Don't be afraid!

Population PK-PD modeling as the basis for individualized dosing in children and critically ill

M. Y. M. Peeters

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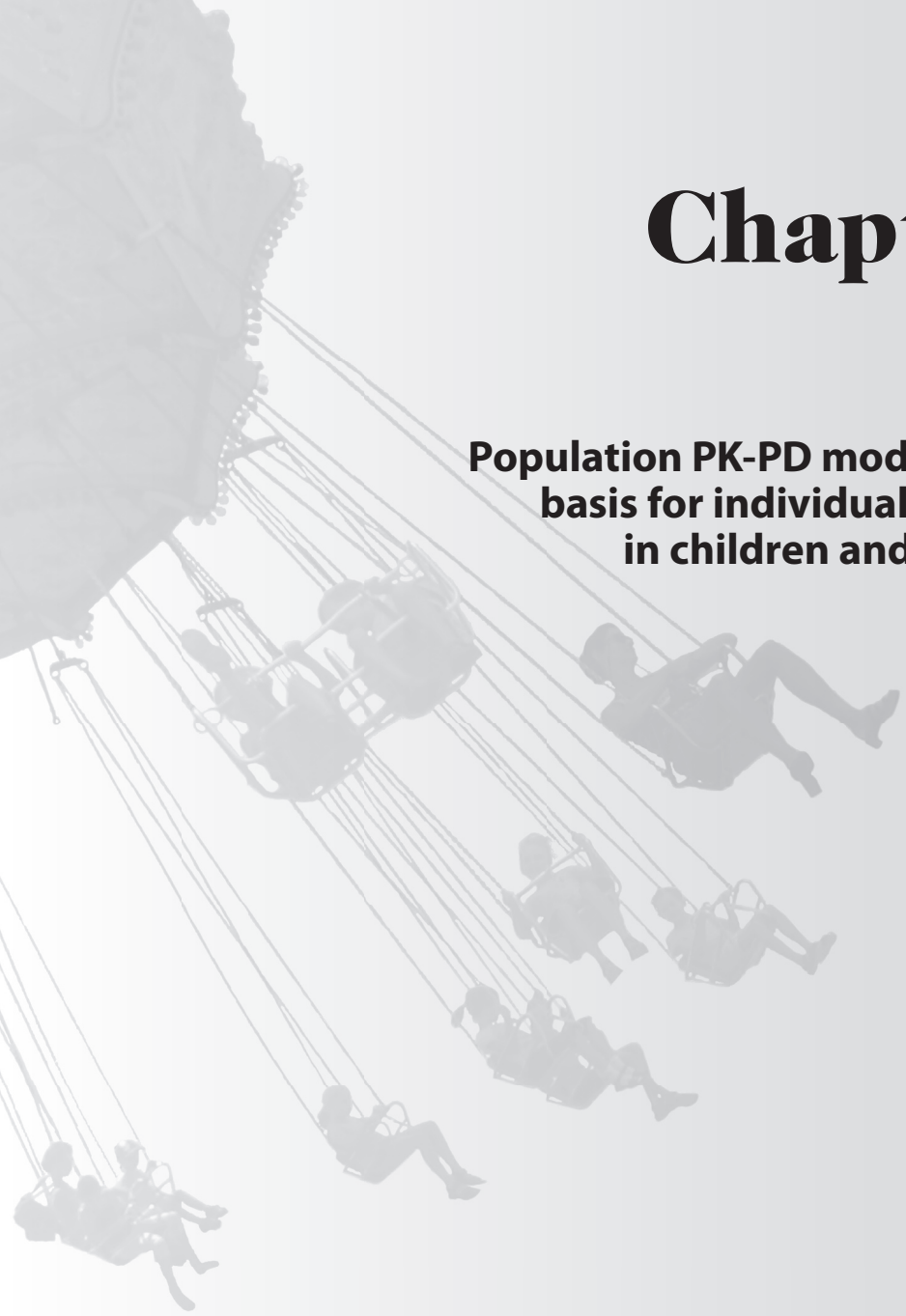

Chapter 1

Population PK-PD modeling as the basis for individualized dosing in children and critically ill

Introduction on sedation in pediatrics and long-term intensive care

Anxiety, agitation, delirium and pain are common in the adult and pediatric intensive care unit ((P)ICU). These "unhealthy" states may lead to increased discomfort, motor activity, self-extubation and psychological derangements leading to hypertension, tachycardia, and even cardiac ischemia. The appropriate treatment of these conditions may lead to a decreased morbidity and mortality in critically ill patients.[1-3] In the past decade, the level of sedation thought to be optimal has changed from deeply sedated and even paralyzed to light sedation.[4] Improvements in ventilator technology have been associated in this respect. In the meantime there is strong evidence that patients who are over sedated may be exposed to excessive mechanical ventilation, leading to associated complications such as ventilator-associated pneumonia,[5] delirium,[6] and post-ICU psychological effects.[7] Daily interruptions of sedation and the use of a sedation protocol have been shown to reduce the length of mechanical ventilation and the length of stay in the ICU.[8-10] In infants and children the increased use of sedatives in the first 24 h of weaning from mechanical ventilation has been associated with failure of extubation.[11] As a result of these and other observations, consensus recommendations to guide analgesic and sedative therapy were provided for both the adult and the pediatric intensive care unit (ICU).[12,13]

