55)] by target controlled infusion depends on the match between the pharmacokinetic dataset integrated in the software and the *in vivo* distribution and elimination of the drug in the patient. Vuyk et al. [(56)] compared five different pharmacokinetic parameter sets of propofol for their effect on the predictive accuracy of propofol target-controlled infusion systems in female patients. In this study, the measured propofol concentrations exceeded the concentrations predicted by the target-controlled infusion device on average by 20%. The median performance error of the

five datasets tested varied between 20% and 100%, stressing the importance of installing a proper pharmacokinetic parameter set.

Similarly, Mertens reported on the predictive performance of remifentanil target-controlled infusion using the Minto parameter set. In general, measured remifentanil concentrations were on average 18% lower than predicted by the target-controlled infusion device. In an offline analysis, Mertens and colleagues reported on the improved predictive performance with the Egan remifentanil pharmacokinetic parameter dataset.[57] Although the parameter set of Egan and colleagues[58] performed best in in the analysis of Mertens et al., a population pharmacokinetic parameter set like that of Minto[35] may prove to beneficial in a more heterogeneous group of patients.

In conclusion, target-controlled infusion devices have been shown to be capable of predicting the actual measured concentrations quite closely, although proper selection of a matching pharmacokinetic parameter set remains important. The Diprifusor® has been shown to accurately predict the measured concentration in a wide variety of patients.

In general, the target-controlled infusion mode of administration of drugs provides a number of practical advantages to the user compared with conventional infusion;

- Improved control and predictability of pharmacodynamic effect achieved;
- Therapeutic concentration achieved rapidly and maintained constant;
- Control over onset time by slow upward titration of target if desired in the elderly;
- Proportional changes in blood concentration rapidly achieved;
- Improved titratability;
- Avoidance of peak blood concentrations and possible risk of toxicity;
- No need for calculating of infusion rates;
- Automatic adjustment for differences in body weight, lean body mass, age or sex if complex model available;
- Displayed effect-site concentration facilitates titration of the blood concentrations;
- Estimation of the time required to reach a lower plasma concentration;
- Target concentration regained automatically after syringe change;
- A more logical and modern approach.

However, may of these advantages have not been proven in outcome studies. Lastly, target-controlled infusion systems can either target the blood concentration or the effect compartment concentration. The only clinically available system, the Diprifusor®, targets and controls the blood concentration.

In conclusion, through target-controlled infusion, the anaesthesiologist is capable of providing anaesthetic drugs in a more controlled manner, allowing a more rapid titration of effect to the

individual needs of the patient.

3. Bispectral Index Monitoring

In 1875, Richard Caton [59] described the EEG as a way of determining cerebral activity on the cortical surface of the skull of animals. Then, in 1937, Gibbs and colleagues[60] discovered that the EEG activity was affected by the administration of anesthetic agents. Because the raw EE is hardly interpretable online, this quest for a clinically useful parameter derived from the EEG has great importance.

In this search, time domains, frequency domain and higher order statistical analysis techniques have been evaluated for their usefulness in the analysis of a depth of anesthesia parameter. Time domain-derived parameters are, for example, the change in total power or median frequency in time, the occurrence of activity in time in certain EEG frequency bands or the frequency of occurrence of burst-suppression. The effect of various anesthetic agents on time domain-derived EEG parameters have been described and claimed to be clinically useful.[61,62]

However, apart from various publications in this field, time domain EEG parameters have never been exploited on a large scale in clinical practice.

The most often used frequency domain analytical method for EEG data is the Fast Fourier Transformation (FFT). During FFT, the EEG signal is sliced into small time period of a few seconds, called epochs. The FFT analysis then results in the projection of the power spectrum versus the EEG frequency in, e.g. the 0-30 Hz range, during each epoch. The FFT in its turn gives rise to the derivation of clinically useful parameters. Two of the most studied FFT derived EEG parameters are the spectral edge and the median frequency. The spectral edge (SE_{95}) is the FFT-derived frequency below which 95% of the power spectrum in the FFT spectrum is found; the median frequency (SE_{50}) is defined as the frequency below which 50% of the power in the FFT spectrum is found. Both SE_{95} and SE_{50} decrease with increasing depth of anaesthesia and increasing blood and CNS concentrations of anaesthetic agents.

Opioid Concentrations correlates very well with the FFT derived parameters. [63,64] With increasing opioid concentration, the EEG changes from a low amplitude high frequency signal to a high amplitude low frequency signal. This results in the FFT as an increase in power at lower frequencies (0-5Hz) with a reduction of power at higher frequencies (10-30Hz) and results in a decrease of the SE_{95} and SE_{50}.

Intravenous anaesthetic agents such as propofol etomidate and methohexitone also correlate very well with frequency domain-derived EEG parameters. With propofol, the EEG amplitude shows a characteristic biphasic response to increasing blood propofol concentrations in all frequency bands.[65] Again, although claimed clinically useful, frequency

domain-derived parameters have never been used on a broader scale in clinical practice. Consequently, the search went on an resulted in the application of higher order statistical analysis of the EEG in recent years, which in the end has resulted in the introduction of the BIS monitor.

Bispectral analysis focuses on the correlation between the phases of the various wave components of which the raw EEG is built. It is a computation of the burst suppression ratio (BSR) and QUAZI, two time domain-derived parameters, the β-ratio, a frequency domain parameter defining the power in the 30-47Hz band relative to the 11-20Hz band, and lastly the SyncFastSlow parameter determined from the bispectrum peaks in the 0.5-47Hz band relative to the 40-47Hz frequency band.[66] An important feature in the calculation of the bispectral index is that the weight of any of these four subparameters in the final calculation (BSR, QUAZI, β-ratio and SyncFastSlow) changes with the level sedation. The β-ratio weighs heavier in the final computation at levels of light sedation, the SyncFastSlow parameter dominates at excitation and surgical levels of anaesthesia and the BSR and QUAZI are more important in the calculation at the most deep levels of EEG depression. The specific weight of the parameters of the BIS at various clinical states has been determined, during the development of the BIS by Aspect Medical Systems, on the basis of a dataset gathered from a group of patients that received various anaesthetics while EEG and behavioral data were collected. In practice, the BIS is determined as a running average over 15-30 seconds of EEG signal collection and visualized as a dimensionless nonlinear parameter between 0 and 100, with 0 equalling no electrical activity and 100 defining the awake state (figure 4). The BIS reflects the awake state at values exceeding 95, a state of sedation at BIS values 65-85, an arousal state depression suited for general anaesthesia at BIS values of 40-65 and burst suppression patterns become evident al BIS levels below 40.[67]

The effect of various anaesthetic agents on the BIS appears to be agent-specific. In general, anaesthetic agents such as propofol, midazolam or thiopental have a strong depressant effect on BIS. Blood propofol concentrations of 2 mg/L decrease the BIS to 60-80, propofol concentrations of 3-6 mg/L the BIS becomes 40-50 and with propofol concentrations exceeding 10 mg/L burst suppression patterns become apparent and the BIS gets close to 0.(68) Pharmacodynamic interactions between agents combined during anaesthesia also affect BIS values. Only very few data describe the effect of combinations on BIS. As already described, opioids reduce propofol requirements for induction of anaesthesia. Parallel to this observation, loss of consciousness with propofol occurs at higher BIS values when opioids are administered prior to propofol than when propofol is given as a sole agent.[69] The significance of this observation is yet unclear.

The most promising application of the BIS may be as a monitor of awake-sedation-unconsciousness levels. In the absence of CNS monitoring, anaesthetic agents are often administered on the basis of the prescribed administration regimens (12-10-8 mg/kg/h step down propofol infusion scheme) that may be adjusted to the response of the individual patient. The prescribed regimens do not take into account the pharmacokinetic of ± 70% or the pharmacokinetic variability of ± 300-400% between patients. This huge interindividual pharmacokinetic-dynamic variability, next to the sometime poor predictability of the surrogate measures of sedation and anaesthesia (e.g. hemodynamic parameters, movement responses to nociception), is the cause of frequent overdosage or underdosage of individual patients during sedation and general anaesthesia. Monitoring of the BIS allows for almost instant focusing, out of the huge inter- and intraindividual pharmacokinetic-pharmacodynamic variability, on the specific needs of the individual patient at any time.

Lastly, BIS monitoring has been incorporated in closed loop systems with a target-controlled infusion device for anaesthesia drug administration with BIS value as the control parameter. In these systems, the target-controlled infusion system thus determines the infusion rate on the basis of the difference between the measured and desired BIS value. Using this system provided safe and reliable anaesthesia, although an initial overshoot in BIS value occurred during induction of anaesthesia [70,71] as well as some oscillation around the set BIS. [72]

The use of BIS has some limitations. Some agents like nitrous oxide and ketamine, induce their effects by mechanisms that the BIS monitor is unable to track. Adding ketamine or nitrous oxide deepens the anaesthetic level but increases the BIS. In the presence of these agents, the BIS monitor should not be used. Electrocautery will make the BIS disappear or increase; pacemakers have also been described to increase the BIS. Electromyographic activity has been claimed to increase the BIS, but later versions like the XP may be less susceptible to this. Lastly, hypothermia decreases the BIS by 1.12 units per ºC decline in body temperature.

As well as articles discussing the commercially available BIS monitor, there is increasing attention in the literature on auditory evoked potentials as a parameter to track changes in the anaesthetic state. Several studies suggest that mid-latency [73] auditory evoked potentials (MLAEP) have potential to be an effective discriminator between the anaesthetised and conscious state. [74,75] These studies even suggest that the distinction between the anaesthetised and awake state is sharper, with less overlap in the ranges of conscious and unconscious values, with MLAEP derivatives than is the case with the BIS. However,

although monitoring of auditory evoked potentials has proven to be be of value for research purposes, at this moment its clinical value remains unclear.

As with the other two strategic tools, the implementation of EEG monitoring by means of the bispectral index, or perhaps in the future through monitoring the auditory evoked potentials, further enhances the ability of the anaesthesiologist to rapidly obtain information on the specific needs of the individual patient

4. Conclusion

This review provides an overview of how intravenous anaesthetic practice has changed over the past 20-30 years, from the administration of anaesthetic agents on the basis of imprecise population data in a more or less “black box” type of patient into a anaesthesia on the basis of individualised pharmacokinetic-pharmacodynamic data with advanced administration devices in a carefully monitored and more “transparent” patient. Increased pharmacokinetic-pharmacodynamic knowledge of anaesthetic agents, together novel administration and monitoring techniques has improved the level of control flexibility and the safety of anaesthetic practice.

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Propofol Reduces the Distribution and Clearance of Midazolam

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INTRODUCTION

Previously, we studied the influence of midazolam on the pharmacokinetics of propofol (1). The most important finding of that study was that midazolam increased blood propofol concentrations by 25% through a reduction in the metabolic, rapid, and slow distribution clearances of propofol. In addition, a reduction in mean arterial blood pressure was associated with propofol pharmacokinetic alterations that increased the blood propofol concentrations even further. In that study, the plasma midazolam concentration, as controlled by target-controlled infusion (TCI), was increased when administered in the presence of propofol, indicative of a possible influence of propofol on the pharmacokinetics of midazolam.

In clinical practice, midazolam is used for preoperative anxiolysis, to assure sedation during regional anesthesia and during ventilation in the intensive care unit and during prolonged procedures to induce and maintain surgical hypnosis perioperatively. In these settings, midazolam is occasionally combined with other sedatives and/or opioids to obtain the desired effect (hypnosis) and limit the side effects (hemodynamic or respiratory depression) (2-5). Various combinations of hypnotic drugs and/or opioids have been shown to exhibit both pharmacokinetic and pharmacodynamic interactions (6), often increasing the effect of the combination. (7-9)

Researchers studying the effect the propofol-midazolam interaction predominantly evaluated the pharmacodynamic interaction. (3,4,10,11) Only 1 study described the pharmacokinetic interaction between propofol and midazolam and reported that propofol affected the clearance of midazolam through a possible competitive inhibition of hepatic CYP 3A4.(8) However in that study, clearance was determined on the basis of the influence of just a 1-hour infusion of propofol on the pharmacokinetics of midazolam that was given as just a single bolus dose. Because propofol and midazolam are at times combined for prolonged periods of time, e.g., for intensive care unit sedation (10), we evaluated this interaction during prolonged infusion.

We hypothesized that prolonged infusion op propofol would affect the pharmacokinetics of midazolam and that hemodynamic factors might play a role in this pharmacokinetic interaction. Therefore, we studied the influence of a 7-hour infusion of propofol on the pharmacokinetics of midazolam and evaluated the influence of various hemodynamic variables.

MATERIALS AND METHODS

Volunteers and Study Protocol

After obtaining approval of the Medical Ethics Committee of the Leiden University Medical Centre and written informed consent, 8 healthy male volunteers, were studied. All volunteers were within 30% of ideal body weight, had no history of renal or hepatic disease standards and were not taking medication within 6 months before 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 in accordance with Leiden University Medical Centre standards.

Volunteers were studied in a randomized cross-over manner during two sessions. During the first session volunteers received a midazolam bolus dose of 0.035 to 0.05 $mg.kg^{-1}$ in 1 min followed by an infusion of 0.035 to 0.05 $mg.kg^{-1}.h^{-1}$ for 59 min (session A, control). During the second study session (session B) the volunteers received the same midazolam infusion scheme as during session A, but now in the presence of a TCI of propofol for 7 hours at a constant propofol target concentration (C_T) of 0.6 or 1.0 $\mu g.ml^{-1}$ using the Diprifusor®. The target controlled infusion of propofol was started 15 min before to the start of the midazolam administration to ensure a semi steady state concentration of propofol at the beginning of the midazolam infusion.

The 2 sessions were separated by a period of at least 2 weeks. Both the C_T (0.6 or 1.0 $\mu g.mL^{-1}$) and the order of the 2 sessions were randomized, such that in half of the volunteers the control sessions preceded the other session and half of the volunteers received a C_T of 0.6 $\mu g.mL^{-1}$ and the other half 1.0 $\mu g.mL^{-1}$. Volunteers fasted from midnight on the night before the study until the last blood sample had been collected. During the administration of propofol, they breathed 30% oxygen in air. When indicated, ventilation was assisted using a face mask to maintain the end-tidal CO_2 partial pressure at <50 mm Hg. After termination of session A and B, the subjects were monitored for another 4 h during which they could recover from residual sedation and then received a light meal before they were escorted to their homes.

Materials

The studies were performed in an operating room. An IV cannula was inserted into a large forearm vein for the infusion of propofol and midazolam and an arterial cannula was inserted into a radial artery for collection of hemodynamic data and blood samples. 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 pulsecontour methodology on the basis of the intra-arterial blood pressure curve with the LiDCOplus monitor (LiDCOgroup plc, London). The LiDCO monitor was calibrated before each experiment. For this purpose, a lithium sensor was connected to the arterial cannula. After 0.2mmol lithium was injected IV, 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 for cardiac output monitoring when compared with traditional thermodilution cardiac output monitoring for up to 8 hours after calibration (LiDCO versus thermodilution; r = 0.86).(12) 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 and saved for further analysis. All volunteers received an infusion of saline of 2 $ml.kg^{-1}.h^{-1}$ during each session.

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 (5 mL) for the determination of the plasma midazolam concentration, were taken 1, 3, 5, 10, 20, 30, 45 and 60 min after the start of the midazolam infusion, and 1, 2, 3, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after termination of the midazolam infusion. Blood samples were taken into heparinised syringes 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).(13) The intra- and interassay coefficients of variation of this method were 2.2% and 2.0 % respectively, for midazolam in plasma in the concentration range of 9.7-1120 $ng.mL^{-1}$. Midazolam assays were conducted within 12 weeks.

During session B, in addition to the sample scheme in session A, an additional arterial blood sample (3 ml) was taken every 60 minutes for determination of the whole 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.(14) The intra- and interassay coefficients of variation of this method were 4.3% and 3.7 % respectively, for propofol in blood in the concentration range of 0.06-6.8 $\mu g.mL^{-1}$. The assays of midazolam and propofol did not interfere because the fluorescence wavelengths of midazolam (217 nm) and propofol (276 nm) do not overlap. This allows a distinct and accurate estimation of the 2 drug concentrations. Measured and predicted propofol concentrations were compared using the Wilcoxon signed rank test.

Statistical Analysis

A first exploratory analysis of hemodynamic differences between sessions 1 and 2 was performed using the Wilcoxon signed rank test (SPSS version 12.5 for windows; SPSS, Chicago, IL). A probability level <0.05 was considered significant. The aim of this analysis was to explore the significance of the hemodynamic changes by propofol and limit the number of hemodynamic variables to be tested as covariate in the population pharmacokinetic analysis by 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 Φ_{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),typical (population) *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 propofol 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 Procedure for Covariates

A pharmacokinetic parameter set was determined on the basis of the plasma midazolam 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]).

To determine the influence of propofol on the 6 midazolam pharmacokinetic parameters, all 64 ($64 = 2^6$, 2 referring to the presence or absence of the covariate, 6 referring to the 6 possible pharmacokinetic parameters) possible combinations for the covariate propofol were evaluated. Propofol was treated as a time-independent covariate. The model with the lowest Akaike's Criterium (AIC) value was considered best.

The hemodynamic parameters that differed significantly between sessions A and B were evaluated as potential covariates to further improve the predictability of the midazolam pharmacokinetic parameter set. The arrhythmic mean of these hemodynamic parameters of the time periods before a blood sample was taken for plasma midazolam concentration analysis 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 midazolam with propofol as covariate included. Again, the combination with the lowest value for AIC was considered best.(15)

To assess the accuracy of the model, we calculated the weighted residual (WR) and the absolute weighted residual (AWR) for each sample.

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

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

The likelihood profile method was used to assess statistical significance of the covariate coefficients. In this method, each coefficient is fixed to a range of values at which the -2 log likelihood (-2LL) is determined (by optimizing the remaining parameters). The 2 values of each coefficient that yield an increase of 3.84 in -2LL constitute the 95% confidence intervals. Finally, internal model selection validation was performed using the bootstrap. In this approach, 1000 bootstrap data sets were subjected to analysis with a set of models and the number of time each model was

selected was counted to asses replication stability.(16) The set of models consisted of those with 1 covariate model added at a time in order of importance according to the objective function values. The final model parameter estimates were also used to obtain 95% confidence intervals (using the percentiles method).

Computer Simulations

The clinical consequences of the influence of propofol on midazolam pharmacokinetics were explored by computer simulation using the final midazolam pharmacokinetic parameter with propofol and heart rate as covariates in a 85-kg male.

Three computer simulations were performed. (1) A computer simulation exploring the influence of the blood propofol concentration of 0 or 1.5 $\mu g.mL^{-1}$ (1.5 $\mu g.mL^{-1}$ was the maximal blood propofol measured in this study) on the midazolam concentration-time profile in the presence of a stable heart rate of 63 beats/min. (2) A computer simulation to evaluate the effect of heart rate on the midazolam concentration-time relationship. For this purpose we explored the influence of a heart rate of 40 and 90 bpm on the midazolam concentration-time profile in the absence of propofol. (3) A computer simulation evaluating the influence of propofol on 50% (the context sensitive half-time) and the 80% decrement time of midazolam. For this purpose we used the final midazolam pharmacokinetic parameters in the presence of a blood propofol concentration of 0 or 1.5 $\mu g.mL^{-1}$ with a stable heart rate of 63 bpm.

RESULTS

All volunteers completed the study without adverse events. Volunteers that received propofol in addition to midazolam were sedated for a longer period of time after the ending of the study. All volunteers stayed in the hospital for 4 h after the end of the study and then were fit to leave the hospital. The mean (± SD) age, weight and height of the volunteers were 25.5 ± 5.8 yr, 85 ± 8.2 kg and 188 ± 5 cm.

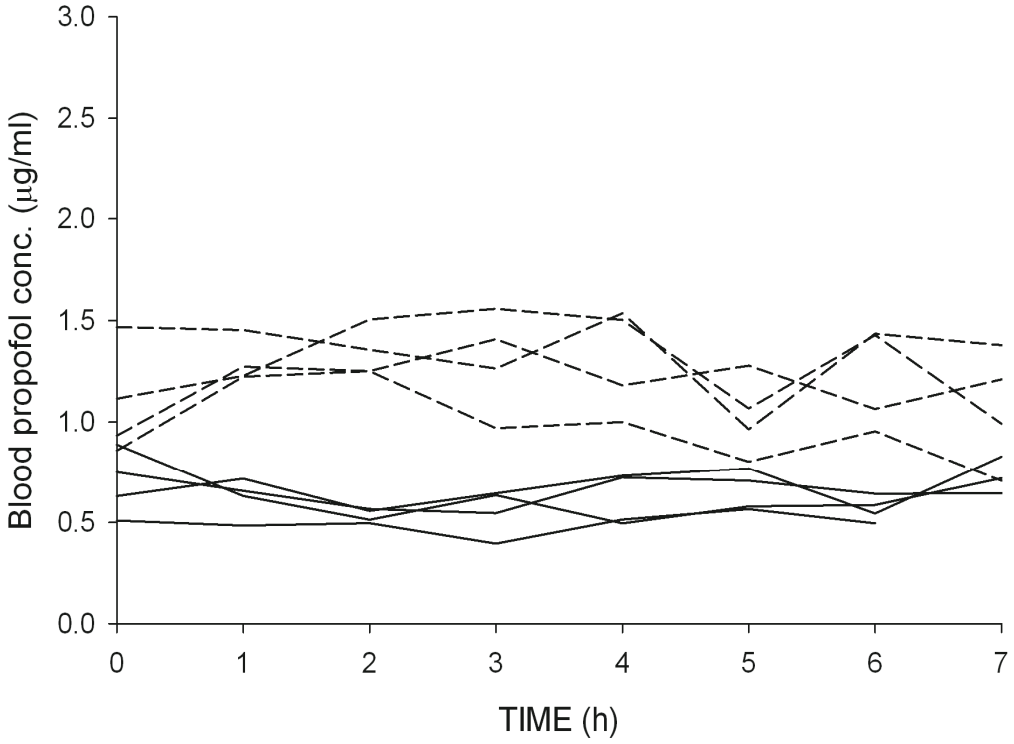

Figure 1. Blood propofol concentration-time curves of the individual subjects during session B. The continuous lines indicate subjects who received a target-controlled infusion of propofol with a target concentration of 0.6 µg/mL; the dashed lines indicate those who received a target of 1.0 µg/mL.

Blood propofol concentration analyses and plasma midazolam concentration analyses were performed within 12 weeks after the end of the study. Blood propofol concentrations were stable in each participant (fig. 1) and were similar as predicted (+2%, $P = 0.378$) in those who received a C_T of 0.6 $\mu g.mL^{-1}$ and significantly higher than predicted (+23%, $P < 0.001$) in those who received a C_T of 1.0 $\mu g.mL^{-1}$. None of the volunteers experienced significant respiratory depression and the end-tidal partial CO_2-pressure never exceeded 50 mm Hg.

During the 16 study sessions 470 blood samples were collected for both midazolam and propofol concentration determination. The analysis of the pharmacokinetics of midazolam in this study is based on 368 measured plasma midazolam concentrations. In the presence of propofol mean arterial pressure, cardiac output and stroke volume were significantly lower and heart rate higher than when midazolam was given as sole drug (table 1). Because of a power failure, hemodynamic data were lost in 1 session. Consequently the pharmacokinetic parameter sets of midazolam without covariates (the naively pooled) and with propofol as covariate are based on the concentration time data of 16 sessions, whereas those with an additional hemodynamic parameter as covariate are bases on hemodynamic data of 15 sessions.