Recommended choices of sedatives in the adult intensive care are: for rapid sedation: midazolam or diazepam; for short-term sedation ($\leq$ 24 h): midazolam; for long-term sedation: lorazepam; and when rapid awakening is crucial: propofol.[12] In pediatrics, midazolam is the recommended and most commonly used sedative.[13]

Midazolam is a short acting benzodiazepine.[14] Disadvantages are the formation of active metabolites by the cytochrome P450 isoenzyme 3A4 which can accumulate, particularly in renal failure,[15] the possibility of the development of paradoxical reactions in children and elderly, and its longer and more variable recovery time after stopping compared to propofol. Moreover, with long-term infusion, drug-drug interactions may become important. Finally, in preterm neonates an increased incidence of poor neurological outcome (as intraventricular hemorrhage) has been reported.[16]

Lorazepam is a benzodiazepine, of which the pharmacokinetics is relatively independent of liver function or co-medication with other drugs.[17] Due to its longer terminal half-life compared to midazolam,[18] questions have been arisen about its value for long-term use.[19]

Propofol (2,6-diisopropyl phenol) allows a quick recovery in patients receiving either short-term or long-term sedation, as well as an easily controllable level of sedation, because of its unique pharmacokinetic profile.[20] Known adverse effects of propofol administration include cardiovascular depression, transient oxygen desaturation and in case of long sedation times (> 72h) a progressive rise in triglycerides, probably due to the fat vehicle.[21] This fact has motivated the development of a more concentrated formulation (60 mg/L; propofol 6%), which reduces fat load three to six times compared to the commercially available Diprivan-10 (Propofol 1%) and Diprivan-20 (Propofol 2%), while maintaining the same pharmacokinetic and pharmacodynamic properties.[22-27] Propofol has also gained great popularity in the pediatric population, but its routine use is not recommended for prolonged use in the intensive

care unit and even contraindicated, because of the association with the "propofol infusion syndrome," which manifests itself as dysrhythmias, heart failure, metabolic acidosis, hyperkalemia, and rhabdomyolysis.[28-30] To date, use of propofol in the ICU in neonates have been reported for short procedural sedation.[31]

Although consensus recommendations have been established for sedation, the management of sedation in the ICU is not ideal in practice.[32-34] As a result optimization of sedation is still a matter of debate.[17,32,35] One of the reasons is that no single dose is appropriate for the critically ill (pediatric) patient, while trial and error may lead to oversedation and adverse events.

Thus, optimal sedation of patients in the ICU requires individualized dosing. The investigations in this thesis focus on the use of population PK-PD modeling as the basis for individualized dosing of sedatives in pediatrics and critically ill.

Mechanisms of intra- and interindividual variability in response

Patients' responses to sedatives are often unpredictable, because of large inter-individual differences in the pharmacokinetics and the concentration-effect relationships between patients.[23,36-41] Especially in critically ill patients who usually present with changing hemodynamic instability and failure of one of more organs, large differences in infusion rates are required to achieve the same degree of sedation. For example the infusion rate of midazolam required has been shown to vary among patients by a factor of five.[42] In pediatric intensive care patients (aged 2 days to 17 years) no clear pharmacokinetic – pharmacodynamic relationship was found.[37] During childhood, many physiological changes take place, which may have an impact on the PK and PD of a certain sedative.

According to the literature, the optimal dose of midazolam may vary as a result of many factors, including hepatic blood flow which may be affected by mechanical ventilation, hepatic and renal function, the condition of patients and the enzyme activity of the cytochrome P450 3A subfamily during the first year of age.[18,40,43,44]

For propofol, covariates as weight, age, gender, cardiac output and albumin have been shown to influence the pharmacokinetics,[23,45-49] whereas an increased sensitivity to propofol has been shown in elderly patients.[50] In children, larger doses are required and it has been suggested that this is due to differences in pharmacokinetics and/or sensitivity.[51,52]

However, large (observed) inter-individual variability in the effect of sedatives remain unexplained so far, which complicates dosing in clinical practice and may indeed increase the risk of over sedation and adverse events.

Research on intra- and interindividual variability in response to sedative drugs

As a response to the clinical need for safe and correct dose administration, dosing schemes should be developed with accurate endpoints.