Table 1 Median (range) Hemodynamic parameters obtained during the 420 min study in session A (without propofol) and session B (in the presence of propofol)

Parameter	Session A median (range)	Session B median (range)	Difference (%)	Significance P-value
HR (beats/min)	63.6 (42.5-79.2)	64.4 (49.1-84.0)	+1.2	0.003
MAP (mm Hg)	72.8 (60.6-91.4)	70.3 (55.7-93.0)	-3.5	<0.001
SVR (dynes.s^{-1}.cm^{-5}	664.6 (463.7-1934.6)	759.1 (524.5-1552.0)	+14.2	0.039
SV (mL/beat)	128.7 (49.8-174.4)	98.8 (69.9-170.8)	-23.0	<0.001
CO (l/min)	7.78 (3.1-11.6)	6.39 (4.1-10.2)	-17.8	<0.001

Figure 2 shows the measured plasma midazolam concentrations in the presence and absence of propofol when targeted at a target propofol concentration (C_T) of 0.6 and 1 µg.mL^{-1}, respectively. In the presence of a C_T: 0.6 µg.mL^{-1} (mean measured blood propofol concentration of 0.62 µg/mL^{-1}) and C_T 1.0 µg.mL^{-1}(mean measured blood propofol concentration of 1.2 µg.mL^{-1}) the plasma midazolam concentrations were 5.0 ± 14.7% and 26.9 ± 9.4% higher than when midazolam was given as sole drug (*P* = 0.115 and <0.001, respectively).

The addition of propofol as covariate significantly improved the pharmacokinetic model of midazolam according to the AIC (Table 2). The pharmacokinetic parameters of midazolam influenced that were influenced by propofol were V1, Cl_1 and Cl_2. With a blood propofol concentration increasing from 0 to 1.2 µg.mL^{-1}, V_1 of midazolam decreased from 5.37 to 2.98 L, Cl_1 decreased from 0.39 to 0.31 L.min^{-1} and Cl_2 from 2.77 to 2.11 L.min^{-1} (fig. 3). Various hemodynamic parameters, when included in the midazolam pharmacokinetic model, reduced the AIC and residual error (σ^2) significantly. Of these hemodynamic covariates, heart rate

contributed most according to the AIC. Midazolam pharmacokinetic parameters influenced by heart rate were V_3, Cl_1 and Cl_2 (table 2, figure 4). Figure 5 shows the results of the optimization process and displays the measured versus the predicted midazolam concentrations for the model without any covariates (Fig 5A) and the population predicted (Fig. 5B) and the individual predicted (Fig. 5C) midazolam concentrations for the model with propofol and heart rate as covariates. In figure 6, the log likelihood profiles are shown. The plots contain lines that denote a 3.84 increase in -2LL from which the 95% confidence intervals for the parameters can be read.

The bootstrap model selection validation resulted in 0%, 10.2% 25.6%, and 64.1% selection frequencies for propofol as covariate on no parameters, V_1, V_1 and Cl_1, V_1, Cl_1 and Cl_2, and 0%, 13.2%, 36.6% and 50.1% with, in addition, heart rate on no parameters, Cl_2, Cl_2 and V_3 and Cl_2 V_3 and Cl_1. The 95% confidence intervals obtained from the bootstrap and likelihood profiles were similar to those that would be obtained by the normal approximations using values and SEs from table 2.

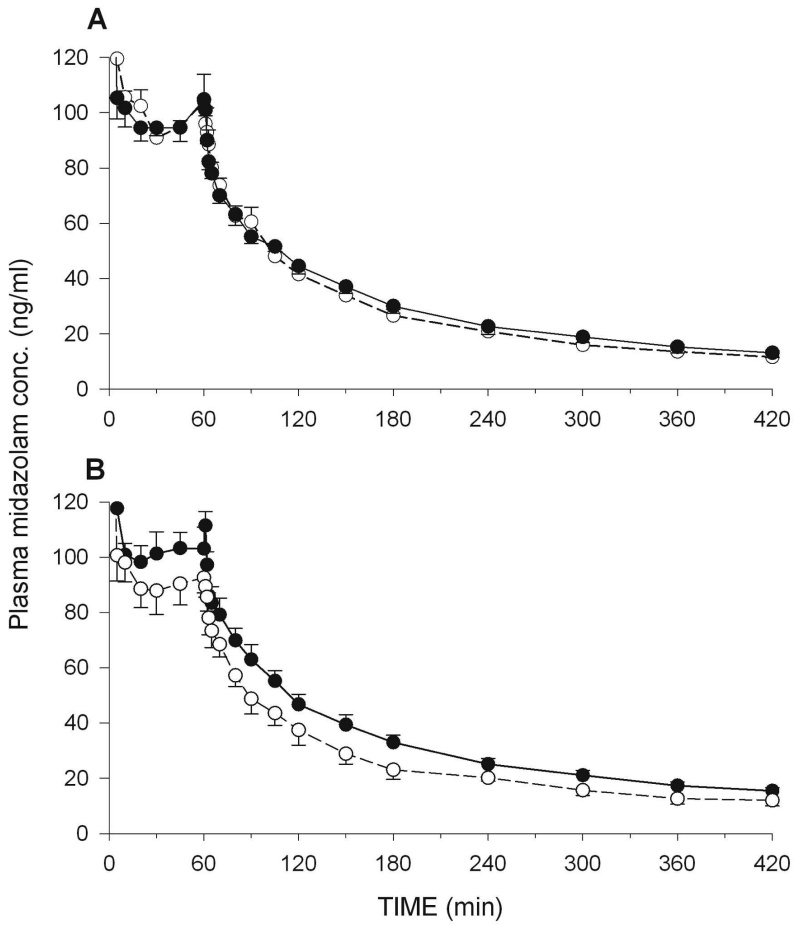

Figure 2. The mean (SE) plasma midazolam concentration-time curves in the volunteers in the presence (continuous line) or absence (dashed line) of a target controlled infusion of propofol of 0.6 $\mu g.mL^{-1}$ (A) or 1 $\mu g.mL^{-1}$ (B). The plasma midazolam concentration-time curves have been normalized to the same midazolam dosing scheme of 0.05 $mg.kg^{-1}$ in 1 minute followed by an infusion of 0.05 $mg.kg^{-1}.hr^{-1}$ for 59 minutes.

Table 2. Population Pharmacokinetic Parameters of Midazolam in the absence of any Covariates (First 3 columns), in the presence of Propofol as covariate (second 3 columns) and with Propofol and Heart Rate as covariates (last 3 columns)

	Midazolam Pharmacokinetic Parameters								
	No covariates			Propofol as covariate			Propofol and Heart Rate as covariate		
	Value	SE	CV%	Value	SE	CV%	Value	SE	CV%
Parameter									
V_1	4.03	0.35	34.5	4.03	0.26	25.3	4.28	0.30	22.9
V_2	26.9	1.12	15.7	26.9	1.14	15.8	26.2	1.13	15.4
V_3	54.2	3.65	23.2	54.1	3.61	22.4	48.6	2.85	19.0
Cl_1	0.36	0.02	17.5	0.36	0.01	14.0	0.36	0.01	12.6
Cl_2	2.90	0.18	26.4	2.90	0.19	23.4	2.49	0.16	20.1
Cl_3	0.38	0.02	14.0	0.38	0.02	14.2	0.36	0.02	11.5
Covariates									
αpropofol, V_1				-4.53×10^{-4}	1.27×10^{-4}		-4.90×10^{-4}	1.29×10^{-4} [(a)]	
αpropofol, V_2									
αpropofol, V_3									
αpropofol, Cl_1				-2.05×10^{-4}	7.69×10^{-5}		-1.88×10^{-4}	7.04×10^{-5} [(a)]	
αpropofol, Cl_2				-2.32×10^{-4}	1.43×10^{-4}		-2.27×10^{-4}	1.32×10^{-4} [(a)]	
αpropofol, Cl_2									
αpropofol, Cl_3									
αHR, V_1									
αHR, V_2									
αHR, V_3							-1.54×10^{-2}	3.50×10^{-3} [(a)]	
αHR, Cl_1							8.95×10^{-3}	6.08×10^{-3}	
αHR, Cl_2							3.10×10^{-3}	6.69×10^{-3} [(a)]	
αHR, Cl_2									
αHR, Cl_3									
Performance measures									
-2LL	1622.991			1604.449 (1495.260)			1473.541		
AIC	1648.991			1636.449 (1527.260)			1511.541		
MDWR (%)	0.62			1.55			0.98		
MDAWR (%)	10.82			10.46			9.87		
σ^2	0.00515			0.00516			0.0048		

Values in parenthesis are -2LL and AIC for 15 volunteers. Parameters V_1-Cl_3 are the parameters of an individual with median covariate values. The median covariate values are 461.697 $ng.mL^{-1}$ for propofol and 63.421 beats/min for heart rate. For example $Cl_1=0.36 \times e^{((-0.000188(C_{prop}-461.697) + (0.00895\ (HR-63.241)))}$.

HR = Heart Rate, V_1 = central volume of distribution, V_1 = 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 variations; SE = standard error of estimate; α = measure of covariate importance (when omitted the covariate is not significant); Prop = concentration of propofol; -2LL = -2 X log likelihood; AIC = -2 LL + 2P, where P is the number of nonfixed parameters; AIC = Akaike's Information-theoretic Criterion; MDWR = Median Weighted Residual; MDWAWR = Median Absolute Weighted Residual; σ^2 = relative residual error

[(a)] Significant covariate (95% confidence interval obtained from the likelihood profile does not contain 0)

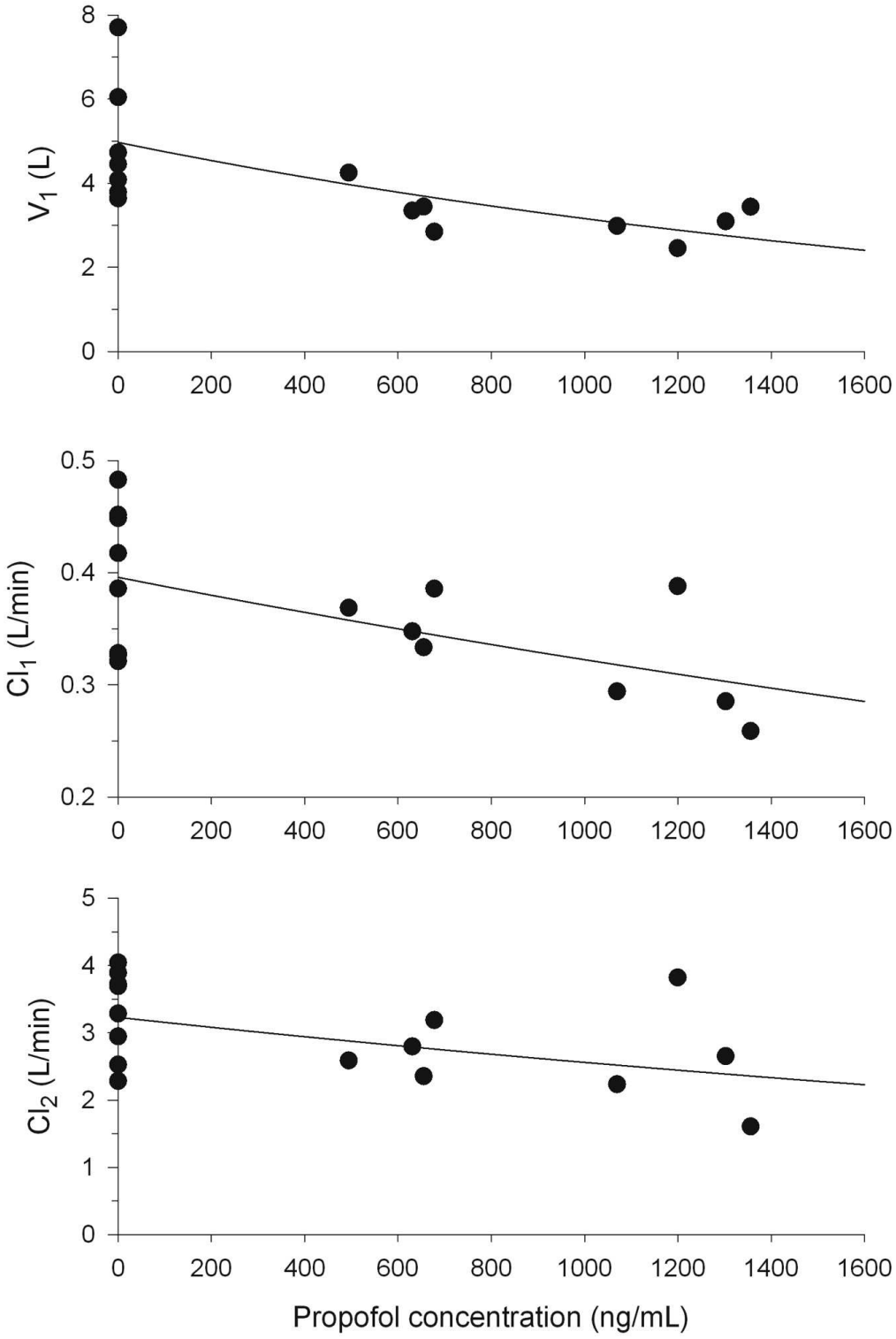

Figure 3. Individual estimates of the initial volume of distribution (V_1), elimination clearance (Cl_1), and rapid distribution clearance (Cl_2) of midazolam obtained from the model without covariates as function of the blood propofol concentration. The regression line results from the NONMEM analysis.

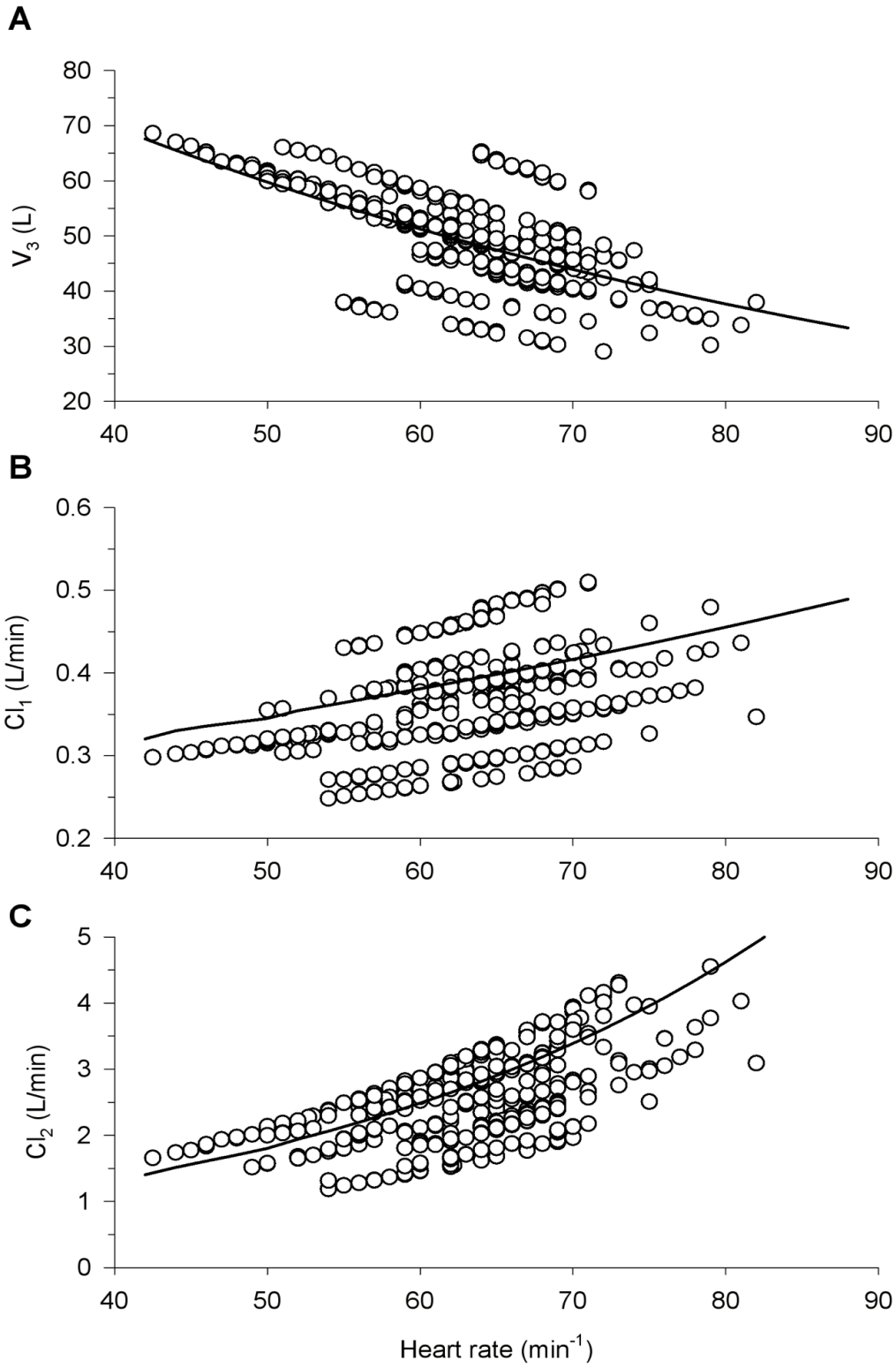

Figure 4. Individual estimates of the slowly equilibrating volume of distribution (V_3), elimination clearance (Cl_1), and the rapid distribution clearance (Cl_2) of midazolam obtained from the model without covariates as function of the heart rate. The regression line results from the NONMEM analysis.

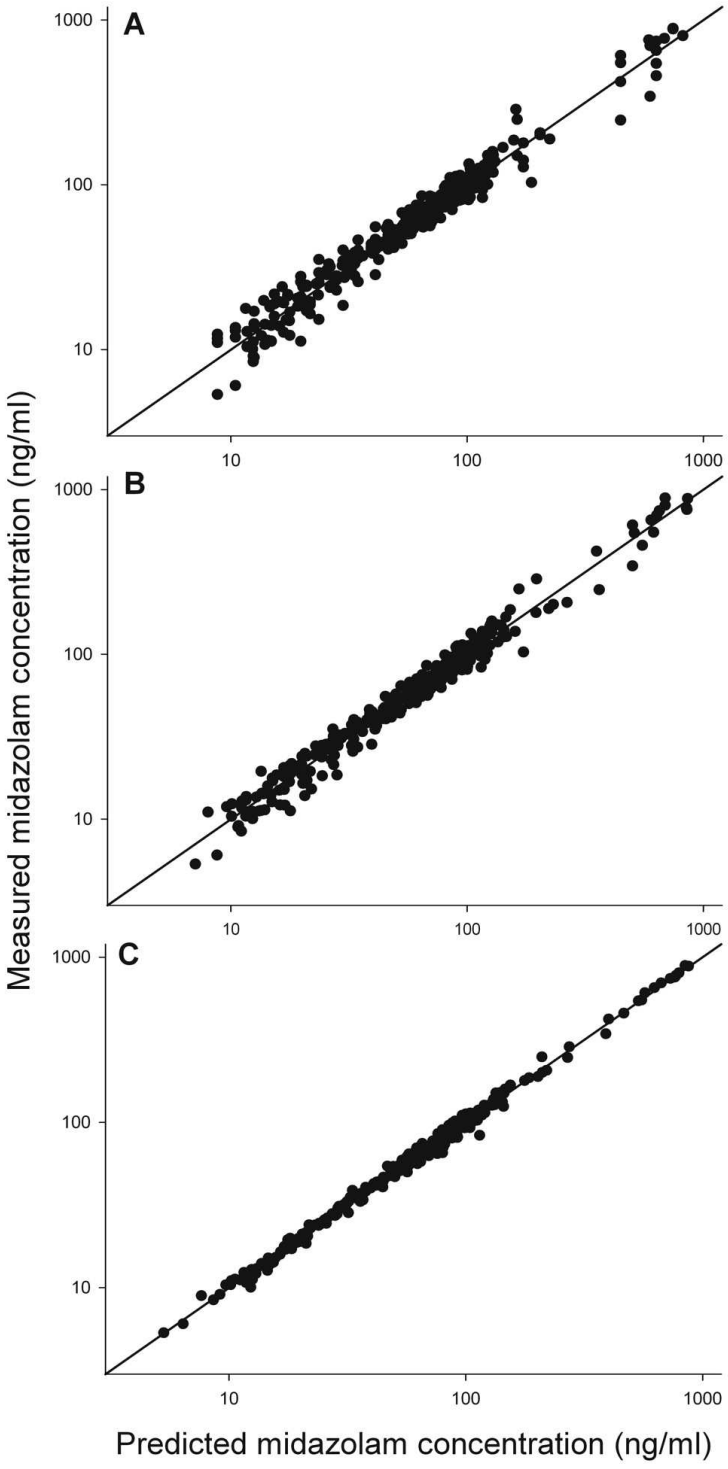

Figure 5. The measured versus the predicted midazolam concentrations for the pharmacokinetic model without covariates (A) and the population predicted (B) and the individual predicted (C) midazolam concentrations for the model with propofol and heart rate as covariates. The straight line indicates x=y

Computer Simulations

The 3 computer simulations using the final pharmacokinetic parameter set offer a clear view of the consequences of the propofol midazolam interaction on the midazolam dose-concentration relationship. (Table 3) In the presence of a blood propofol concentration of 1.5 $\mu g.mL^{-1}$, midazolam concentrations are increased (Fig.7). The simulations revealed that in the presence of propofol the bolus dose of midazolam should be reduced by 25% for short term midazolam dosing schemes to obtain a similar midazolam plasma concentration-time profile as in the absence of propofol. When midazolam is given for an infusion of several hours the simulation suggest that an additional reduction of 15% in the midazolam infusion rate is required to obtain equal midazolam concentrations in the presence of and absence of propofol.

In figure 8 the influence of heart rate on midazolam pharmacokinetics is explored. The computer simulations show that varying the heart rate from 45 to 90 bpm the predicted midazolam concentration changes to a limited degree. Heart rate affects predominantly the initial distribution of midazolam. The influence of propofol on the pharmacokinetics of midazolam furthermore becomes evident in Figure 9. The concomitant administration of propofol at a blood concentration of 1.5 $\mu g.mL^{-1}$ (the maximal measured blood propofol concentration in this study) leads to a slight increase in the CSHT and a significant lengthening of the 80% decrement time of midazolam.

Table 3. Pharmacokinetic parameters of Midazolam (based on the final Pharmacokinetic Parameter Set with Propofol and Heart Rate as covariates) for various Propofol and Heart Rate Values as used in the Computer Simulations

Propofol (µg/mL)	0	1.5	0	0
Heart Rate (min^{-1})	63	63	40	90
V_1	5.37	2.57	5.37	5.37
V_2	26.2	26.2	26.2	26.2
V_3	48.9	48.9	69.7	32.3
Cl_1	0.39	0.30	0.32	0.50
Cl_2	2.73	1.94	1.34	6.30
Cl_3	0.36	0.36	0.36	0.36

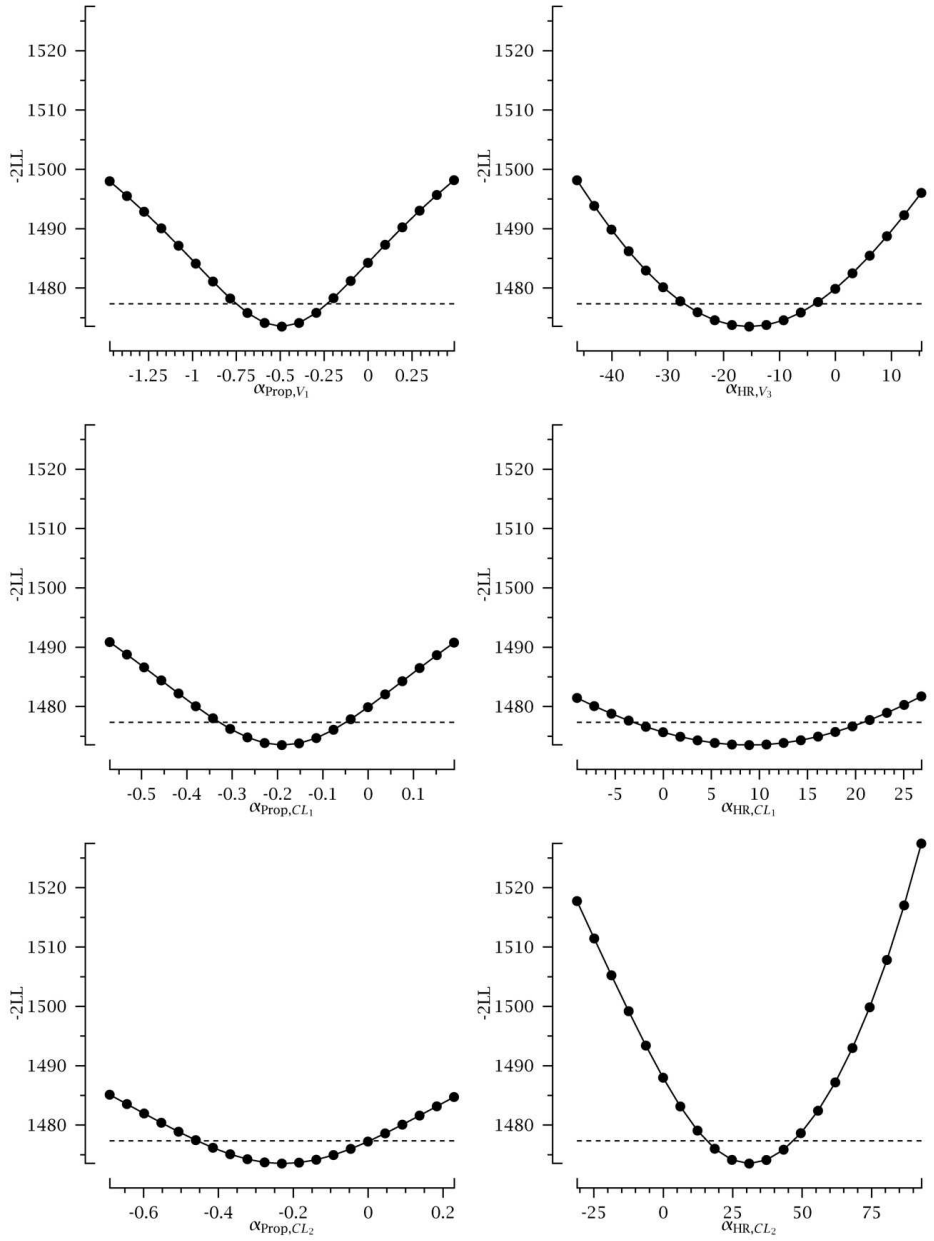

Figure 6. Likelihood profiles for the 6 covariate coefficients of the final model. The plots contain lines that denote a 3.84 increase in -2 log likelihood (-2LL) from which the 95% confidence intervals for the parameters can be read. The values for the x-axes have been multiplied with a value of 1000 for clarity.

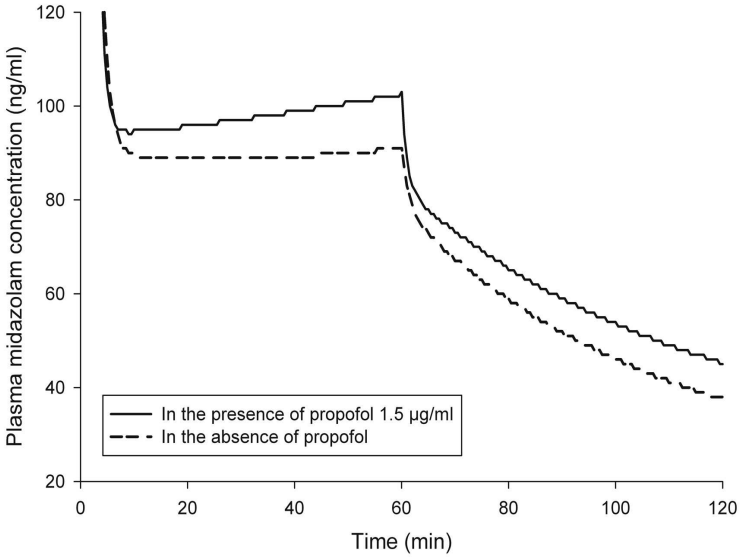

Figure 7. The concentration-time profile of a simulated midazolam infusion scheme (0.05 $mg.kg^{-1}$ in 1 minute followed by a continuous infusion of 0.05 $mg.kg^{-1}.hr^{-1}$for 59 minutes) in the presence of a blood concentration of 0 and 1.5 $\mu g.mL^{-1}$, with a steady heart rate of 63 bpm.

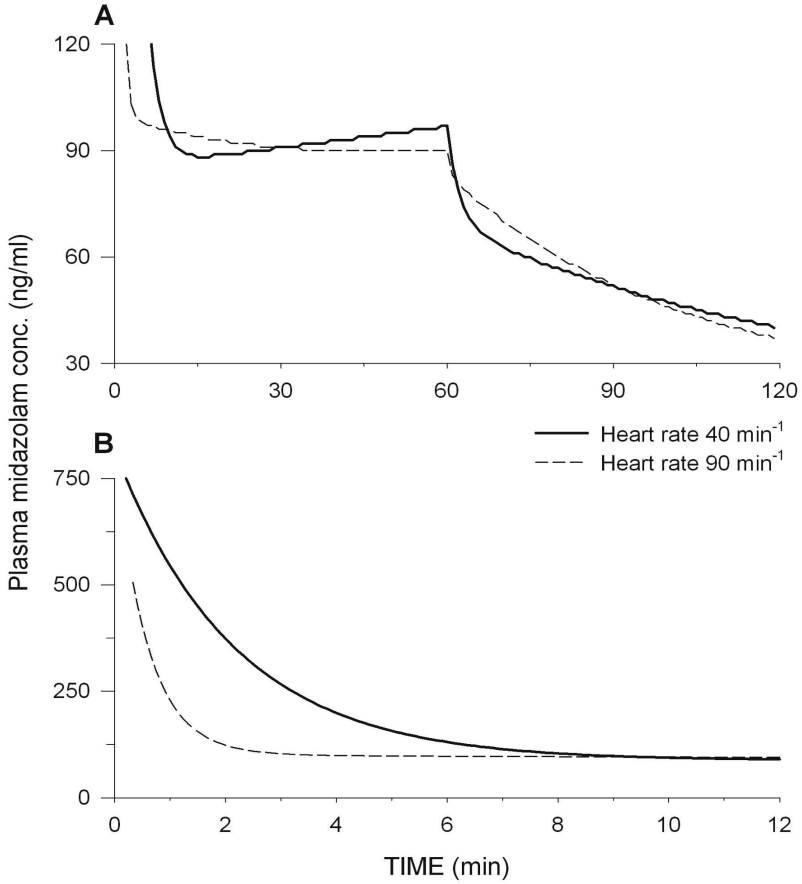

Figure 8. The concentration-time profile of a simulated midazolam scheme (0.05 $mg.kg^{-1}$ in 1 minute followed by a continuous infusion of 0.05 $mg.kg^{-1}.hr^{-1}$for 59 minutes) in the presence of a heart rate of 40 and 90 bpm, with a constant blood propofol concentration of 1.2$\mu g.mL^{-1}$. Simulation for the time span of 120 minutes (A) and for the initial 12-minute time period (B).

DISCUSSION

We studied the influence of propofol on the pharmacokinetics of midazolam. We hypothesized that propofol would alter the pharmacokinetics of midazolam. The results of this study confirmed our hypothesis. The most important finding of this study is that propofol (C_{blood}: 1.2 $\mu g.mL^{-1}$) increased midazolam concentrations by 26.9%. In the presence of propofol midazolam is administered in a smaller central compartment from which midazolam is cleared and distributed less rapidly to peripheral tissues.

Next to the primary findings of this study, we identified heart rate as the hemodynamic parameter that further improved the pharmacokinetic dataset of midazolam. Although heart rate improved the pharmacokinetic model of midazolam (as based on the AIC), computer simulations revealed this effect to be of limited clinical importance.

Interaction Mechanisms

The pharmacokinetic parameter set of midazolam without covariates described in this study corresponds well with midazolam pharmacokinetic parameter sets in the literature.(17-20) Our pharmacokinetic parameter set corresponds most closely with that by Buhrer et al.(18) probably because of similarities in the study design and the population studied, with comparable midazolam dose regimen.

Midazolam, with its metabolism mainly through cytochrome 3A3, 3A4 and 3A5, (21-23) is subject to numerous pharmacokinetic interactions on the basis of enzyme inhibition or induction in the liver and possibly the kidneys (24-26) The concentration shifts caused by these CYP 450 interactions that affect the clearance of midazolam are huge (up to 1000%), but in practice these interactions occur infrequently. (27) The interactions between anaesthetic drugs, however, occur more frequently, even daily, but induce concentration shifts that are less significant. (8,26)

In general, interactions between anaesthetic agents lead to an increase in the concentrations of the drugs combined. For example, alfentanil has been shown to increase blood propofol concentrations through a decrease in the elimination clearance and distribution clearance of propofol.(28) Propofol has been shown to increase alfentanil concentrations by decreasing the elimination clearance, rapid and slow distribution clearances of alfentanil.(29) Co-administration of propofol increased remifentanil concentrations through both a decrease in the central volume of distribution and distributional clearance of remifentanil by 41% and elimination clearance by 15%.(30)

The results of our study follow the above described patterns such that in the presence of propofol (C_{blood}: 1.2 $\mu g.mL^{-1}$), plasma midazolam concentrations were increased (26.9%). Both hemodynamic and enzymatic factors may be responsible for this interaction.

In contrast, to propofol that is known for its high hepatic extraction ratio (>0.9),(31) midazolam is a drug with an intermediate extraction ratio of 0.55(23). Therefore, the

clearance of midazolam may be affected by changes in hepatic blood flow, free fraction, and intrinsic hepatic enzyme activity. Propofol is generally known for its hemodynamic depressant effects an may reduce hepatic blood flow(32). In addition, in our study, the mean arterial pressure, stroke volume, and cardiac output were reduced in the presence of propofol (Table 1). This suggests that, at least to some extent, the reduction in clearance described in this study (Cl_1 from 0.40 to 0.31 $L.min^{-1}$ -20%) may be caused by a propofol induced reduction in hepatic blood flow.

In addition, propofol is known as a CYP450 3A4 inhibitor (33). In contrast to enzyme induction that may take several weeks to develop, competitive inhibition of CYP activity may occur almost instantaneously because of the competition of two drugs (e.g. propofol and midazolam) for the enzyme's active site. A short-term exposure to propofol at blood concentrations of 3 $\mu g.mL^{-1}$ reduced the CYP 3A4 activity by approximately 37%.(8) Therefore we conclude that the propofol induced reduction in the metabolic clearance of midazolam likely is the result of both the hemodynamic depressant and enzymatic inhibitory effects of propofol.

In addition to the propofol related reduction in midazolam clearance, hemodynamic alterations induced by propofol also influence the distribution pharmacokinetics of midazolam. Next to the influence of heart rate on the initial distribution, the hemodynamic-depressant effects of propofol are also responsible for the reduced transfer of midazolam to the peripheral tissues by reduction in Cl_2 by 44.5% from 2.77 $L.min^{-1}$ to 2.11 $L.min^{-1}$ in the controls. From table 1, the difference in heart rate between sessions A and B seems obscure and only significantly different between sessions because of the power of paired testing. Nevertheless, the addition of heart rate significantly reduced AIC (Δ-AIC, Table 2) the residual error (σ^2, Table 2) and the interindividual variability (CV%, Table 2)

Observation of the raw heart data and the residual errors in each individual finally taught us that this apparent discrepancy is explained by the fact that heart rate does not so much reduce the interindividual variability or the variability between sessions A and B but minimizes variability within each individual.

Finally model selection stability as assessed by the bootstrap showed that the replication stability was robust; in other words, the final models presented have a higher probability of being selected than simpler ones. The 95% confidence intervals as derived from the log likelihood profiles (Fig. 6) for the covariate effect on propofol on Cl_2 and heart rate on Cl_1, included 0. Although these covariate effects did not attain statistical significance, inclusion of those effects may be still of importance for prediction because they were selected by AIC. This is in agreement with the arguments for predictor selection as described by Steyerberg. (34)

In conclusion when midazolam and propofol are combined, (3-5,35) propofol increases the midazolam concentrations by a reduction in the central volume of distribution and the

metabolic and rapid distribution clearances of midazolam in a concentration dependent manner. Inclusion heart rate significantly improved the predictive performance of the midazolam pharmacokinetic model affecting the initial distribution of midazolam and reducing the intraindividual variability. The propofol-midazolam pharmacokinetic interaction allows for a 25% reduction of the midazolam bolus dose during short-term combined administration (2-3 hours). Although the influence of midazolam on propofol pharmacokinetics is predominantly by hemodynamic alterations (1), the results of this study suggest that propofol affects midazolam pharmacokinetics both through enzyme inhibition and hemodynamic alterations.

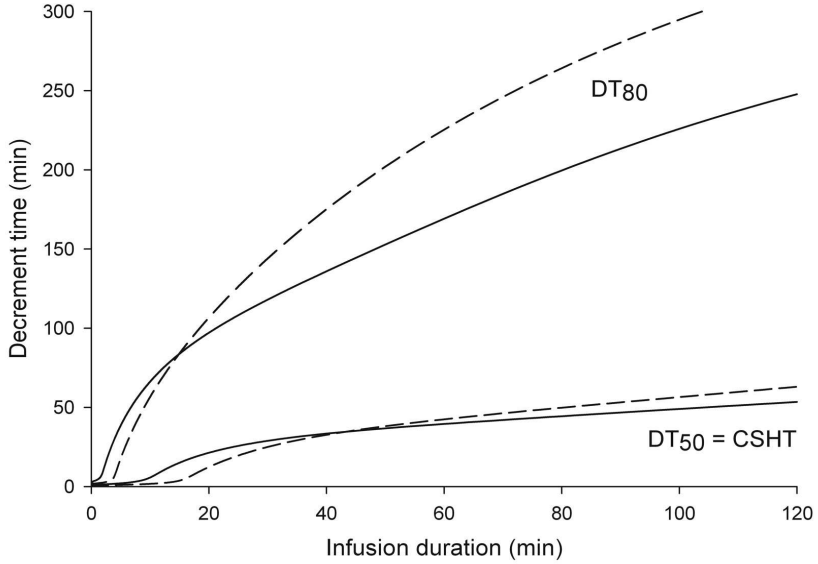

Figure 9. Context sensitive half-time (CSHT = 50 decrement time) and 80% decrement time of midazolam in the absence (continuous line) and in the presence of a blood propofol concentration of 1.5 µg.mL^{-1} (dashed lines), using the final midazolam pharmacokinetic data set in the presence of a blood propofol concentration of 0 or 1.5 µg.mL^{-1} with a stable heart rate of 63 bpm.

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Low Bispectral Index Values in Awake Volunteers Receiving a Combination of Propofol and Midazolam

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Introduction

The Bispectral index (BIS) is increasingly used to monitor the level of unconsciousness during surgical anaesthesia and consciousness sedation.[1] Generally, an intraoperative BIS of 40-60 is considered sufficient to maintain adequate hypnosis for surgery. [2, 3] Recently, a new version of the BIS® monitor has been introduced: the BIS-XP® (Aspect Medical Systems, Newton, MA). The BIS-XP® is said to exhibit improved resistance to artifacts form electrocautery devices and to detect and filter interference from electromyographic activity and other conditions commonly encountered during monitored anesthesia care sedation that may cause artifacts.

We report three cases in which volunteers receiving combinations of propofol and midazolam as a part of a pharmacokinetic-dynamic interaction study remained responsive to verbal command, although the BIS-XP values were at, or just above 40.

CASE REPORTS;

With the approval of the Leiden University Medical Center ethics committee and informed consent from the subjects, a study on the pharmacokinetic-dynamic interaction between propofol and midazolam at varying concentration combinations was performed. For each subject, the electroencephalogram was recorded continuously using the BIS® Quatro sensor (Aspect Medical Systems), placed as prescribed on the left side of the skull and connected to the BIS-XP®. For all subjects, the impedance was low (on the order of 2–4 kΩ), and the signal quality index was high (0–100; well above 50) at the times of sedation assessments. The processed electroencephalogram variables were stored on a disk for off-line analysis. In addition, the electrocardiogram, transcutaneous arterial oxygen saturation, end-tidal carbon dioxide concentration, respiratory rate, and arterial blood pressure were monitored continuously throughout the study.

The volunteers breathed spontaneously through a mask with an inspiratory oxygen fraction of 40%. All three volunteers maintained adequate spontaneous respiration and were hemodynamically stable throughout the study. After a 10-min baseline recording period, a target-controlled infusion of propofol was started using the Diprifusor® (AstraZeneca, Macclesfield, United Kingdom) with maintenance of a constant target propofol concentration for 435 min. Fifteen minutes after the start of the target-controlled infusion of propofol, midazolam was given as a rapid infusion for 1 min, followed by a slower continuous infusion for 59 min. At regular intervals, when blood samples were taken from the arterial line for analysis of blood midazolam and propofol concentrations, the level of sedation was assessed by verbal command and/or mild prodding.

Case 1

The first subject was a 27-yr-old man who weighed 85 kg and was 185 cm tall. The target propofol concentration for this subject was 0.6 μg/ml, and the initial and secondary midazolam infusion rates were 0.05 mg · kg^{-1} · min^{-1} and 0.05 mg · kg^{-1} · h^{-1}, respectively (total midazolam dose in 60 min, 8.5 mg). For the awake volunteer, the BIS exceeded 95 in the absence of any medication. Then, with the target propofol concentration of 0.6 μg/ml, the BIS was maintained at 97 after blood-effect site equilibration (fig 1).Thereafter, during the first 40 min after the start of the midazolam administration, the BIS decreased to ≈ 60 during unstimulated periods and increased to 98 after verbal stimulation. Forty minutes after the start of the midazolam infusion, the BIS gradually decreased further to 40 at the end of the midazolam infusion. Unexpectedly, throughout the study period the volunteer remained responsive to verbal commands and/or mild prodding at the shoulder to a degree equivalent to an Observer's Assessment of Alertness/Sedation score between 2 and 4, even at BIS levels of 40–45.

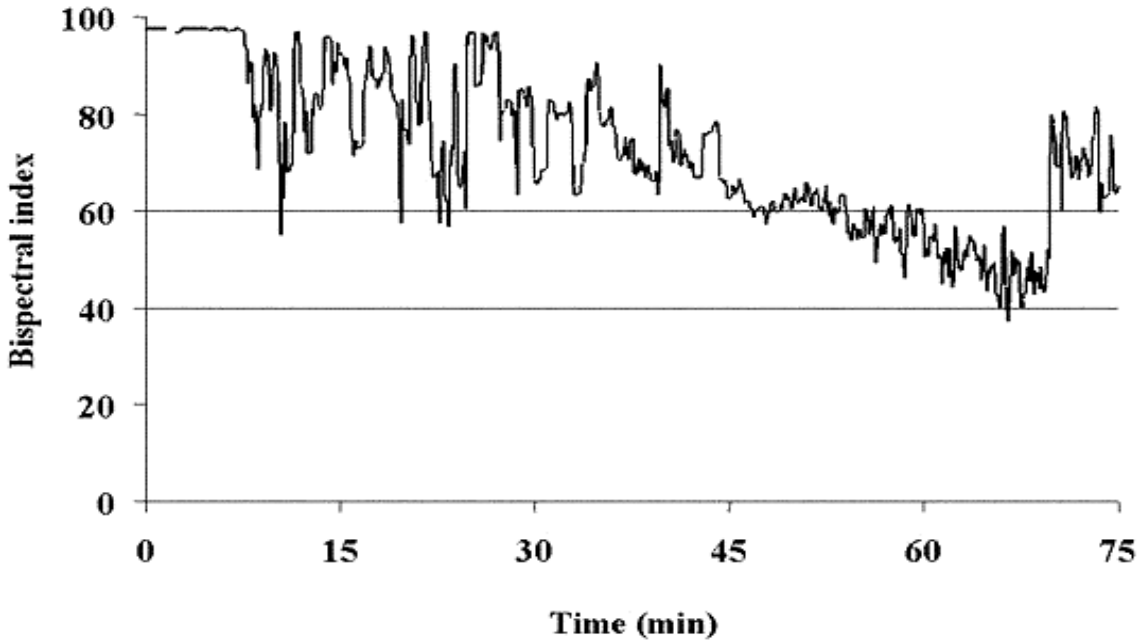

Fig 1. The Bispectral Index (BIS) versus time in case 1. Time 0-5 min displays the last 5 min (*i.e.,* the time after blodd-effect site equilibration) of the 15 min period, when only propofol was given by a target concentration of 0.6 μg/ml. At time 5 midazolam was added at 0.05mg.kg^{-1} for 1 min followed by a continuous infusion of 0.05mg.kg^{-1}.h^{-1} for 59 minutes. All three volunteers maintained adequate spontaneous respiration and hemodynamic stability throughout the study period. At time 65 min, the midazolam infusion was terminated, but the target-controlled infusion of propofol was still continued. The area considered to be associated with adequate hypnosis for surgery (BIS 40-60) is shown within the gridlines. The volunteer was responsive to verbal command and/or mild prodding at all times.

Case 2

The second subject was a 25-yr-old man who weighed 100 kg and was 195 cm tall. The target propofol concentration for this subject was also 0.6 μg/ml, and the initial and secondary midazolam infusion rates were 0.05 $mg.kg^{-1}.min^{-1}$ and 0.05 $mg.kg^{-1}.h^{-1}$, respectively (total midazolam dose in 60 min, 10 mg). For the awake volunteer, the BIS exceeded 95 in the absence of any medication. Then, with propofol at a target concentration of 0.6 μg/ml, the BIS was maintained at 97 after blood-effect site equilibration (fig 2.) Thereafter, within 3 min after the start of the midazolam administration, the BIS decreased to 67 and gradually decreased further to as low as 40 at the end of, and just after termination of, the midazolam infusion. Again, throughout the study period the volunteer remained responsive to verbal commands and/or mild prodding at the shoulder to a degree equivalent to an Observer's Assessment of Alertness/Sedation score between 2 and 4, even at BIS levels of 40–45. We then decided to monitor the next volunteer even more closely and to record the next session on videotape.

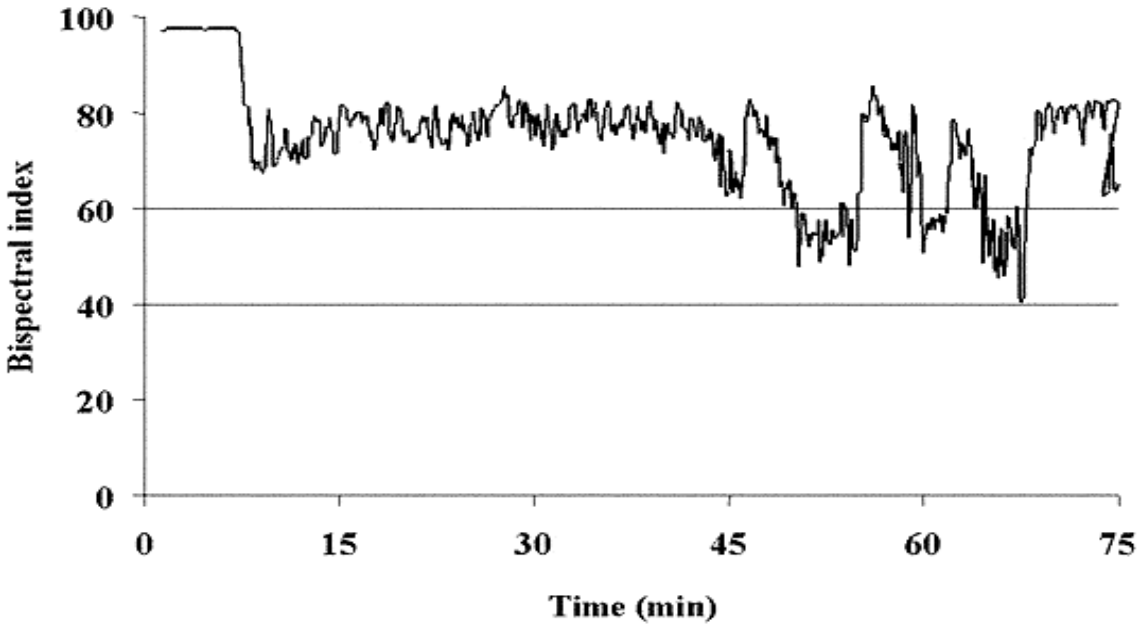

Fig 2. The Bispectral Index (BIS) versus time in case 2. Time 0-5 min displays the last 5 min (*i.e.,* the time after blodd-effect site equilibration) of the 15 min period, when only propofol was given by a target concentration of 0.6 μg/ml. At time 5 midazolam was added at $0.05mg.kg^{-1}$ for 1 min followed by a continuous infusion of $0.05mg.kg^{-1}.h^{-1}$ for 59 minutes. All three volunteers maintained adequate spontaneous respiration and hemodynamic stability throughout the study period. At time 65 min, the midazolam infusion was terminated, but the target-controlled infusion of propofol was still continued. The area considered to be associated with adequate hypnosis for surgery (BIS 40-60) is shown within the gridlines. The volunteer was responsive to verbal command and/or mild prodding at all times.

Case 3

The third subject was a 25-yr-old man who weighed 87 kg and was 187 cm tall. The target propofol concentration for this subject was 1 µg/ml, and the initial and secondary midazolam infusion rates were 0.035 $mg.kg^{-1}.min^{-1}$ and 0.035 $mg.kg^{-1}.h^{-1}$, respectively (total midazolam dose in 60 min, 6 mg). With written informed consent and Leiden University Medical Center Ethics Committee approval, we gathered digital video data from this session until the termination of the midazolam infusion. For the awake volunteer, the average BIS was 96 in the absence of any medication. With a target-controlled infusion of propofol of 1 µg/ml, the BIS decreased to a mean level of 92 after blood-effect site equilibration (fig 3) Then, within 3 min after the start of midazolam administration, the BIS decreased to values as low as 44. During midazolam administration, the BIS varied between 40 and 60. Again, throughout the study period the volunteer remained responsive to verbal commands and/or mild prodding to a degree equivalent to an Observer's Assessment of Alertness/Sedation score between 2 and 4, even with BIS levels of 40–45. The videotape, displayed as a Web enhancement, furthermore provides data on the responsiveness of this volunteer at low BIS levels.

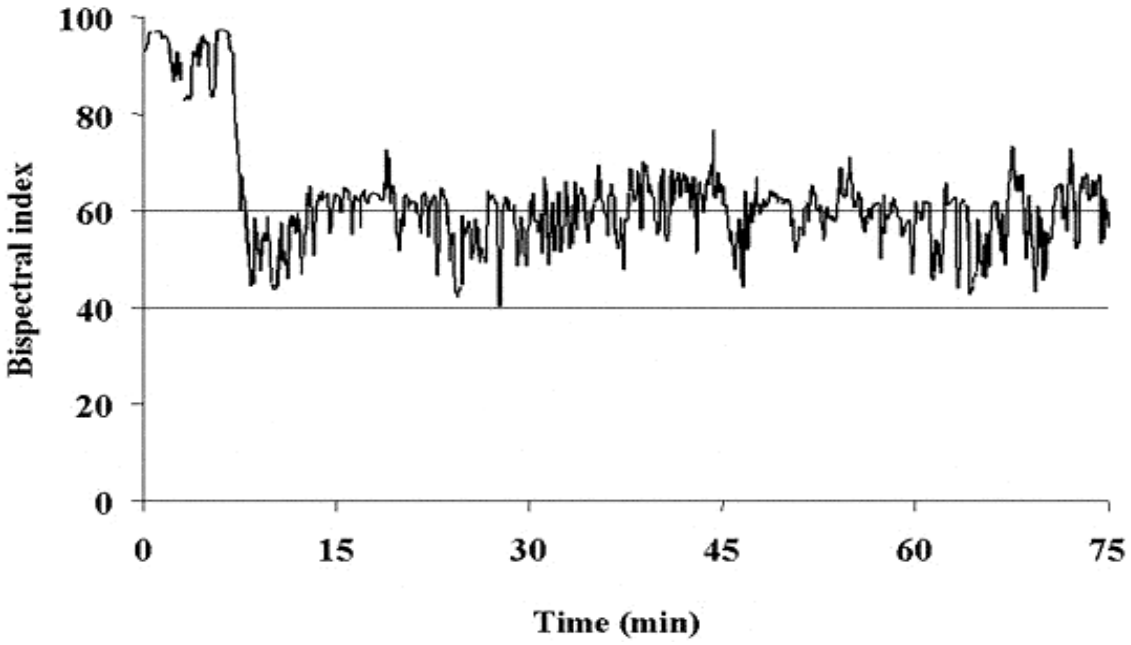

Fig 3. The Bispectral Index (BIS) versus time in case 3. Time 0-5 min displays the last 5 min (*i.e.,* the time after blood-effect site equilibration) of the 15 min period, when only propofol was given by a target concentration of 1 µg/ml. At time 5 midazolam was added at 0.035$mg.kg^{-1}$ for 1 min followed by a continuous infusion of 0.035$mg.kg^{-1}.h^{-1}$ for 59 minutes. All three volunteers maintained adequate spontaneous respiration and hemodynamic stability throughout the study period. At time 65 min, the midazolam infusion was terminated, but the target-controlled infusion of propofol was still continued. The area considered to be associated with adequate hypnosis for surgery (BIS 40-60) is shown within the gridlines. The volunteer was responsive to verbal command and/or mild prodding at all times.

Discussion

We describe three cases in which the BIS-XP® provided BIS values of 40–50 for volunteers who were responsive to verbal commands while receiving a combination of propofol and midazolam. In our hospital, we tend to administer propofol infusion regimens during propofol-opioid anesthesia on the basis of the BIS level. Based on the current literature, we advise our residents to maintain the BIS level between 40 and 60 intraoperatively[2]. Most of our patients receive midazolam for premedication. The observations described herein therefore raise various questions that are relevant to our daily clinical practice.

Two issues must be considered when interpreting our observations in relation to data from the current literature. First, most data in the literature were determined using earlier versions of the BIS® monitor. Second, few data exist from careful evaluation of the effect of combinations of agents on the BIS.

Regarding the first issue, it may well be that the BIS-XP® provides lower BIS values than previous versions at similar hypnotic levels in similar subjects. As stated earlier, the BIS-XP® is claimed to be less sensitive to artifacts of the electromyographic activity than earlier versions of the BIS® monitor[4]. Previously, it was reported that electromyographic activity falsely elevates the BIS. Introducing a version that is less sensitive to this may thus result in lower BIS levels in the absence of full muscle relaxation (as occurs in most patients).

Regarding the second issue, we note that the electroencephalographic activation induced by both propofol and midazolam has been difficult to interpret and model in the past[56]. It may well be that the particular combination of propofol and midazolam at these low concentrations is not part of the BIS-behavioral database on which the BIS calculation is based. As a result, the electroencephalographic pattern induced by this combination may well be misinterpreted by the BIS® monitor as an electroencephalographic pattern associated with a patient experiencing a surgical hypnotic sedation level instead of actually being responsive to verbal commands. However, to our knowledge, no controlled studies have been done to examine hypnotic drug interactions and their effect on BIS, especially not using the BIS-XP®.

In conclusion, we report on the responsiveness of three volunteers with BIS-XP® values of 40–50 while receiving a combination of propofol and midazolam. The case reports draw attention to the relationship between the BIS and the responsiveness of patients as derived by the BIS-XP® in the presence of a combination of two hypnotic agents. The BIS user should be aware that the BIS is a measure of drug effect, not an independent measure of brain function. Consequently, the clinical anesthesiologist has no guarantee that a particular BIS will relate to the desired effect when a particular drug, or combination of drugs, is not part of the data file used to train the algorithm of the BIS calculation. As such, the case reports stress the need for further investigation of both the BIS-XP® itself and the effect of combinations of hypnotic agents on the BIS-XP®. Furthermore, the case reports stress the

need for careful interpretation by the anesthesiologist of the BIS-XP® values in the clinical setting as long as the scientific basis for the clinical application of the BIS-XP® is not yet completely clear.

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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.

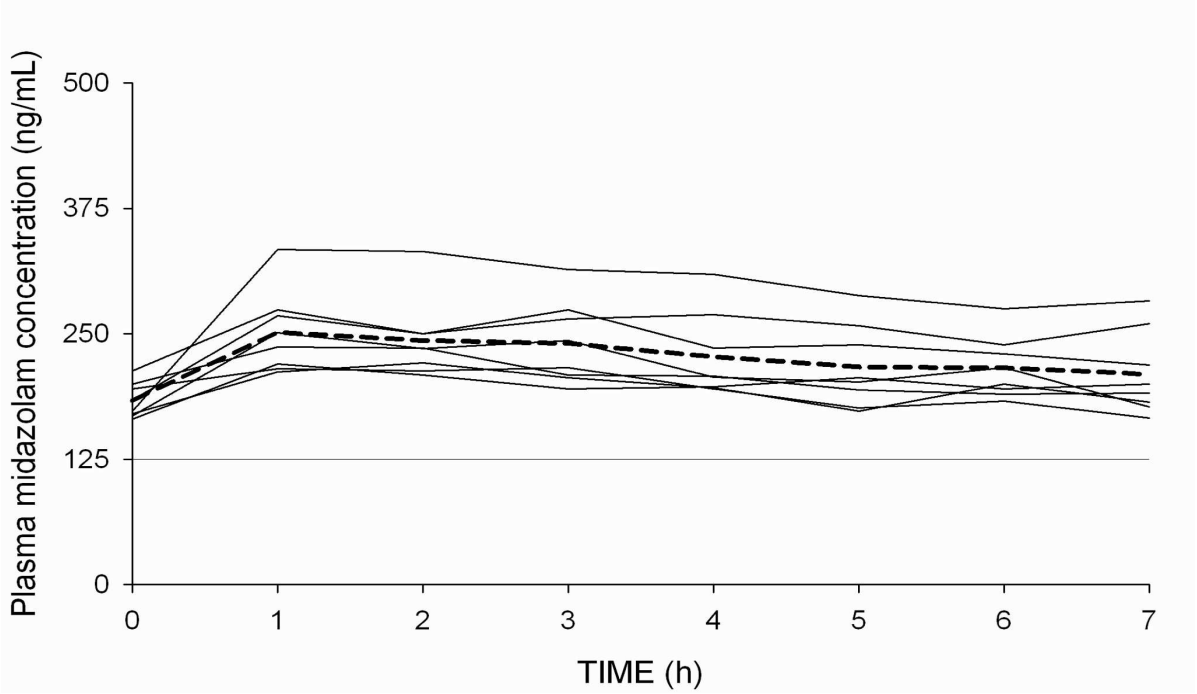

Figure1. Plasma Midazolam Concentration-time data of the individual subjects during session B when midazolam was given at a constant target midazolam of 125 ng/mL.

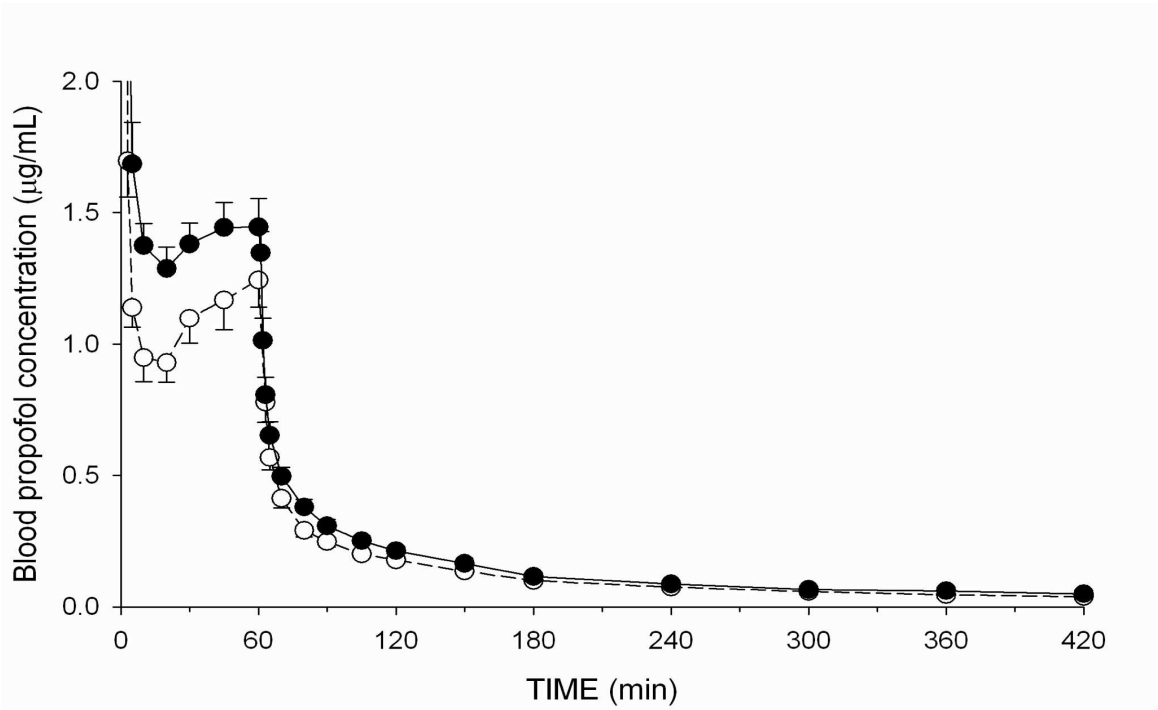

Figure 2. Mean (SE) blood propofol concentration-time curves in the volunteers in the presence (continuous line, closed circles) or absence (discontinuous lines, open circles) of a target-controlled infusion of midazolam with a target concentration of 125 ng/ml

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.

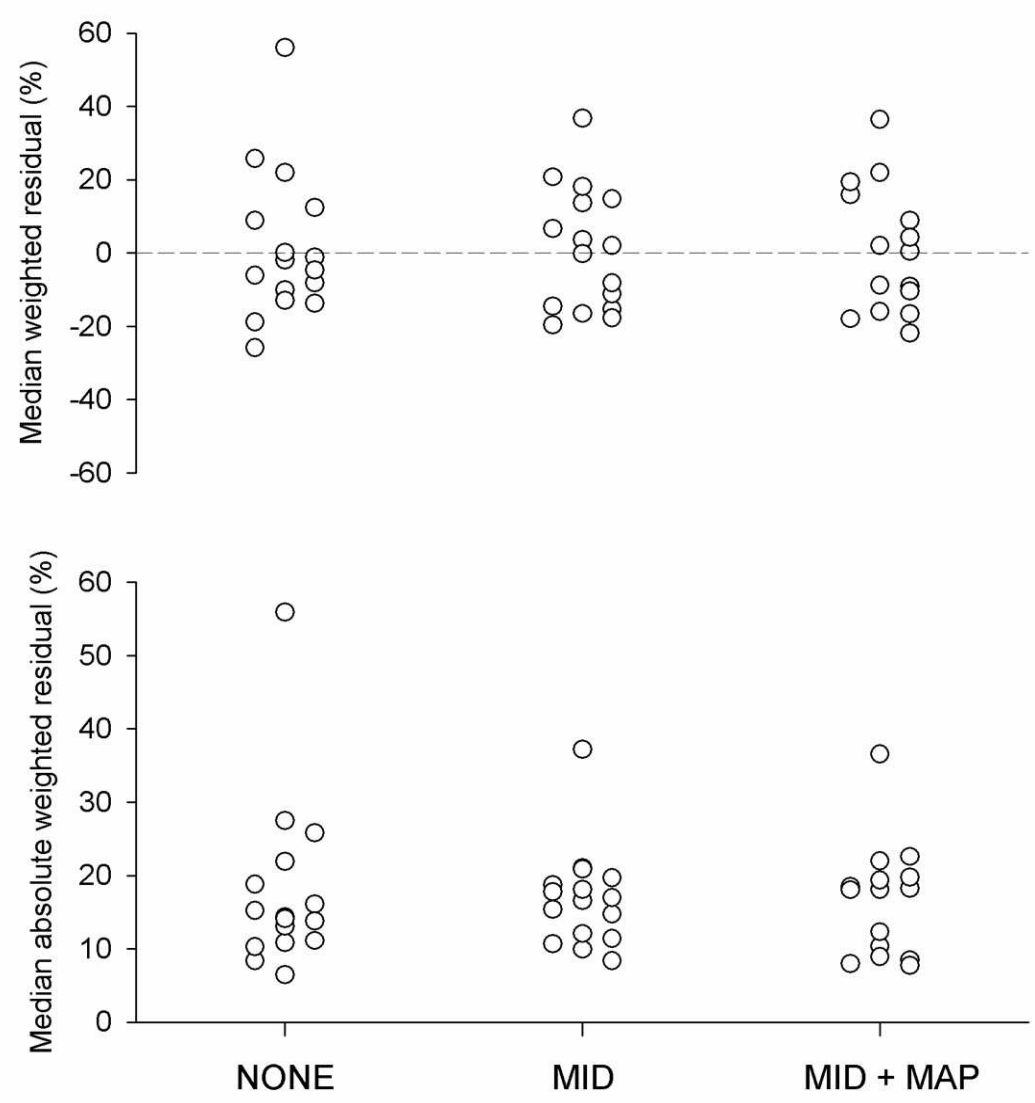

Figure 3. Population median weighted residuals (MDWR) and median absolute weighted residuals (MDAWR) (lower panel) determined for the pharmacokinetic models displayed in Table 2.

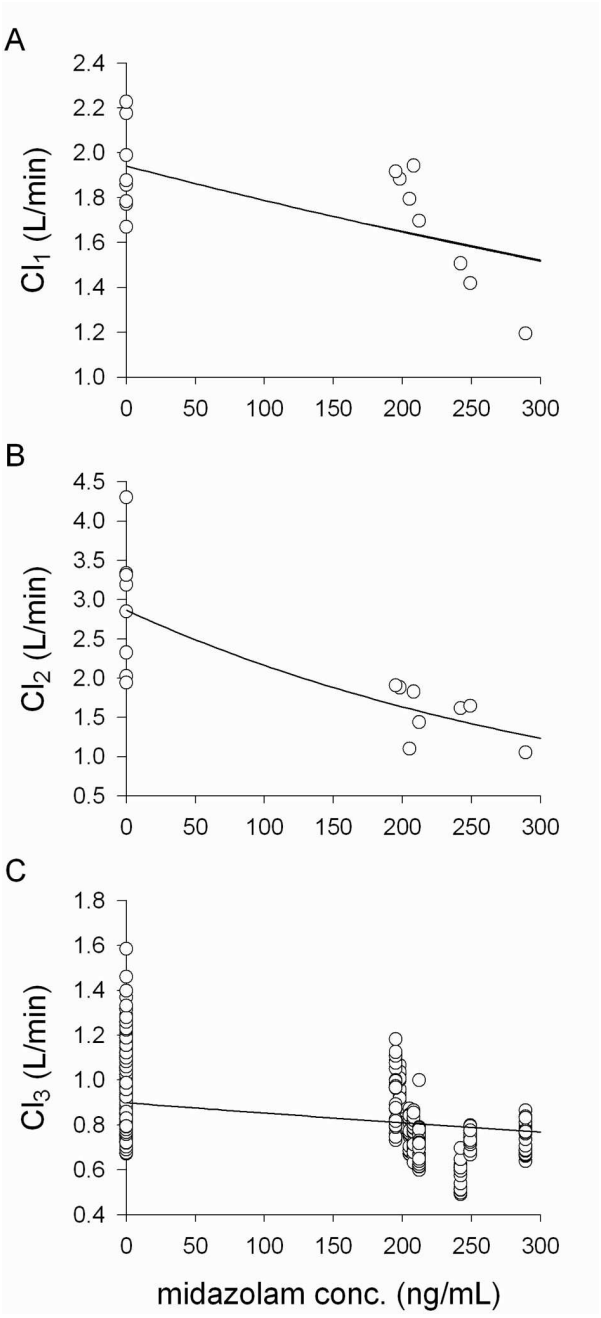

Figure 4. Individual estimates of (A) the elimination clearance (CL_1), (B) rapid distribution clearance (CL_2) and (C) slow distribution clearance (CL_3), obtained from the model without covariates as function of the plasma midazolam concentration. The regression line results from the NONMEM analysis.

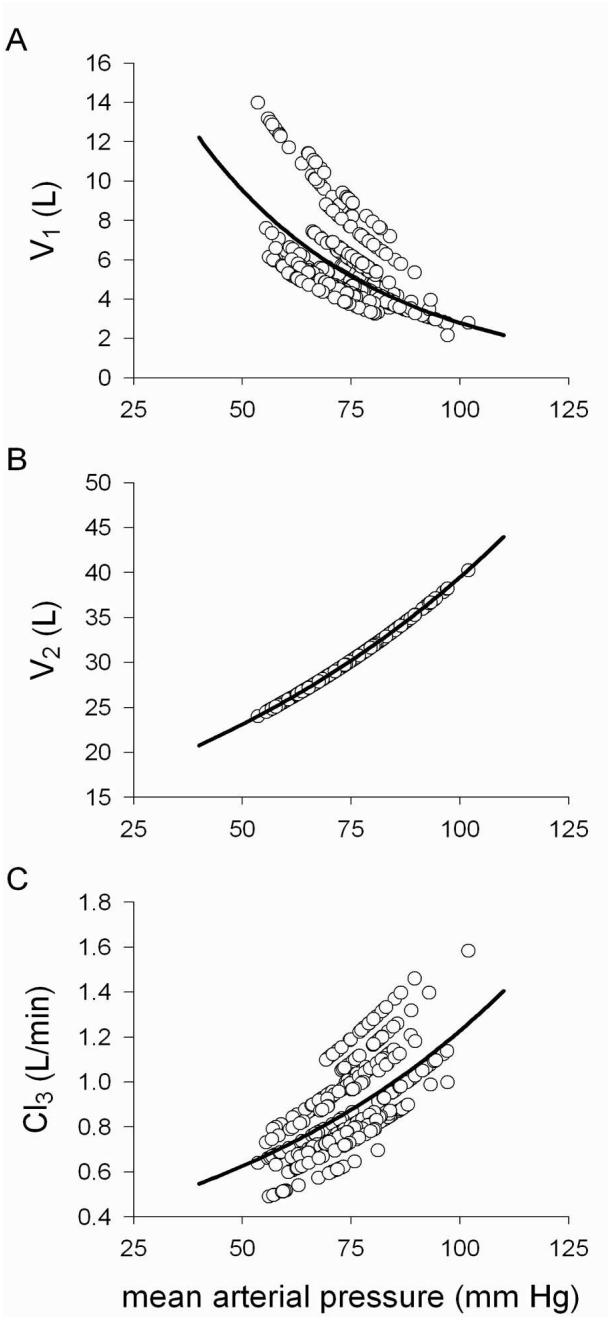

Figure 5. Individual estimates of (A) the central volume of distribution (V_1), (B) rapidly equilibrating peripheral volume of distribution (V_2), and (C) slow distribution clearance (CL_3), obtained from the model without covariates as function of the MAP. The regression line results from the NONMEM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

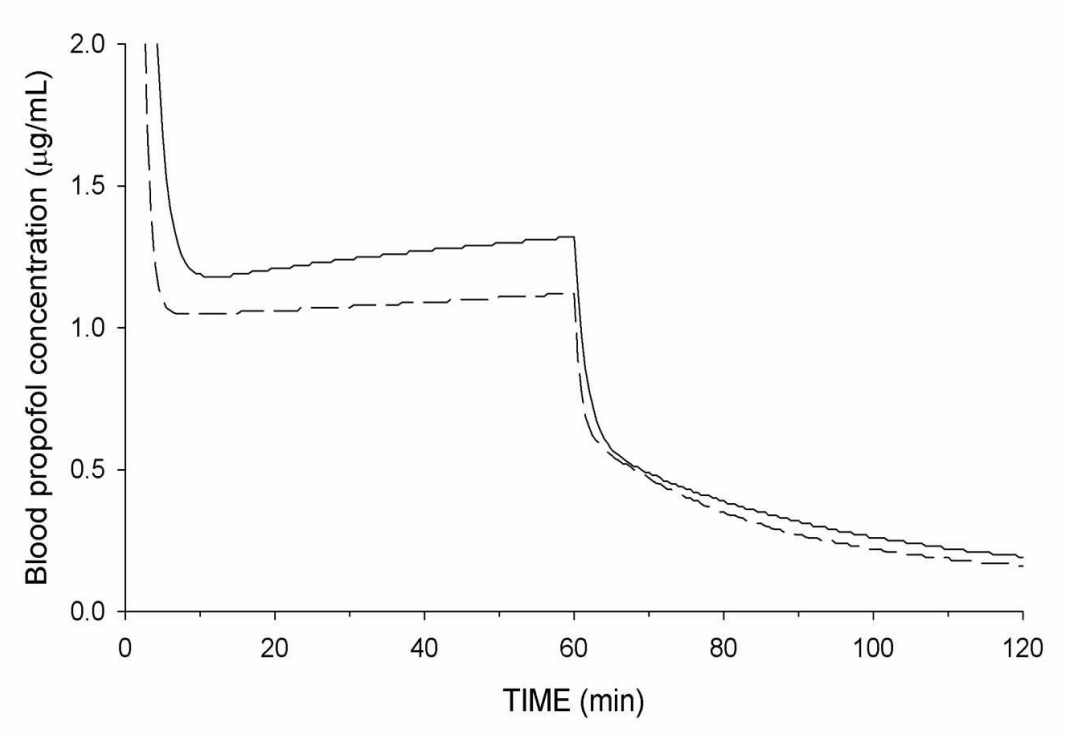

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Figure 6. Computer simulation of the influence of midazolam at a concentration of 0 (discontinuous line) and 225 ng/mL (continuous line) on the propofol concentration-time relationship with a propofol infusion scheme as used in this study (1mg/kg in 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.

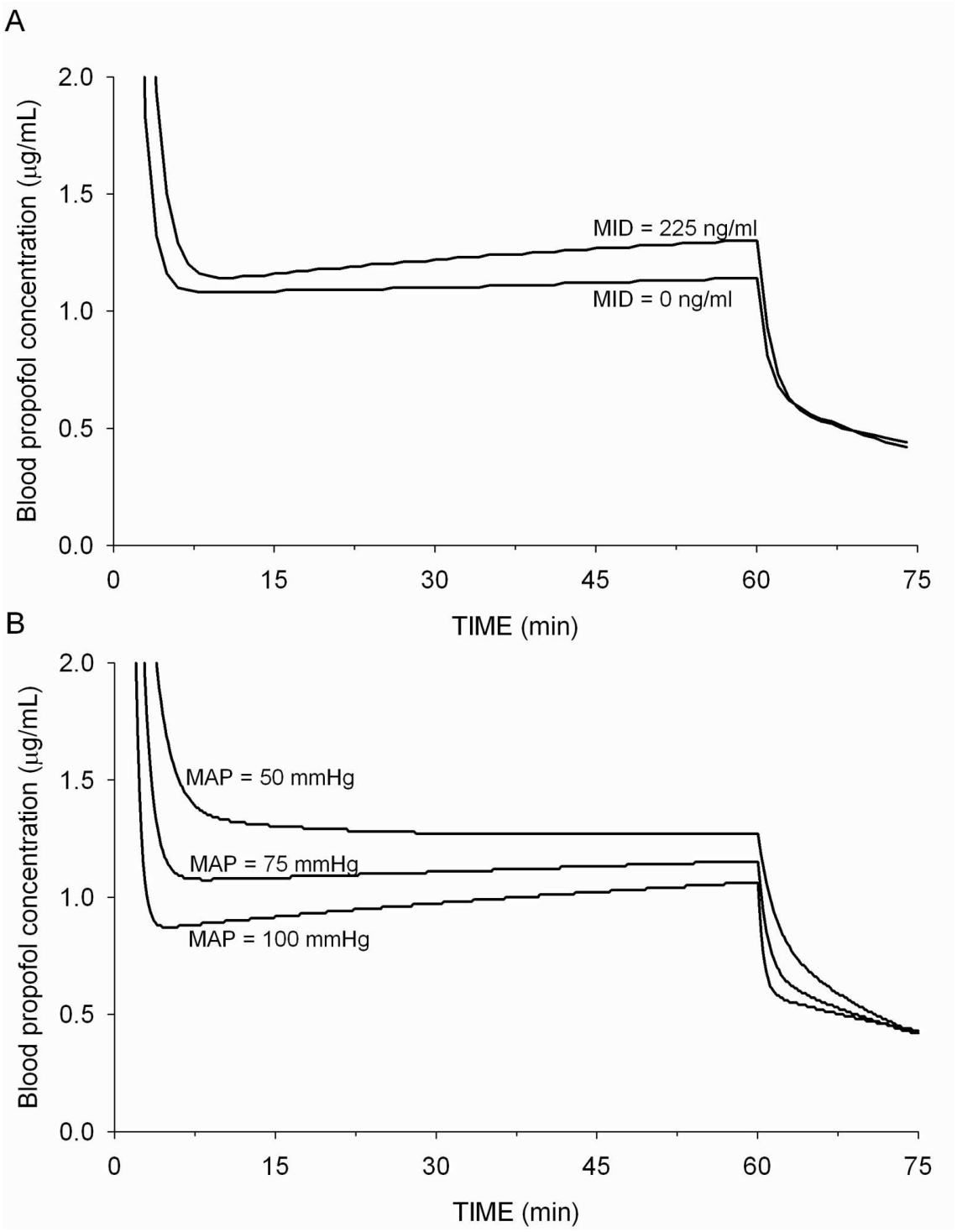

Figure 7. (A) the concentration-time profile of a simulated propofol infusion scheme (1 mg/kg in 1 min followed by 2.5 $mg.kg^{-1}.h^{-1}$ for 59 min) in the presence of a plasma midazolam concentration of 0 and 225 ng/mL at a stable MAP of 74 mm Hg.

(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.

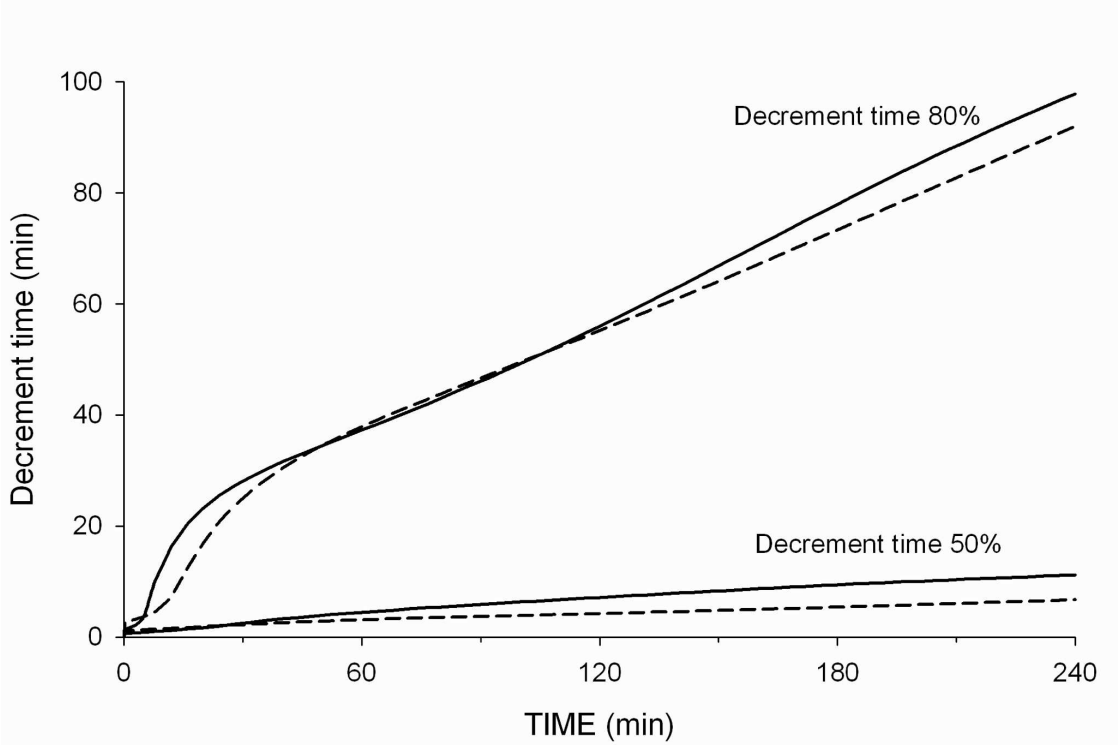

Figure 8. Context sensitive half time (CSHT = 50% decrement time) and 80% decrement time of propofol in the absence (continuous line) and in the presence of a plasma midazolam concentration of 225 ng/mL (discontinuous line) using the final propofol pharmacokinetic parameter set with a MAP of 78 and 68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

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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.

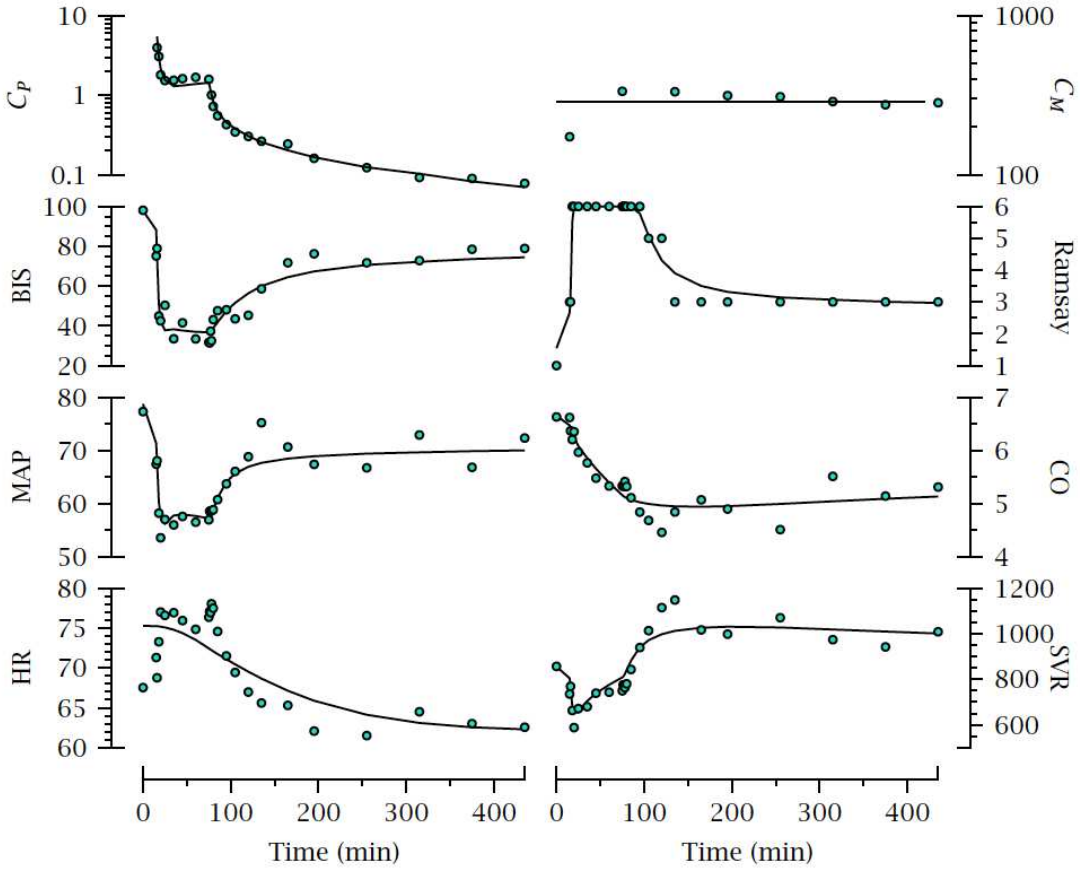

Figure 1.

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.

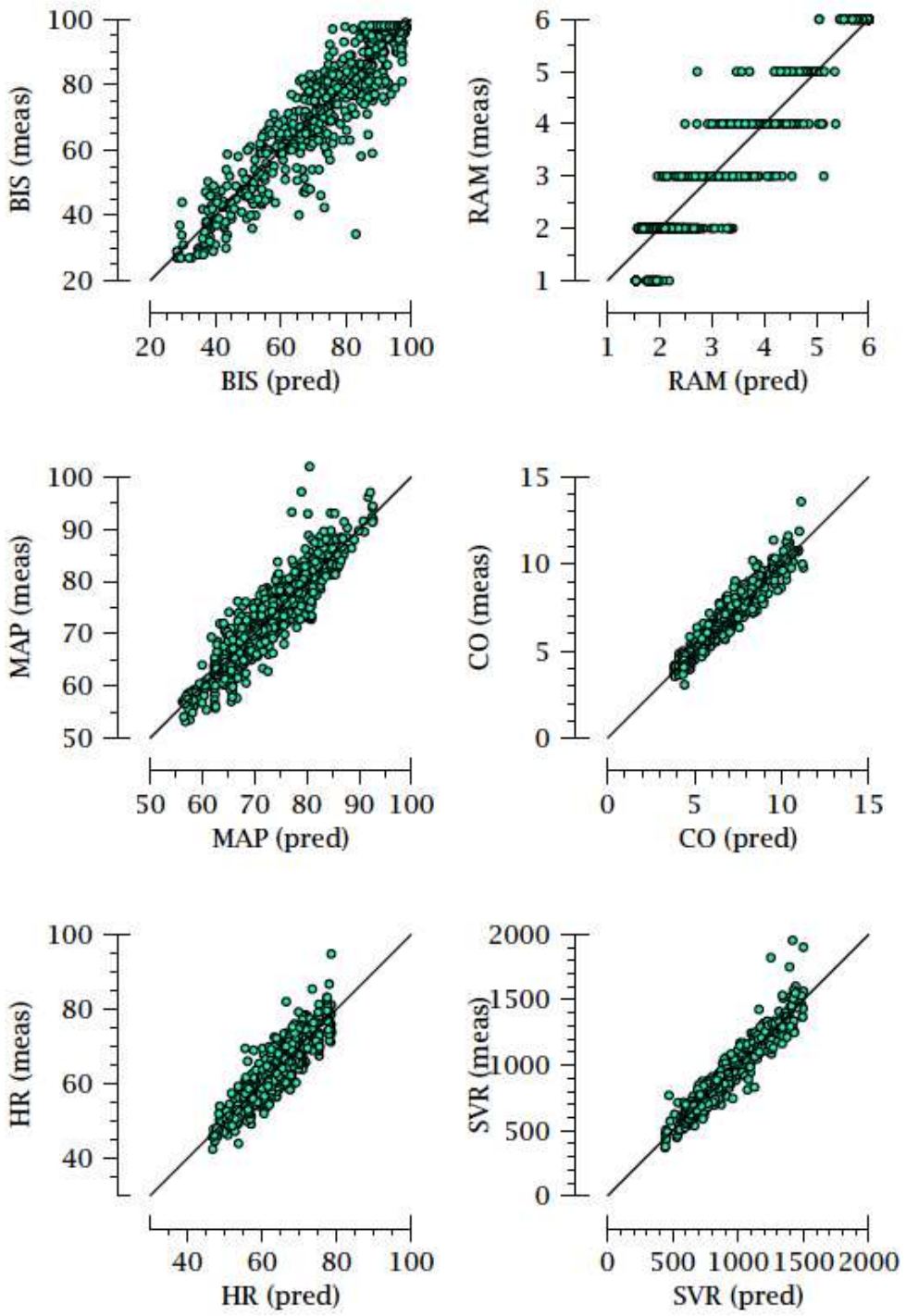

Figure 2.

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.

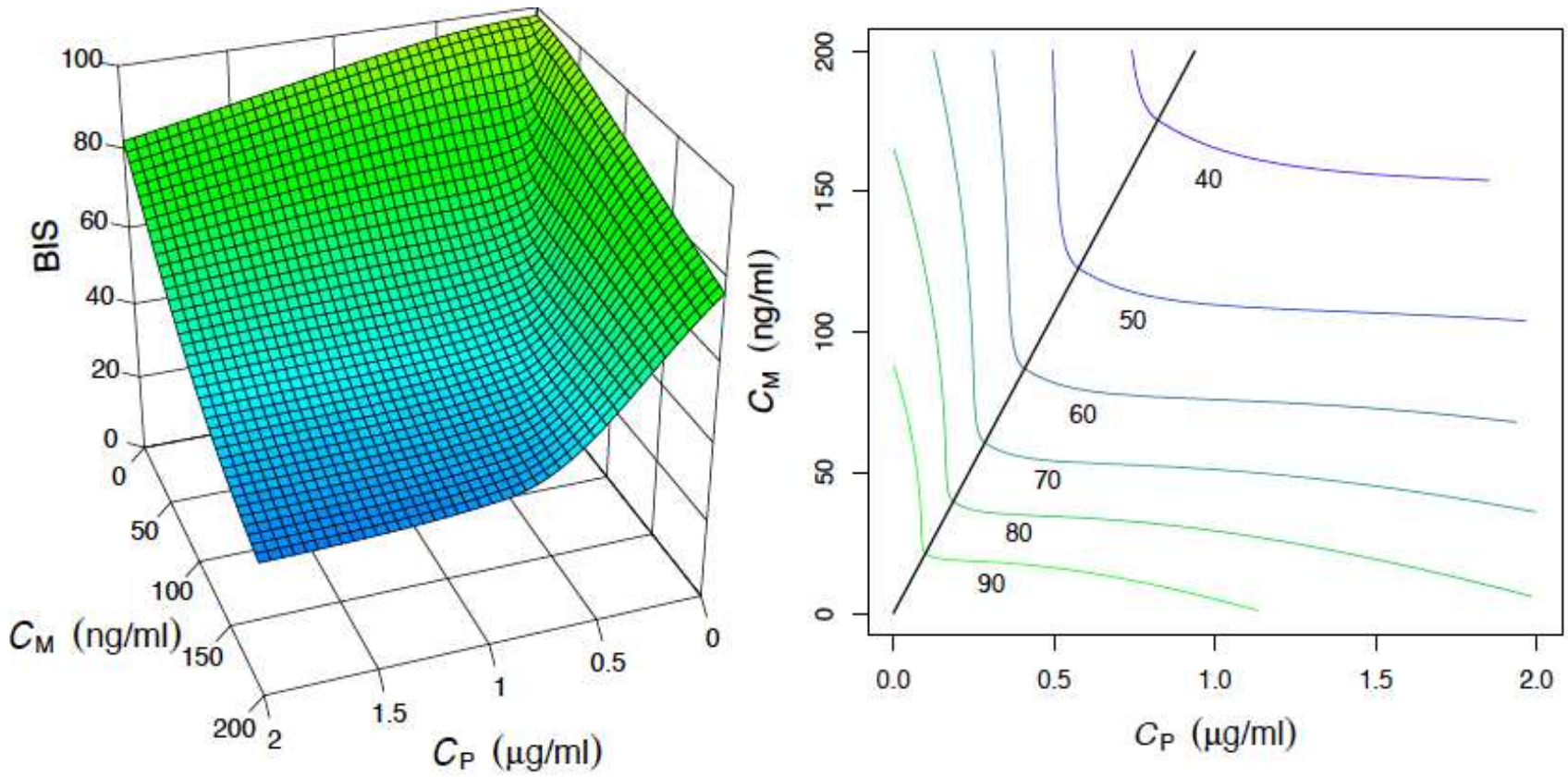

Figure 3.

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).

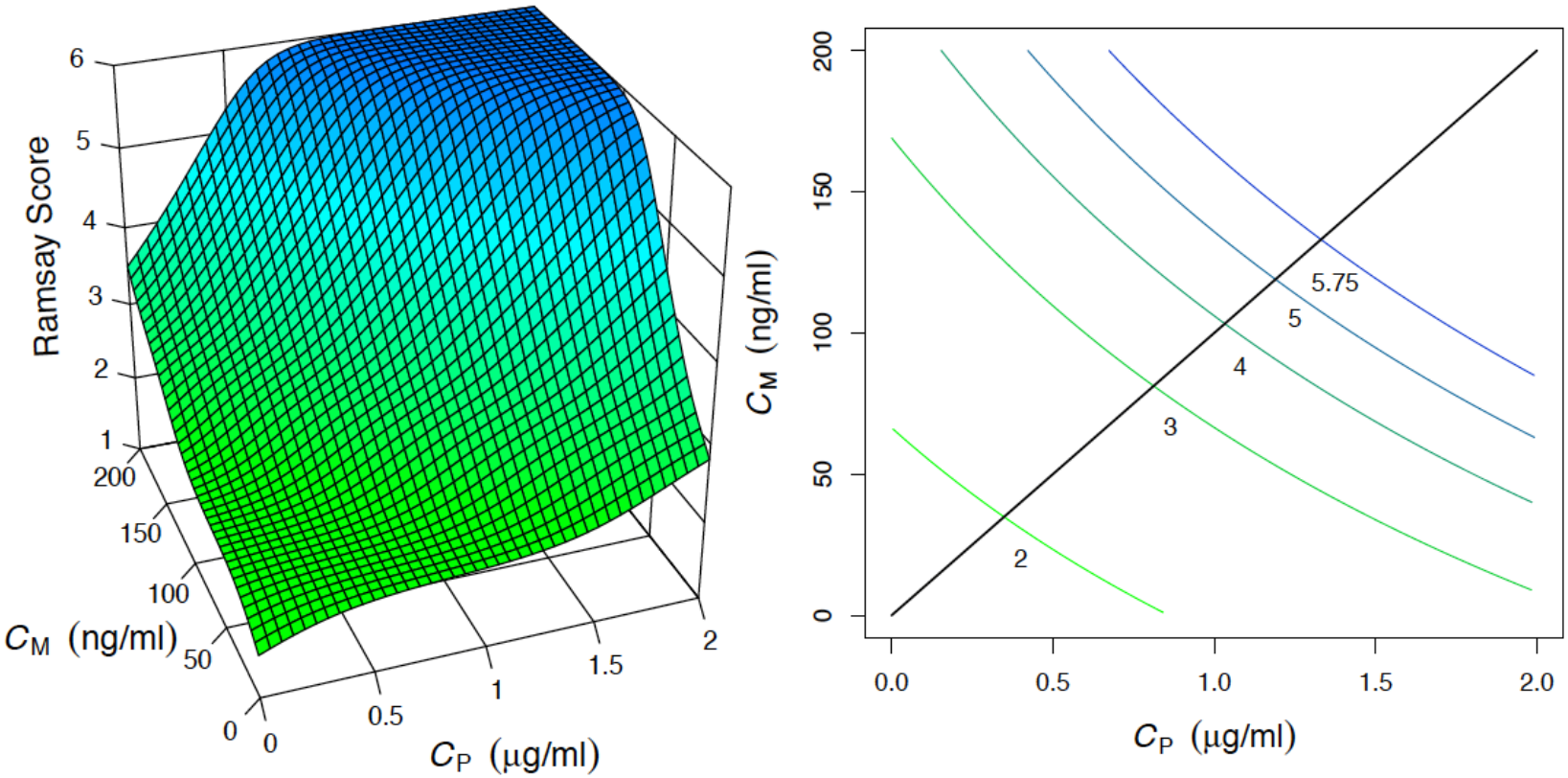

Figure 4.

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**).**

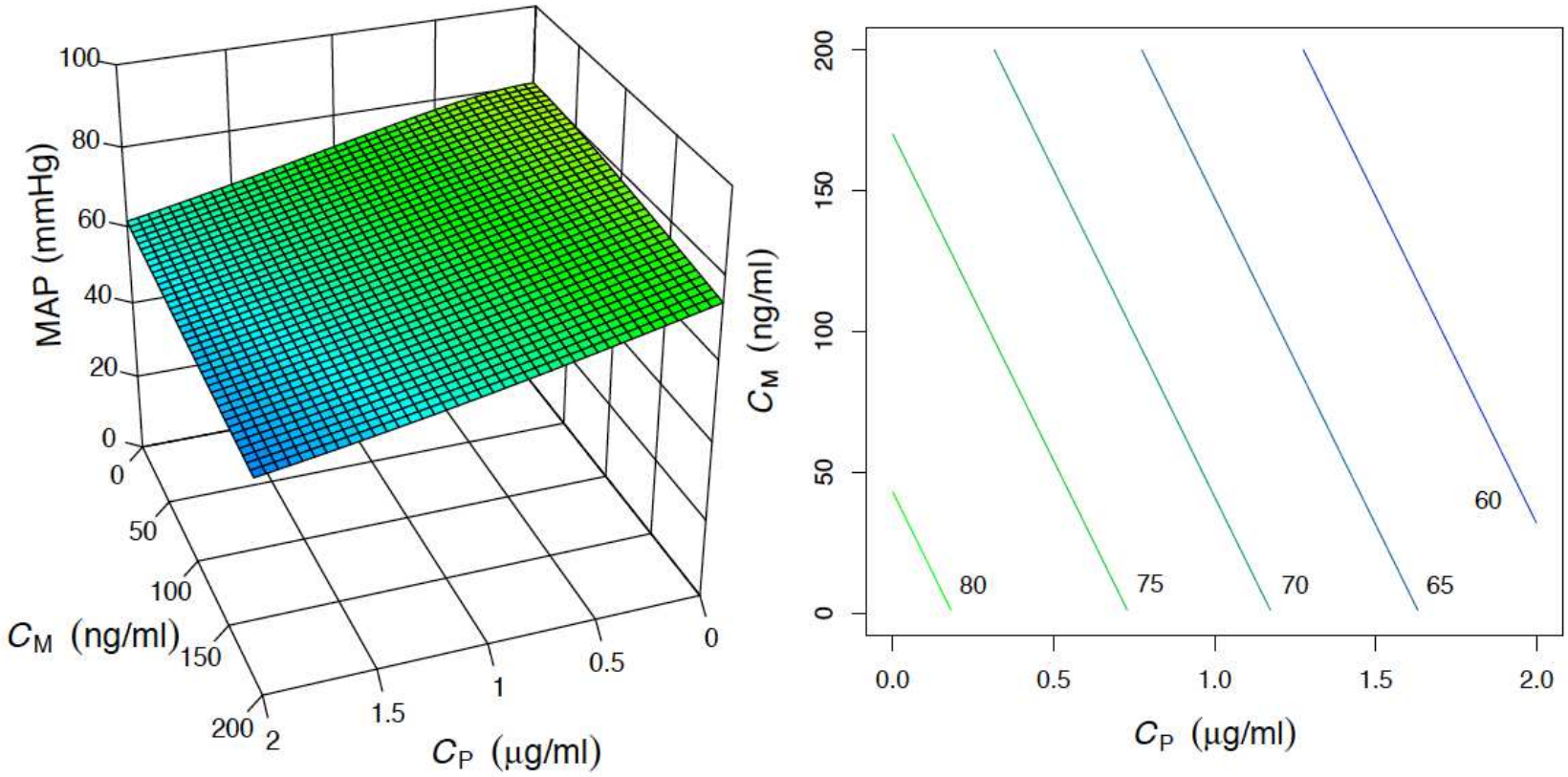

Figure 5.

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.

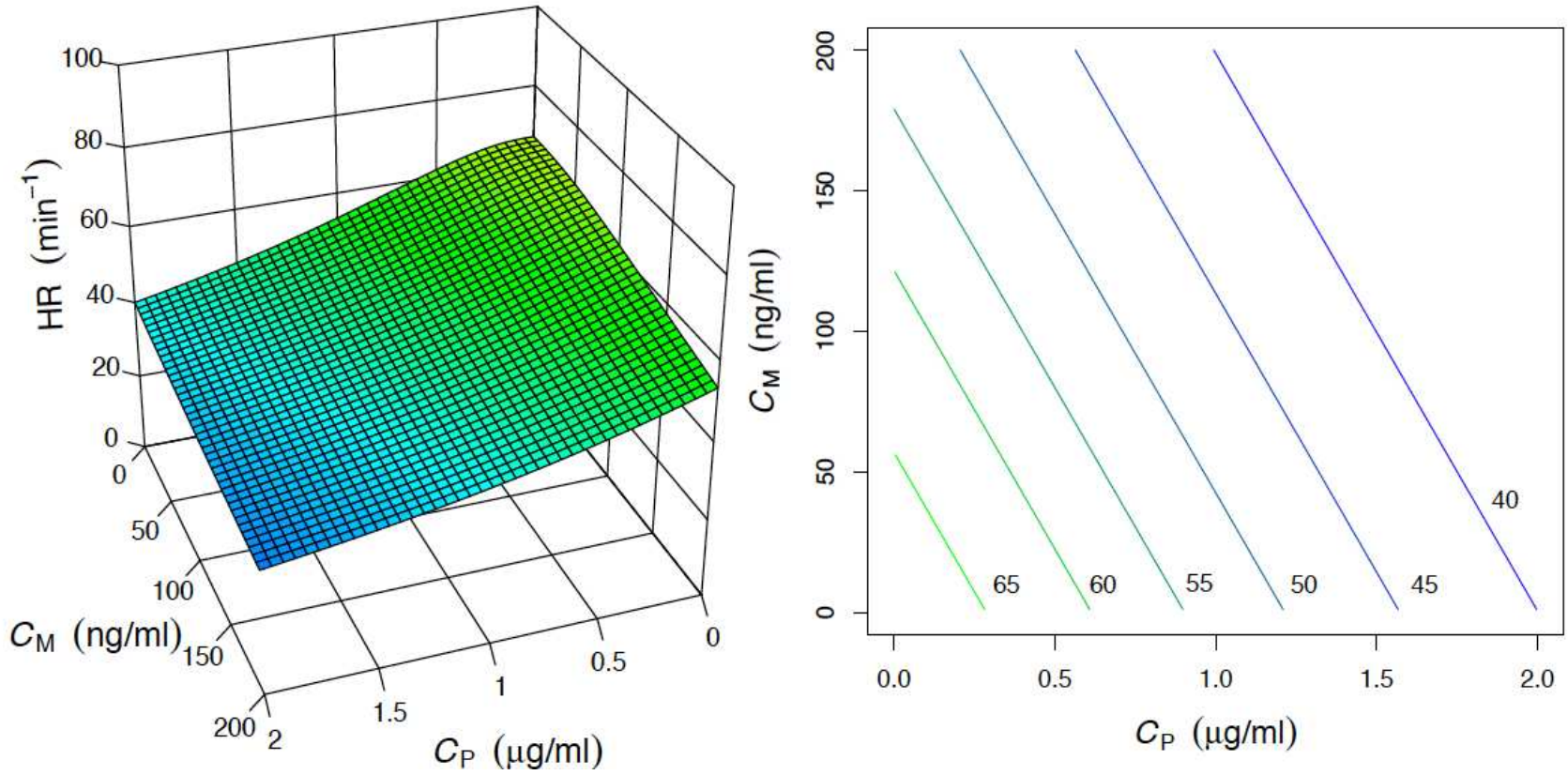

Figure 6.

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.

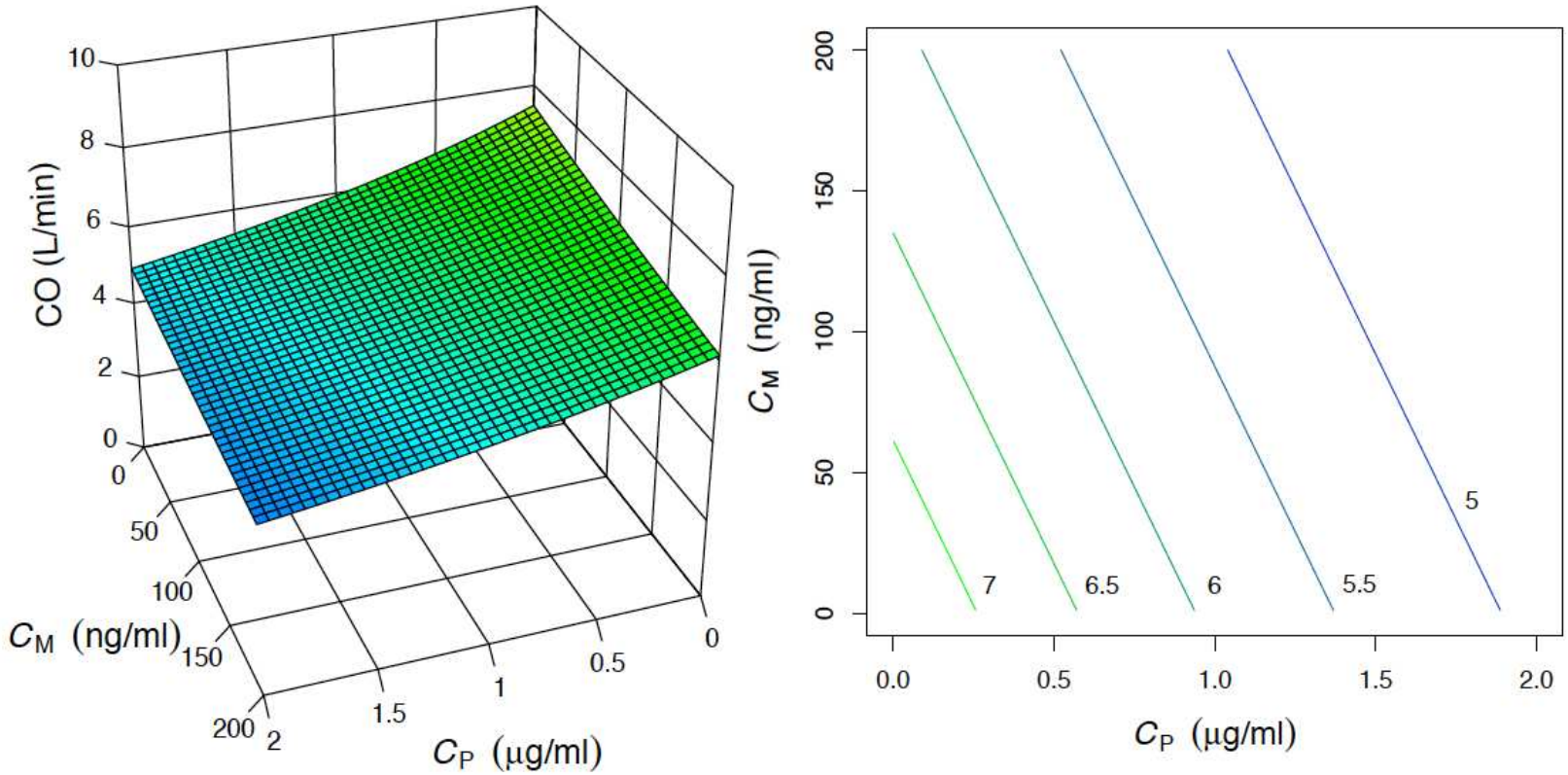

Figure 7.

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.

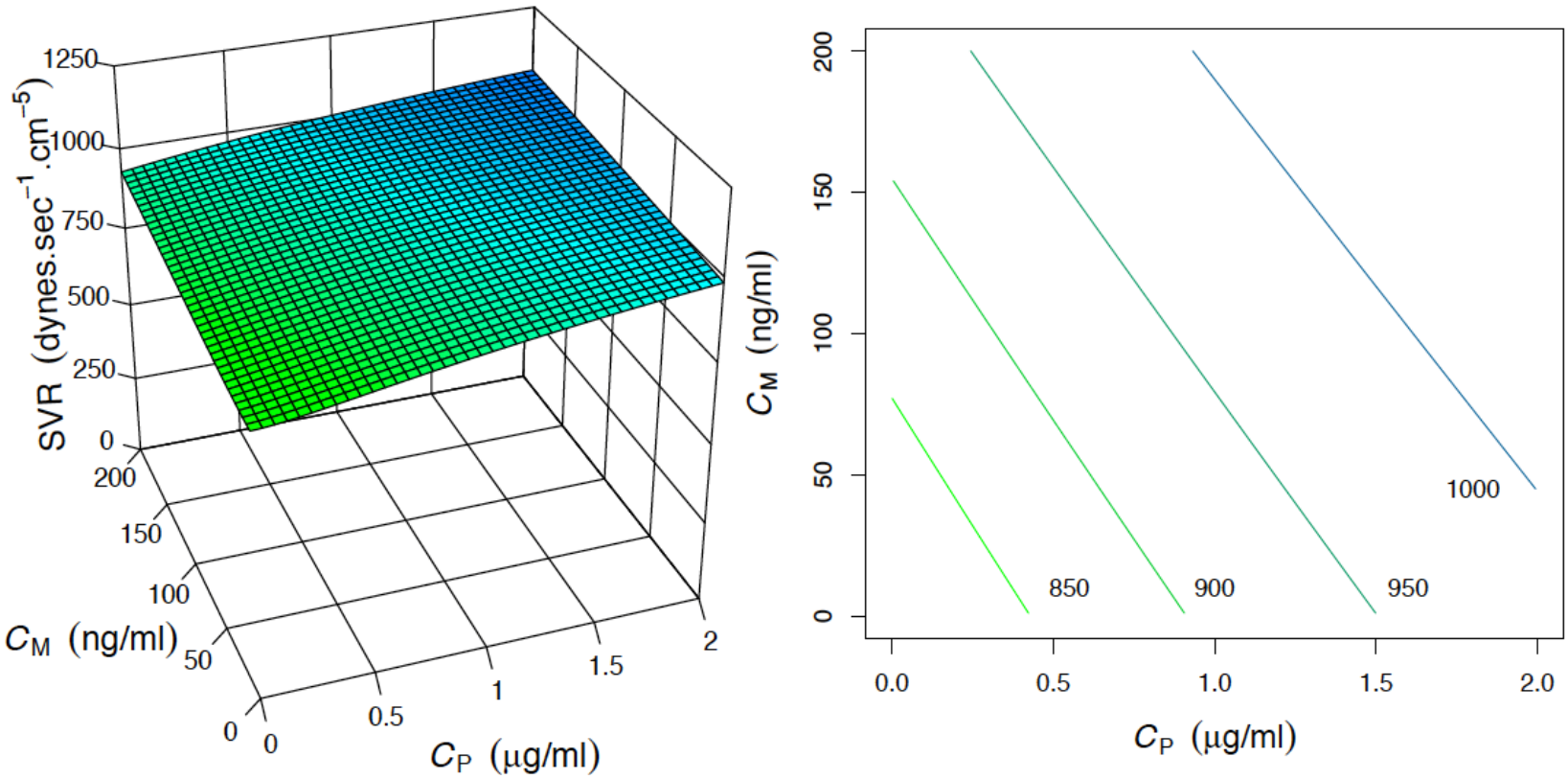

Figure 8.

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).

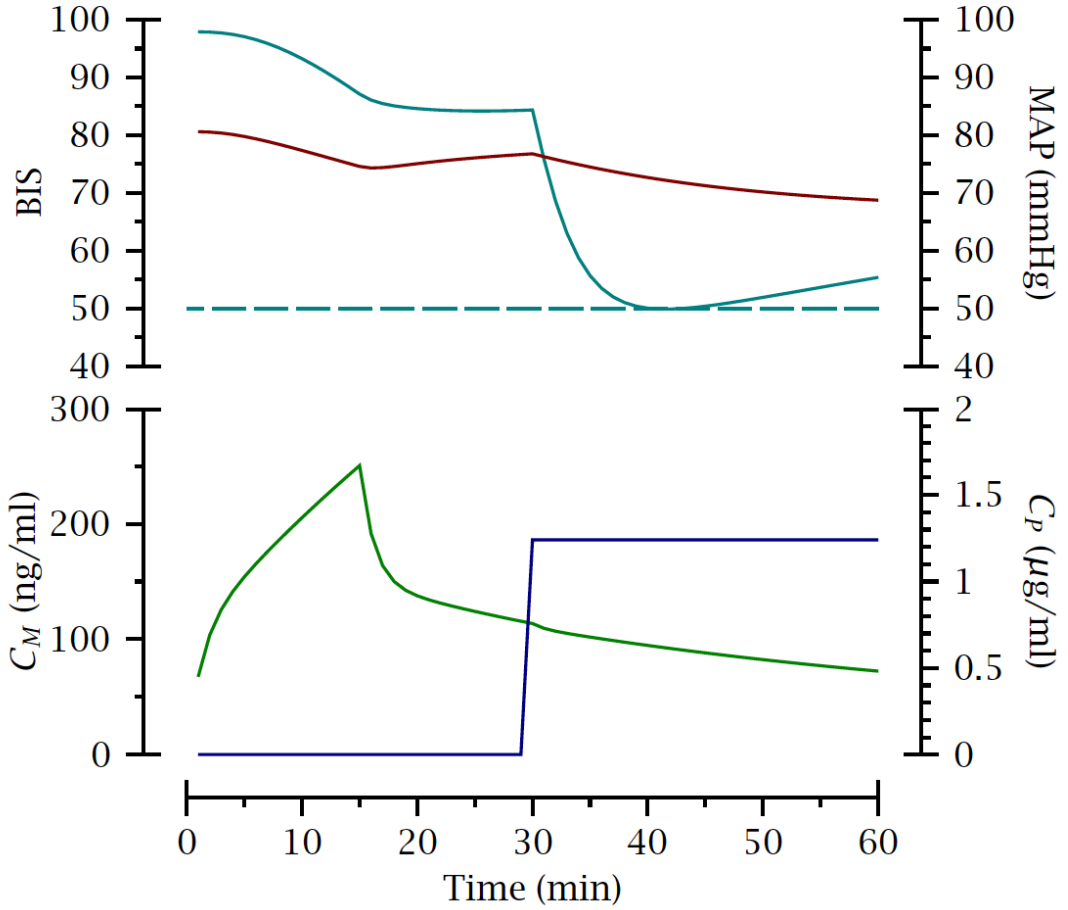

Figure 9. Computer simulation of the hemodynamic consequences of a clinical scenario with midazolam premedication of 15 mg per os (~ 7.5 mg IV) 30 min prior to propofol induction aimed at reaching a BIS of 50.

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.

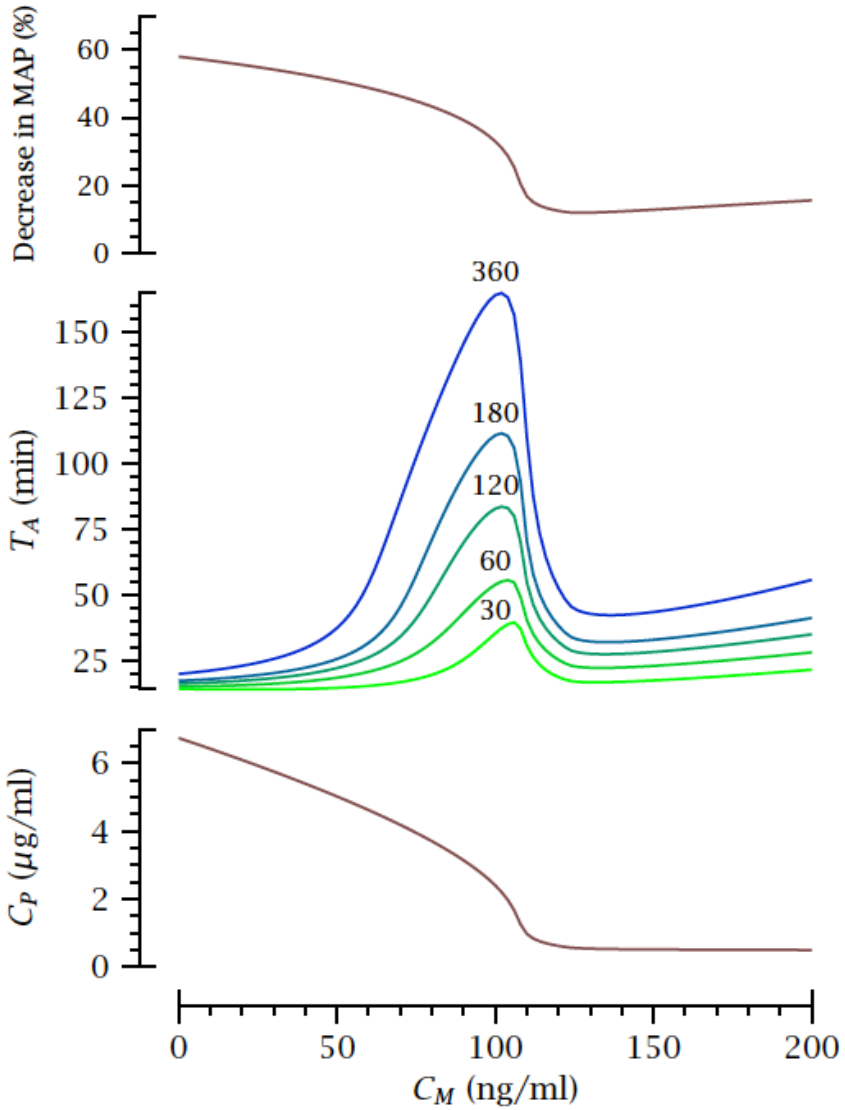

Figure 10. Computer simulation of the complex interplay of the pharmacokinetic and pharmacodynamic interaction between propofol and midazolam on BIS, MAP and return to consciousness (time for BIS to return from BIS = 50 (~unconsciousness) to BIS = 75 (~eye opening) after termination of propofol-midazolam 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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Optimizing IV drug administration by applying PK/PD concepts.

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Summary :

This review discusses the ways in which anaesthetists can optimize anaesthetic-analgesic drug administration by utilizing pharmacokinetic and pharmacodynamic information. We therefore focus on the dose-response relationship and interactions between intravenous hypnotics and opioids. For intravenous hypnotics and opioids, models that accurately predict the time course of drug disposition and effect can be applied. Various commercially or experimentally drug effect measures have been developed and can be implemented to further fine-tune patient individualized drug titration. The development of advisory and closed-loop feedback systems which combine and integrate all sources of pharmacological and effect monitoring, has taken the existing kinetic-based administration technology forwards towards a total coverage of the dose-response relationship.

Introduction :

A wide spectrum of pharmacological actions (analgesia, hypnosis, and suppression of somatic and autonomic responses to noxious stimuli) are needed to control the general anaesthetic state [1]. When administering (intravenous) drugs, a thorough understanding of the dose-response relationship is essential for achieving the specific therapeutic drug effect while minimizing side effects. Rational drug dosing depends on the understanding of both the pharmacokinetics and dynamics of the compounds in use and their drug interactions [2]. With an ageing population, and growing demand for more complex surgical procedures in patients with limited physiological reserves, the need to fine-tune anaesthetic management in order to optimize peri-operative care is greater than ever.

In current practise, intravenous drugs are commonly administered using standard dosing guidelines, an approach which ignores inter- and intra-individual variability in the dose-response relation. It has been proven that incorporating pharmacokinetic-dynamic information as an additional input to guide clinical anaesthesia can result in better patient care [3]. As such, it is important that anaesthetists learn and understand basic anaesthetic pharmacological principles and apply the available pharmacology-based technology into their daily clinical practice. This review discusses possible ways in which clinical pharmacology information can be used to optimize intravenous drug administration. For this purpose we will focus on the dose-response relationship and interactions among intravenous hypnotics and opioids.

"Everything starts with education":

Knowledge on drug disposition and effect should be considered as essential for the practice of anaesthesia. Although most of the established residency programs world-wide do incorporate basic pharmacology teaching, clinical pharmacology remains a challenging topic to teach, and the extrapolation of theoretical principles such as drug distribution and clearance into clinical practise in the operating theatre remains difficult.

Modern computer technology has facilitated the incorporation of this theoretical knowledge into pharmacokinetic simulation software packages, enabling clinicians to simulate the time course of drug disposition and drug effect while drugs are being administered and their effects are being measured. Computer simulations are frequently used in anaesthesia as a

part of training and assessment[4]. Simulation technology and teaching methods have advanced significantly over the last years and have the potential to improve the competency of anaesthetists and ensure a safer use of intravenous anaesthetic drugs [5]. By teaching clinical pharmacology through simulations, anaesthetists will be able to answer questions such as: Which plasma and effect-site concentration are reached when injecting propofol 2mg/kg? Is the offset of drug effect when administering alfentanil different if it is administered for 30 minutes compared with 5 hours? In what way are propofol and remifentanil interacting? The various software packages available are able to predict hypnotic and opioid drug behaviour, helping the clinician to make the transition from "dose thinking" towards "concentration thinking" [3].

Pharmacokinetic-dynamic based drug administration.

The dose-effect relationship can be divided into three parts : the relationship between dose administered and blood concentration (the pharmacokinetic part), the relationship between effect organ concentration and therapeutic effect (the pharmacodynamic part) and the coupling between pharmacokinetics and dynamics (figure 1, partially). Figure 2 shows that the time course of drug concentration for most intravenous hypnotics and opioids can be described by compartmental models depicting drug distribution and clearance. As the plasma is not the site of drug effect, hysteresis exists between the blood concentration and the clinical effect. Extending the pharmacokinetic model with an effect compartment enables modelling of the effect-site concentration of the drug, which represents this delay. This extension only requires one additional transfer constant, called *keo* [6]. The relationship between the effect-site concentration and clinical drug effect is thought to be governed by a static (time-independent), non-linear (sigmoidal) relationship. In theory, a change in effect-site concentration should directly translate into a change of clinical effect without time delay. However, with currently available models, various technological limitations and biological sources of variability might alter this relationship and as a result, in clinical practice, targeting the effect-site concentration to that associated with a specific clinical endpoint (e.g. loss of consciousness) may be associated with changes in clinical effect over the next few minutes[7]. Manual bolus and/or continuous infusion schemes do not easy result in steady state concentrations (except after long lasting infusions) and so, technology which enables accurate maintenance of targeted concentration can be beneficial. A target controlled infusion (TCI) is an infusion controlled by a computer or microprocessor in such a manner as to achieve a user-defined drug concentration in a "body compartment" of interest. These systems use multi-compartmental pharmacokinetic models to calculate the infusion rates

required to achieve the target concentration. A clinician using a TCI system to administer an intravenous hypnotic or opiate is thus able to set a desired ("target") drug concentration, and then adjust it based on clinical observation of the response of the patient or on measurements of drug effect. A computer or microprocessor performs the complex calculations, and controls the infusion pump. Classically, plasma or effect-site concentrations are targeted [8]. The development of target-controlled infusion (TCI) technology, have enabled clinicians to better manage the complex relationship between dose, blood-concentration, effect-site concentration and clinical effect.

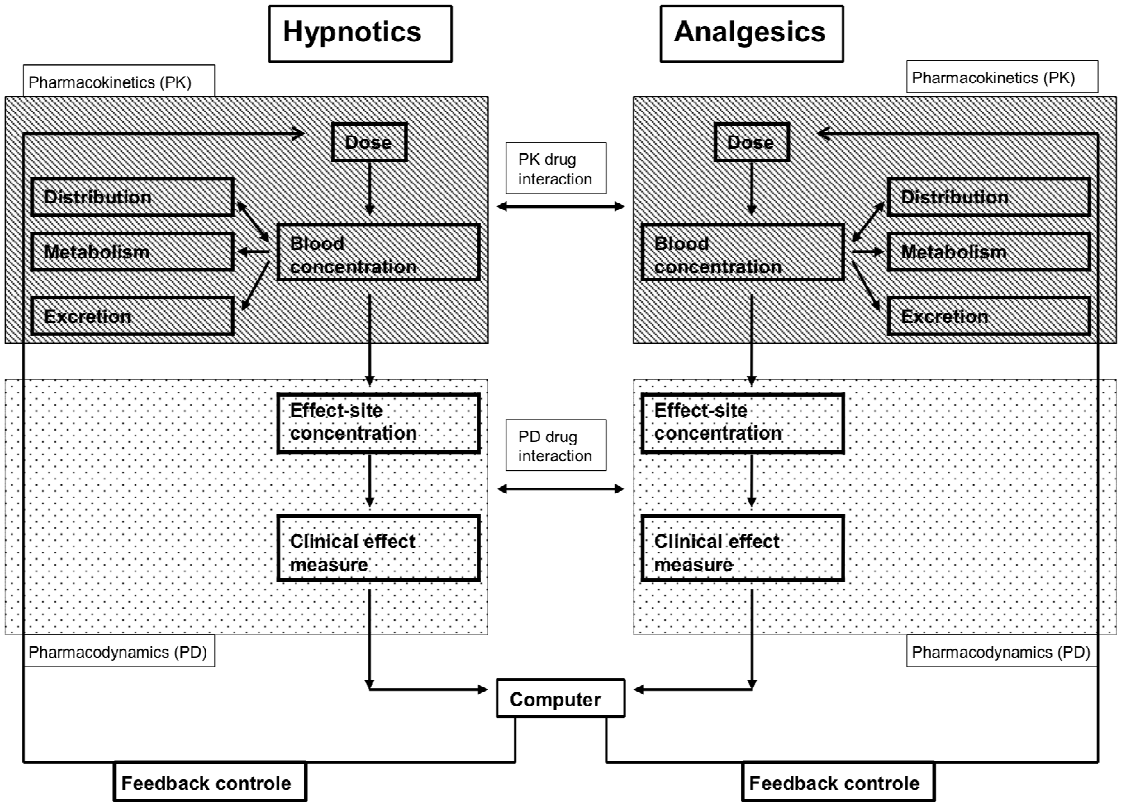

Figure 1 : dose-response relationship and interaction between hypnotics and analgesics.

For most of the intravenous hypnotics and opioids used in daily practice, PK/PD models with clinically acceptable accuracy are programmed into commercially available TCI pumps. For propofol, two adult models are commercially available - the Marsh and the Schnider model [9-11]. Masui and colleagues [12] recently combined measured plasma concentration data from four different studies in which various propofol infusion regimens were used – bolus, short infusion, long infusion and TCI – and then tested the ability of different pharmacokinetic models to predict the concentrations for all of the regimens. He concluded that the model

published by Schnider and coworkers [10, 11], although imperfect should be recommended to be used for TCI and advisory displays. Unfortunately, the Schnider model effect-site control algorithm has been implemented differently in the various commercially available infusion pumps, so, users have to be informed and cautious when using specific equipment [13] as this might result in different dosing and effect [7]. Masui et al [14] studied the front-end PK and PD of propofol and concluded that a combined pharmacokinetic-dynamic model consisting of a multi-compartmental model with a lag time, presystemic compartments and a sigmoidal maximum possible drug effect model accurately described the early phase pharmacology of propofol during infusion rates between 10 and 160 $mg.kg^{-1}.h^{-1}$. They also found that age was a covariate for lag time and infusion rate influenced kinetics, but not dynamics. Further studies are required to reveal if or not these more complex model is clinically relevant compared with the classical one.

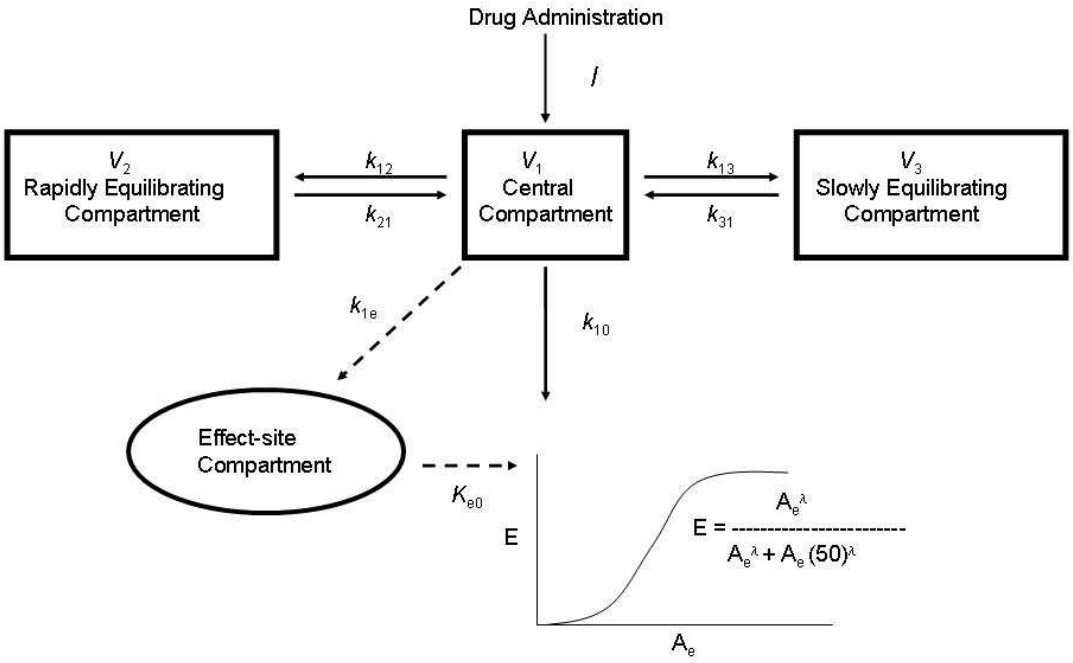

Figure 2: Dose-response relationship for one drug. Pharmacokinetics are depicted as a multicompartmental model. Pharmacodynamics are shown as a sigmoidal Emax model. Kinetics and dynamics are linked by a effect-site compartment. (Modified from [96] with permission).

For the opioids a better consensus exists than for propofol, and so only one model for remifentanil ("Minto" [15, 16]), sufentanil ("Gepts"[17]) and alfentanil ("Maitre" [18-20]) has been selected for use in commercially available TCI systems.

As most of the above mentioned models have been developed in specific populations, their use in children the elderly and morbidly obese patients is still limited. Caution should be applied when extrapolating and using the models in groups differing from the original validating population [13]. Cortinez et al [21] proved that an allometric model using total body weight as the size descriptor of volumes and clearances was superior to other size descriptors to characterize propofol pharmacokinetics in obese patients.

For the opioids there are no models suitable for use in children, whereas for propofol two models have been implemented for control of TCI in children in commercially available pumps - the Kataria and Paedfusor model [22, 23]. An integrated PK/PD model enabling effect compartment control TCI for children is still lacking and the accuracy of these paediatric propofol models is still under debate [24, 25]. For children, various limitations are still present and have been described in recent reviews by Anderson [26] and Constant.[24]. Additionally, more experimental modelling strategies have been applied.

The first commercially available TCI system was the Diprifusor® (AstraZeneca, UK), which incorporated the Marsh model. It only allowed plasma controlled TCI as the important of the effect compartment was not fully appreciated at the time it was developed. Initial reports suggested benefits of this technology compared to manual infusion [27-30]. More recently, others have not shown that plasma controlled propofol TCI systems facilitate more accurate control of anaesthetic depth than manually controlled infusions [31, 32]. This might be due to the fact that the plasma is not the site of drug effect. Effect compartment controlled TCI may offer better control of the dose-response relationship [33-35]. For deep sedation in spontaneously breathing patients Moerman and colleagues [36] found that the combination of remifentanil and propofol offered better conditions for colonoscopy than propofol alone; and that TCI remifentanil administration was associated with reduced propofol dosing and a lower incidence of apnea and respiratory depression, compared to manually controlled administration. Others have confirmed this finding [37]. For other opioids such as sufentanil, TCI administration has been proven to be accurate and safe[38].

Pharmacokinetic and dynamic models have other potential operating room applications. Commercially available systems called "drug-displays" also provide on-line information of the

predicted plasma and effect-site concentrations of the given drugs. This allows the clinician to learn more about the concentration-clinical effect relationship when administering the drug in a combined bolus and continuous infusion model[39]. In addition, commercial pumps can also be connected to PC software programs to provide on-line predictions of plasma and effect-site concentrations. An example of such a program is RUGLOOP, developed by De Smet and Struys and available at "http://www.demed.be" [3].

Measuring clinical drug effects :

Beneficial kinetics and a fast onset and offset facilitate optimal drug administration and titration during anaesthesia. In contrast with "slow" drugs, the clinical effect of intravenous hypnotics and opioids can be measured online in a minute to second time frame. Better monitoring of the therapeutic effects has become available with the introduction of hypnotic effect monitors. As this equipment measures cerebral drug effect, it has to be considered as an integral part of anaesthetic pharmacology. For the first time in the history of the specialty, anaesthetists are able to differentiate and measure the two chief components of anaesthetic effect, hypnosis and analgesia, by using specific effect monitors.

However, much work has still to be done. Various commercially available systems exist, but the extent to which they have been validated is variable, and some required further research to be validated as measures of cerebral drug effect. To facilitate this the relationship between drug effect-site concentration and clinical effect has to be better defined. As shown in figure 2, a sigmoidal Emax model is mostly used for this, but in specific conditions more complex models might be required [40]. In addition, validation on clinical endpoints such as loss and return of consciousness is required. Clinical utility should be proven and finally, patient outcome should be enhanced by applying this new technology. For some of these monitors, some of these goals are already reached and published in the literature. For others major research is still required [41].

In contrast to the hypnotic cerebral drug effect monitors, real "analgesic drug effect monitors" do not yet exist. This is due to the complexity of pain physiology and the fact that what is required is a measure of the balance between nociception and antinociception during anaesthesia. The nature and severity of surgical stimuli change constantly and responses to noxious stimuli, such as movement and hemodynamic changes, are modulated by multiple factors. In an attempt to optimize the titration of opioids in relation to the noxious stimulus and the resulting adrenergic activation, various measures of the status of the autonomic nervous system have been studied. The success of these based on skin conduction [42], heart

rate variability [43] and variability of pulse plethysmography, [44] has been variable [45, 46]. Recently, the multivariate surgical stress index (SSI) (GE healthcare, Helsinki, Finland) (now commercially called “SPI” or “Surgical Pleth Index”), based on a sum of the normalized pulse beat interval (PBI) and the photoplethysmographic pulse wave amplitude (PPGA), has been developed as a measure of the nociception-antinociception balance [47]. Some correlations between SSI during stimulation and remifentanil concentrations have been found. [48]. Using SSI to titrate remifentanil compared with standard clinical practice during surgery resulted in less remifentanil usage, improved hemodynamic stability and less movement during surgery [49].

If immobility is considered as an important clinical endpoint of hypnotic and analgesic drug titration, then prediction of movement responses to noxious stimuli during anaesthesia is beneficial [50-52]. The RIII reflex, a component of the nociceptive flexion reflex, is a polysynaptic spinal withdrawal reflex elicited by stimulation of nociceptive Aδ afferents. It is assessed by analyzing the biceps femoris muscle electromyogram during electrocutaneous stimulation of the ipsilateral sural nerve. This approach remains experimental and is not commercially available for clinical use [51, 52].

Given the close relation between the propofol effect-site concentration and BIS [53], Luginbühl and colleagues hypothesised that the predicted effect-site concentrations of propofol and remifentanil together with an appropriate interaction model could provide sufficient information to predict responsiveness of an anesthetized patient to noxious stimuli. Thus they developed the novel noxious stimulation response index (NSRI), computed from hypnotic and opioid effect-site concentrations using a hierarchical interaction model and found that NSRI conveys information that better predicts the analgesic component of anaesthesia than EEG derived measures [54].

Individualizing the dose-response relationship :

Target-controlled infusions, as described above, are based on population based PK/PD models. The model parameters in the infusion device are those of the typical patient and are usually adjusted for factors known influence these parameters, such as weight, height, age and gender. As such, TCI ignores residual inter-individual variability, thereby limiting the accuracy of the estimated drug concentration for the individual. Fortunately, this inaccuracy can be limited if the model is built during a study which explores a wide variety of possible covariates using parametric modelling, ideally non-linear mixed-effects modelling [55, 56]. Caution is needed when applying model-based drug information to an individual patient with

co-morbidity such as cardiac disease, obesity, diabetes, nephropathy, alcoholism, and to children and the elderly, if similar subjects were not part of the original study population. Because of this, no single regimen applies to all patients. Some guidance can be found in the effective concentrations at which 50 % and 95 % of patients have accurate clinical effect [57].

The resulting inaccuracy of absolute concentrations based on population models requires the clinician to manually titrate the dose regimen or target concentration for the individual patient based on observations of the desired therapeutic effect. Using one of the mentioned therapeutic effect monitors, the clinician is able to do so rationally. As a result, one could argue that if one has to titrate to a specific therapeutic effect anyhow, advanced drug administration systems are not required. In defence of TCI, it has been shown that the use of TCI technology facilitates rapid achievement of therapeutic concentrations at the site of drug action, the so-called “effect-site concentration” [33-35]. It is already possible in clinical practice to combine both sources of dose-response information - the effect-site concentrations displayed by the TCI system, and drug effect information shown by the hypnotic effect monitors, to guide hypnotic drug administration. Proof exists that the combined information offers a higher degree of care [58].

Clinicians usually apply a reactive approach, by selecting a dose based on a variety of considerations, observing the effect thereof and adjusting the dose if required [59]. Accurate titration can produce clinical benefits but requires a high standard of clinical expertise and is a labor-intensive process that may divert the clinician’s attention from critical actions resulting in paradoxically suboptimal therapy or even threatening the patient’s safety. “Closed-loop controllers” are computer programs designed to maintain a targeted effect by adapting and optimizing the drug administration. In closed-loop control, the user (patient or clinician) only selects and enters the desired effect variable to be maintained. The application of closed-loop systems for drug administration is complex and requires a perfect balance for all the basic components of such a system: 1) a continuously available control variable representative for the targeted therapeutic effect; 2) a clinically relevant set-point or target value for this variable 3) a control actuator which is, in this case, the infusion pump driving the drug; 4) a system, in this case a patient 5) an accurate, stable control algorithm. Although closed-loop systems to control hypotics and analgesics using continuously measured pharmacodynamic drug effect measures are not yet available commercially, various experimental systems have been developed and tested over the last 40 (!) years [60, 61]. Recently, various groups tested BIS-guided propofol administration using proportional-integral-derivative (PID) closed-loop control and found that it was clinical feasible and outperformed manual drug titration [62-66].

Unfortunately, PID control might suffer from a lack of patient individualization leading to oscillation during control and therefore, Struys and De Smet [67-69] developed a model-based patient-individualized closed loop control system for propofol administration using the Bispectral Index as a controlled variable. They tested their system, which uses Bayesian methodology for patient-individualization, during anaesthesia for ambulatory surgery and found a high level of accuracy and feasibility [70, 71]. As all previous examples lack the possibility of predictive control, Ionescu et al. developed the Robust Predictive Control Strategy which can be applied for propofol dosing using BIS as a controlled variable during anesthesia [72]. So far, most closed-loop systems offer only "single-input-single-output control". As hypnotics and analgesics are mostly co-administered during anaesthesia, multiple-input-multiple output controllers are a logical next step, but have yet to be developed and tested. In addition to a measure of hypnotic drug effect, these systems will also require an accurate measure of the nociception-antinociception balance during anaesthesia [73].

During sedation and post-operative analgesia, patient controlled drug delivery allows the patient to optimize drug titration, and as such this can also be defined as a closed-loop system. Patient demands represent positive feedback, whereas lack of responsiveness can be used for negative feedback. Doufas et al. showed previously that failure to respond to an automated responsiveness monitor (ARM) precedes potentially serious consequences of loss of responsiveness [74, 75]. Recently, they showed that ARM dynamics in individual subjects compare favorably with clinical and electroencephalogram endpoints and that the ARM could be used as an independent guide of drug effect during propofol-only sedation [76]. This technology has now been implemented in Sedasys ® (Ethicon endoSurgery, Cincinnati, Ohio, USA) to provide propofol sedation during endoscopic procedures [77]. Previously, others have also shown the applicability of patient-controlled drug administration for hypnotic [78]and analgesic [79-81] drugs.

Combining hypnotics and analgesics :

To reach the highest standards of care, optimal titration of both anaesthetic and analgesic drugs is required. Classically, opiates are used to manage the balance between nociception and antinociception and short acting hypnotics are widely used to titrate the hypnotic component of anesthesia. When optimizing the balance between hypnotic and analgesic action, the primary concern is to ensure an accurate level of the hypnotic component of anesthesia. Both awareness caused by inadequate anesthesia, and the hemodynamic side-

effects caused by an excessive anaesthetic depth should be avoided as they may compromise outcome. [82-84]

Next, optimal and rationale opioid titration is required. As such, the dose-response relationship of both drugs should be optimized. It should be taken into account that intravenous hypnotics and opioids demonstrate both kinetic and dynamic interactions. Pharmacodynamic interactions between opioids and intravenous hypnotics are clinically very significant and have been studied in detail using response surface methods [85-89]. Response surface models are powerful sources of information on drug interactions as they combine information about any isobole and the concentration response curve of any combination of the drugs involved [90]. Using the different mathematically described response surface, one can predict the corresponding drug effect for any two (or more) drug concentrations of the interacting drugs [91] .

The information of hypnotic-analgesic drug interaction together with data from estimated drug concentration and on-line effect-monitoring can be combined in a powerful pharmacodynamic advisory tool that estimates the complete dose-response relation, facilitates optimal dose titration, and improves patient care [92, 93] Recently, various display systems have been developed and tested. Schumacher et al. proposed an advisory system that leaves the anaesthetist in complete control of dosing but provides real time information about the estimated drug concentrations, predicted combined effect, and estimated wakeup time resulting from his actions. Additionally, this device displays the optimal drug concentration ratio for a given effect in the typical patient [94]. Albert and co-workers developed a pharmacological display system that can be used to accurately model the concentration and effect of anaesthetic drugs administered alone and in combinations, on-line, in the operation room, thereby visualizing the sedation, analgesia and muscle relaxation status of a patient based on general population models that have been corrected for body mass, age, and sex [95]. Various advisory systems became recently commercially available. Two examples, Smart Pilot View (Dräger, Lübeck, Germany) and GE Navigator (GE Healthcare, Helsinki, Finland) are depicted in figures 3 and 4, respectively.

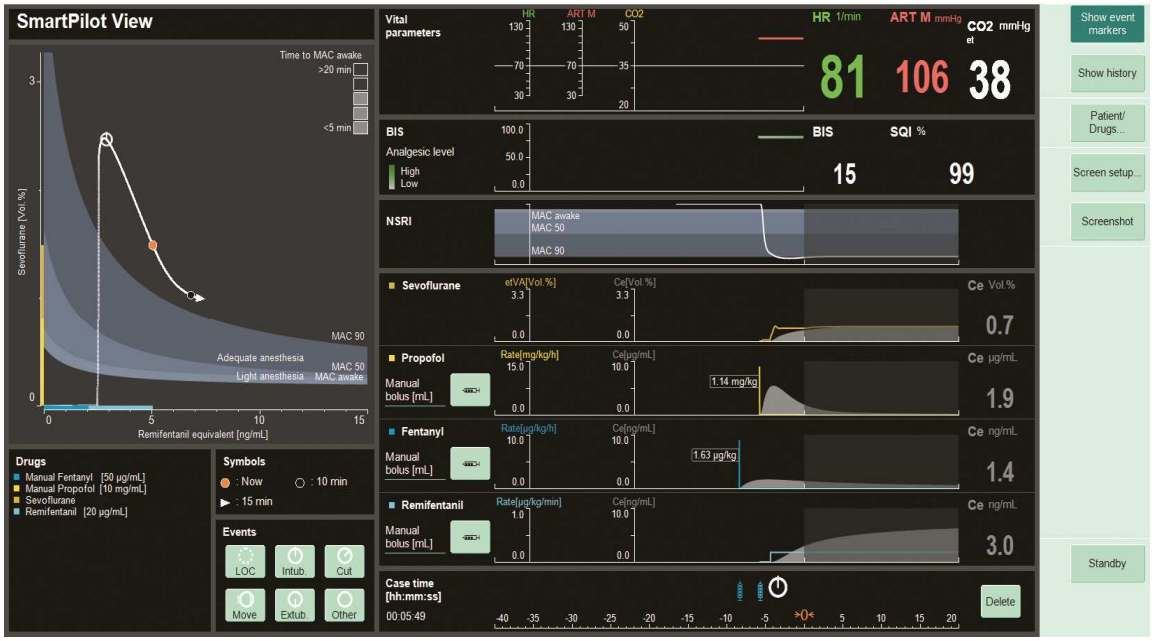

Figure 3 : Smart Pilot View (Dräger, Lübeck, Germany). This display represents a balanced anesthetic case using a volatile agent, propofol, remifentanil, and fentanyl. It uses a topographical plot of the interaction between hypnotic – and analgesic drugs (left plot) and represents the vital signs and Bispectral Index Scale (BIS), dose and effect over time. Furthermore it introduces the noxious stimulus response index (NSRI) as a new parameter (right plots). The topographical plot on the left illustrates the synergistic interaction of hypnotic – and analgesic drugs with gray-scaled isoboles. MAC 50 and 90 indicate the probability of loss of response to skin incision (MAC: minimum alveolar concentration). MAC awake indicates the probability of wake up. Fentanyl is converted into remifentanil equivalents so its contribution can be accounted for on the isobole plot. The plots on the lower right represent the time course for each drug over the past 40min to 4h and 20 minutes into the future. A series of symbols (light green buttons) are used as Event Markers during a surgical procedure (e.g. loss of consciousness, intubation, incision). These markers are useful to mark the individual reaction or non reaction of the patient and see if the patients individual reaction will correspond to the level of anesthesia, which is represented by the isoboles calculated from the behind lying algorithms. (SmartPilot® View, reprinted with permission, © Dräger Medical GmbH, Lübeck, Germany).

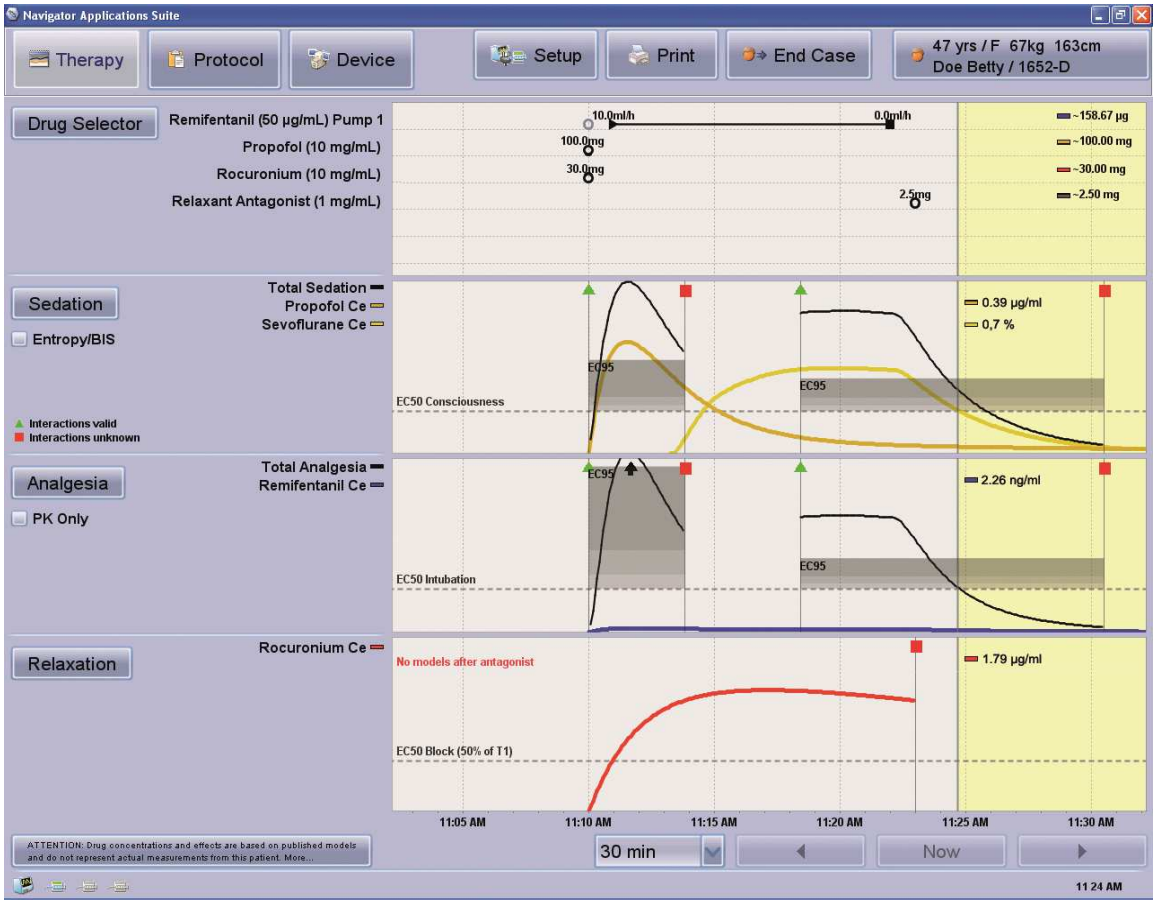

Figure 4: GE Navigator (GE Healthcare, Helsinki, Finland).display provides a tool for modelling and visualization of PK/PD models for common anaesthetic (inhaled and i.v.) drugs. In addition, it provides a model for the synergistic effects of propofol (or inhaled agents) and the fentanyl family. The calculated effect-site concentrations are displayed in a time-based graphical format. The total effect trace (the black line shown in the sedation and analagesia windows) visualizes the combined synergistic effect of the analgesic and sedative drugs. The displayed effects include level of sedation according to loss of consciousness probablility, level of analgesia according to the probability of response to intubation (high pain stimuli), and level of neuromuscular block. The drug models are calculated for up to 1 h into the future providing predictive drug modelling for drug concentration and quantative complex drug interactions. (Navigator Therapy Display, reprinted with permission, © 2010 General Electric Company, Helsinki, Finland).

In conclusion, by implementing PK/PD based information, the anaesthetist should be able to optimize anaesthetic-analgesic drug administration. For both intravenous hypnotics and opioids, models to accurately predict the time course of drug disposition and effect can be applied. Various commercially available and some experimental drug effect measures have been developed and can be implemented to further fine-tune patient individualized drug titration. All sources of pharmacological and effect monitoring can be combined into anaesthetic advisory and closed-loop feedback systems enlarging the existing kinetic-based administration technology towards a total coverage of the dose-response relation.

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Summary, conclusions and future perspectives.

This thesis describes the day to day interaction between propofol and midazolam as encountered in every day practice. The direct interaction of premedication given to patients before surgery has profound implications. The propofol induction dose can be decreased with respect to the target BIS. Besides the interaction mechanisms of propofol and midazolam, the pharmacological backgrounds of propofol-opioid interactions are given. The future perspectives of PK-PD modeling and the use of additional informative techniques are given in the last chapter.

Chapter 1: This chapter describes the Propofol-Opioid combinations that are widely used in today's anaesthetic practice. Over the past twenty years the pharmacology of these agents has been described in increasingly greater detail. Together with novel administrating devices and improved anaesthetic depth monitoring, this has created a basis for the optimisation of the administration of propofol-opioid anaesthesia. This article describes the current strategies regarding the application of this type of anaesthesia, focusing on three strategic tools: application of the pharmacokinetic-pharmacodynamic knowledge of propofol and opioids, with particular attention to pharmacodynamic interactions between them; the use of state-of-the-art administration techniques; and the application of bispectral index monitoring. Together, these techniques have improved the level of control, the flexibility and the safety of anaesthetic practice.

Chapter 2: We studied the influence of propofol on the midazolam pharmacokinetics. 8 health male volunteers were studied in a random crossover manner, during which they received either a midazolam bolus infusion in 1 minute followed by an infusion for 59 minutes. During the second session they received the same midazolam infusion and a TCI controlled infusion of propofol. Midazolam plasma levels and whole blood propofol concentrations were measured. In the presence of a mean blood propofol concentration of 1.2 µg/ml, the plasma midazolam concentration increased by 26.9 ± 9.4% compared with midazolam given as single drug. Propofol (C_{blood}:1.2 µg/ml) reduced midazolam central volume of distribution from 5.37 to 2.98 L, elimination clearance from 0.39 to 0.31 L/min and rapid distribution clearance from 2.77 to 2.11 L/min. Inclusion of heart rate further improved the pharmacokinetic model of midazolam.

Chapter 3: during our research we encountered three volunteers who were enrolled in our study that were deeply sedated when given the combination of propofol and midazolam. This deep sedation was recorded with online BIS-XP logging and recording of Ramsey scores.

BIS values of 40-60 were recorded, which in daily practice are regarded as surgical depth of anesthesia. Although the volunteers were deeply sedated they were responsive to questions and could answer simple mathematical questions. The effect is partly due to midazolam because of the effect on the EEG. Spindles (low voltage, high frequency EEG) are interpreted as a sign of a high-level anaesthesia, but are merely an effect of midazolam.

Chapter 4: During the reverse study session eight healthy male volunteers were studied on 2 occasions in a random crossover manner. During session A volunteers received propofol 1 mg/kg in 1 min followed by an infusion of 2.5 $mg.kg^{-1}.h^{-1}$ for 59 min. During session B, in addition to this propofol infusion scheme, a TCI of midazolam (constant C_t: 125 ng/ml) was given from 15 min before the start until 6 h after termination of the propofol infusion. Arterial blood samples were taken for blood propofol and plasma midazolam concentration analysis until 6 h after termination of the propofol infusion. Nonlinear mixed-effects models examining the influence of midazolam and hemodynamic parameters on propofol pharmacokinetics were constructed using Akaike's criterion for model selection. In the presence of midazolam (C_{blood}: 224.8 ± 41.6 ng/ml) the blood propofol concentration increased by 25.1 ± 13.3 % compared to when propofol was given as single agent. Midazolam (C_{blood}: 225 ng/ml) reduced propofol 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. Inclusion of mean arterial pressure (MAP) further improved the propofol pharmacokinetic model.

Chapter 5: we have studied the pharmacokinetic interactions between midazolam and propofol. In this chapter we explore the pharmacodynamic interactions between propofol and midazolam. Our aim was to find the optimal dosing that ensures hemodynamic stability and unconsciousness. The groups that have been studied and the dosing schemes used in the studies are not large enough to reach our goal. We can elude a part of the answers but with respect to a final and definitive answer we will have to study more volunteers with a wider range of dosing schemes. We have found that there is a trend towards synergism between propofol and midazolam for BIS endpoints. During the reconnaissance phase of the PD data and the first calculations a synergistic model was found for propofol and midazolam. The data have been submitted and the reviewers have given us very useful comments. NONMEM interaction with 3D modelling is a useful tool for direct visualization of interaction.

Chapter 6: This review discusses the ways in which anaesthetists can optimize anaesthetic-analgesic drug administration by utilizing pharmacokinetic and pharmacodynamic information. We therefore focus on the dose-response relationship and interactions between intravenous hypnotics and opioids. For intravenous hypnotics and opioids, models that

accurately predict the time course of drug disposition and effect can be applied. Various commercially or experimentally drug effect measurement techniques have been developed and can be implemented to further fine-tune patient individualized drug titration. The development of advisory and closed-loop feedback systems which combine and integrate all sources of pharmacological and effect monitoring, has taken the existing kinetic-based administration technology forwards towards a total coverage of the dose-response relationship.

Future perspectives for intravenous based anesthesia are good. When all developments are considered, there is a thorough basis from which the patient will benefit directly.
The conclusions that can be drawn from this thesis are

Education and study on PK-PD interactions between opioids and Propofol is beneficial for patients, with shorter duration of anesthesia while minimizing side effects.

Pharmacokinetic propofol midazolam interactions prove to be of clinical importance for everyday practice, with regards to induction and maintenance dose.

Pharmacodynamic interactions between propofol and midazolam appear to be synergistic.

Interaction display and effect monitoring during surgery for education and training will be an interactive and useful tool in the operating room.

Future perspectives:
Completion of the pharmacodynamic interaction between propofol and midazolam depends on the implementation of a step up and down model wise approach to the study. At this moment the interaction appears to be synergistic a supplemental study must be considered to draw final conclusions. This thesis has proven that the interaction is worth studying and with a renewed approach will give a more subtle and complete view of this interaction. Introducing the results of the study in display monitoring for surgery with the possibility of introducing premedication, and will be helpful in the OR.

Nederlandse Samenvatting

Anesthesie wordt gegeven voor een groot aantal verschillende chirurgische procedures. Patiënten krijgen een combinatie van slaapmedicijnen en pijnstilling voor de inductie en onderhoud van de anesthesie. Naast deze combinatie van medicatie wordt spierverslapping gegeven zodat de chirurg de operatie kan uitvoeren.
De combinatie van medicijnen die zorgt voor bewusteloosheid en pijnstilling tijdens de operatie heeft als potentieel nadeel dat deze ook de autonome stabiliteit van de patiënt kan ontregelen. Het is dan ook van groot belang dat de anesthesioloog kennis heeft van de pharmacokinetiek, hoe wordt een medicijn door het lichaam opgenomen en afgebroken, en de pharmacodynamiek, wat doet het medicijn met het lichaam.

In hoofdstuk 1 wordt de optimalisatie van de combinatie van anesthetica en analgetica besproken. De anesthesioloog moet steeds meer nadruk leggen op de behoefte van de individuele patiënt waarbij gebruik wordt gemaakt van de farmacologische kennis die is opgebouwd in de laatste 30 jaar. Met deze kennis kan de anesthesioloog de dosis van de gebruikte medicatie aanpassen aan de individuele behoefte zodat alle patiënten snel in slaap kunnen worden gebracht waarbij deze zo stabiel mogelijk zijn en na de operatie weer snel wakker kunnen worden. Met deze kennis hebben de patiënten zo min mogelijk last van bijwerkingen. Het gebruik van deze kennis gaat samen met de toepassing van een aantal zogenaamde “state of the art” technieken. Het gaat hier om gebruik van target-controlled-infusion (TCI). Tot voor kort werden slaapmiddelen manueel toegediend waarbij geen rekening werd gehouden met de individuele karakteristieken. TCI gebruikt de karakteristieken van een individuele patiënt voor het bereiken en onderhouden van een stabiele bloed of plasmawaarde van een anestheticum. De diepte van de narcose kan worden gemonitored door middel van een afgeleide van het EEG, de Bispectral Index monitoring (BIS). BIS correleert sterk met de diepte van de narcose zodat de diepte van de narcose kan worden aangepast aan de behoefte van de individuele patiënt.

In hoofdstuk 2 en Hoofdstuk 4 worden Propofol en Midazolam samen gegeven, waarbij wordt gekeken hoe deze elkaar beïnvloeden. Midazolam is een slaapmiddel dat veel wordt gebruikt voor preoperatieve anxiolyse, langdurige sedatie op de intensive care en soms bij langdurige ingrepen. Propofol en midazolam worden soms gecombineerd en onderzoek naar de interactie was met name op het gebied van pharmacodynamiek, waarbij de rol van het cytochroom in de lever de focus van het onderzoek was. Wij hebben de rol van de interactie onderzocht tijdens langdurige infusies middels TCI. Tijdens de sessies kregen de vrijwilligers

eerst een target controlled infusie met ofwel midazolam of propofol. Na 15 minuten werd een tweede infusie gestart met ofwel propofol of midazolam. Gedurende de gehele sessie werden arteriële bloedmonsters genomen welke later werden bepaald in het laboratorium. Ook werden alle hemodynamische data digitaal opgenomen voor latere verwerking.
In de uiteindelijke PK-set voor midazolam, blijkt dat de toevoeging van hartslag (slagen per minuut) de tijd-concentratie beschrijving van de gevonden waarden nog beter weergeeft.

Table 3. Pharmacokinetic parameters of Midazolam (based on the final Pharmacokinetic Parameter Set with Propofol and Heart Rate as covariates) for various Propofol and Heart Rate Values as used in the Computer Simulations

Propofol (µg/mL)	0	1.5	0	0
Heart Rate (min^{-1})	63	63	40	90
V_1	5.37	2.57	5.37	5.37
V_2	26.2	26.2	26.2	26.2
V_3	48.9	48.9	69.7	32.3
Cl_1	0.39	0.30	0.32	0.50
Cl_2	2.73	1.94	1.34	6.30
Cl_3	0.36	0.36	0.36	0.36

Bij een gelijktijdige infusie van propofol en midazolam is een reductie nodig van ongeveer 15% om de midazolamconcentraties te verkrijgen die zijn ingesteld met de TCI.
Naast deze reductie is er ook een duidelijk verschil in de 80% decrement time. Deze waarde geeft aan dat de klaring van midazolam uit het bloed afneemt.
In het omgekeerde onderzoek is eerst midazolam TCI gegeven, zodat er een stabiele waarde in het bloed was. Daarna is een infusie van propofol gegeven. Midazolam geeft een verhoging van de propofolconcentratie. De klaring van propofol uit het bloed is sterk afgenomen. Bij het uiteindelijke model waarin alle covariaten zijn opgenomen blijkt dat toevoeging van de Mean Arterial Pressure (MAP) het pharmacokinetische model verder verbetert. (zie Tabel)

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	

In hoofdstuk 4 beschrijven wij een aantal vrijwiligers die tijdens de studie die gesedeerd waren tijdens de studie met lage BIS waardes. Ook de Ramsey scores, een maat voor diepte van de sedatie, gaven dat aan. De gemeten BIS waarden waren tussen de 40 en 60, wat gezien wordt als een chirurgische narcose. Hoewel deze vrijwilligers diep waren gesedeerd waren konden deze vrijwilligers gemakkelijk wekbaar en konden simpele vragen beantwoorden. Het effect wat werd gezien is zeer waarschijnlijk het effect van midazolam. Spindles op het elektro-encefalogram (EEG) worden door de BIS geïnterpreteerd als een diepe narcose

.

In **hoofstuk 5** komen hoofdstuk 2 en 4 samen. Alle data van de onderzoeken worden samen genomen en word gekeken naar de pharmacodynamische interacties. Het doel van het onderzoek is het vinden van de optimale dosering voor de combinatie van propofol en midazolam waarbij zo min mogelijk bijwerkingen optreden en de patiënt hemodynamisch stabiel is. Binnen het onderzoek lijkt er een trend te zijn naar synergie tussen propofol en midazolam. Hierbij verstreken de beide middelen elkaar en is er minder van beide nodig, wat weer leidt tot minder bijwerkingen. Met name als er gekeken wordt naar het eindpunt BIS lijkt deze samenwerking zich uit te betalen. Gezien de grootte van de groepen is het nog wel nodig om aanvullend onderzoek te doen om deze synergie definitief vast te stellen.

In **Hoofdstuk 6** wordt een overzicht gegeven van de verschillende manieren waarop de anesthesist gebruik kan maken van de PK-PD informatie die er beschikbaar is, waarbij de focus ligt op de dosis-respons relatie en interactie tussen intraveneuze hypnotica en opiaten. Er zijn op dit moment modellen die de PK-PD van de hypnotica goed kunnen voorspellen. Daarnaast zijn er ook commerciële en experimentele metingen beschikbaar voor anesthetica die nog beter de individualisering van de dosis-respons relatie van patienten kunnen verfijnen. Als laatste komen ook de closed-loop systemen aan bod welke pharmacologische- en effect-metingen integreren en combineren. Effecten van en bloedwaarden van hypnotica

kunnen zo als een geheel worden gezien en geven de anesthesioloog direct inzicht in de individuele behoefte van patienten.
De conclusies die dan ook kunnen worden getrokken uit deze studies zijn dan ook:

- Onderzoek naar en onderwijs over de PK-PD interacties tussen propofol en opiaten is belangrijk voor patientenzorg. Het leidt tot een kortere anesthesie met minder bijwerkingen.
- Pharmacokinetische interacties tussen propofol en midazolam zijn klinisch belangrijk, met betrekking tot de inductie en onderhoudsdosis van de narcose
- Interacties tussen propofol en midazolam op pharmacodynamisch vlak lijken synergistisch te zijn wanneer men kijkt naar BIS als waarde
- Het visueel weergeven van de interacties tussen en effecten van anesthetica voor onderwijs is een interactieve en waardevolle toevoeging in de operatiekamer

Toekomstperspectieven: hernieuwd onderzoek naar de pharmacodynamische interactie tussen propofol en midazolam zal een nog beter beeld geven van deze interacties. Op dit moment lijkt deze interactie synergistisch van aard te zijn, maar toegevoegd onderzoek zal dit kunnen uitwijzen. Het implementeren van deze interacties binnen de interactie display zal een waardevolle toevoeging zijn aan de dagelijkse praktijk.

Curriculum Vitae

De auteur van dit proefschrift is geboren op 3 augutus 1974 in Utrecht. In 1993 deed hij eindexamen op het VWO van het Maartenscollege in Haren. In 1993 startte hij met de opleiding geneeskunde aan de Rijksuniversiteit in Groningen. Met een tussenjaar in de Verenigde Staten in Galveston (Tx), waar hij onderzoek deed bij het Galveston Shriners Burns Institute for Children, bij D.N Herndon behaalde hij zijn artsexamen in 2000. Na de opleiding geneeskunde startte hij als AGNIO op de intensive Care van de Weezenlanden in Zwolle. In 2001 startte hij met de opleiding Anesthesiologie als AGIKO onder Prof.Dr J.W. van Kleef. In nauwe samenwerking met Dr. J. Vuyk is het onderzoek wat heeft geresulteerd in dit proefschrift staan beschreven opgezet.

Na de opleiding is de auteur werkzaam geweest in St. Antonius Ziekenhuis in Nieuwegein. Sinds 2008 is de auteur werkzaam als anesthesioloog in het Universitair Medisch Centrum Groningen als staflid met aandachtsgebied cardiothoracale anesthesie.

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