Several observational sedation scoring systems have been developed and tested in a variety of clinical settings.[53] The Ramsay score,[54] a six point scale, is the most widely used scale for monitoring sedation in adult ICU patients as well as in clinical research. The Ramsay score has a demonstrated good inter-rating reliability,[55] but it has been criticized by the fact that it is based on a motor response. In children, the COMFORT scale[56] is recommended,[13] which scores the variables – mean arterial blood pressure, heart rate, muscle tone, facial tension, alertness, calmness/agitation, respiratory behavior and physical movement –after a 2-min period of observation. The COMFORT-behavior (COMFORT-B) scale,[57,58] is a reliable alternative and is routinely used in most PICUs in the Netherlands. The Bispectral Index (BIS) is based in part on a bispectral analysis of the electroencephalogram. In the bispectral analysis, the weight factors of the various subparameters were assigned in a multivariate model based on a prospectively collected database of EEG recordings from adults and matched to the corresponding states of hypnosis. The BIS algorithm uses a complex formula with advanced techniques to define a dimensionless BIS value from 0 (complete cortical EEG suppression) to100 (fully awake).[59] The Bispectral index has been developed as a tool to measure the level of consciousness during anesthesia and has theoretical benefits in comparison to clinical measures of sedation, because it assesses sedation continuously and may provide an objective, quantitative measure of the level of sedation. The Bispectral index has been approved for use in the operating room. However, it is also used to evaluate depth of sedation in the ICU patients. BIS values have shown a marginal to good correlation with sedation scores in children and adults.[60-62] In pediatric patients older than 1 year of age, the technology appears to perform in a similar manner to the adult population. In younger infants, brain maturation and development may render processed EEG measures unreliable. Technical limitations have been reported for the critical care environment such as EMG interference[63] and influence of environmental factors.[64] As a result, at present the BIS requires more validation before its role is established in the (P)ICU.[12,13,62]

An important tool for development of dosing guidelines is pharmacokinetic and pharmacodynamic modeling. In particular, Nonlinear Mixed Effect Modeling (NONMEM) is an interesting approach for clinical practice, as it describes and explores factors (covariates) influencing intra- and inter-patient variability, in contrast to traditional study designs in which variability is typically minimized by restricting inclusion criteria.[65] The approach analyses data from all individuals simultaneously which may be sparse and unbalanced. As frequent sampling is not necessary, the method is also of special interest for application in children and in particular in neonates due restrictions in the maximum number of blood samples that may be obtained. The population model comprises three sub-models: 1) structural, 2) statistical and 3) covariate model. The structural (PK or PD) sub-model describes the overall trend in the data. For the PK, this can be a two-compartment model and for the

PD (e.g. the level of sedation, this may be a sigmoid E_{max} model for continuous data such as the COMFORT-B and BIS or a proportional odds model for categorical data such as the Ramsay sedation scale. The statistical sub-model accounts for variability by using two levels of random effects: inter-individual variability and intra- or residual variability. The covariate sub-model expresses relationships between covariates and PK or PD model parameters, using fixed effects parameters. Covariate analysis involves the modeling of the distribution of the individual parameter estimates as a function of patient characteristics (e.g. age, body weight, gender), pathophysiological factors (e.g. renal or hepatic function), genetic/environmental factors and/or the concomitant use of other drugs, which may influence the PK and/or PD. The identification of predictive covariates for variability provides the scientific basis for rational and individualized dosing schemes. In NONMEM parameters are estimated via a maximum likelihood approach, whereby the joint function (the objective function) of all model parameters and the data (the observations) is evaluated. The maximum likelihood parameter estimates are the parameter estimates yielding the greatest probability that the given data occur. Goodness of fits plots including observations *vs.* individual predictions, observations *vs.* population predictions, weighted residuals *vs.* time and population predictions *vs.* weighted residuals are used for diagnostic purposes of both pharmacokinetic and continuous pharmacodynamic data. For categorical pharmacodynamic data "naïve pooled observed" probabilities are defined. Furthermore, the confidence interval of the parameter estimates, the correlation matrix and the visual improvement of the individual plots are used for evaluation. For the identification of covariates, scatter plots of covariates *vs.* individual post-hoc estimates and the weighted residuals are valuable for visualization of potential relationships followed by stepwise testing for statistical significance. For testing the developed model, external validation provides the most stringent method. When a test data set is not available and the sample size is small (especially in pediatric studies), the bootstrap approach can be useful, in which the mean parameter values obtained by repeatedly fitting the final model to the bootstrap replicates are compared to the final parameter estimates from the original data set.

In the meantime, population PK-PD modeling has been successfully implemented in many clinical studies, mostly initiated by the industry and it is encouraged for use in clinical investigations in children nowadays. In children, only 25-50% of drugs used are licensed for this population.[66,67] As a result, the common approach for dosing of unlicensed or off-label drugs in children is to use clinical data from adults and to adjust the dose according to the child's weight.[68] It has been amply demonstrated that this may result in adverse events because the differences in pharmacokinetics and pharmacodynamics in different age groups, governed by differences in (organ) function which may change independent of body weight. The European Medicines Agency and the Pediatric Working Party (EMEA/496777/06) have recently released a priority list of off-patent medicinal products for pediatric studies to increase the availability of licensed drugs. Unfortunately, NONMEM is not often applied in clinical (pediatric) practice. Most clinicians view this approach and the models as complicated, requiring technically sophisticated knowledge without proven clinical utility. We believe that in particular interaction between clinicians and experts in PK-PD modeling may result in rational dosing guidelines for drugs currently used in clinical practice.

Objective of the thesis

The overall goal was to develop novel strategies to individualize sedative dosing in the special group of infants and critically ill patients, on the basis of population pharmacokinetic-pharmacodynamic (PK-PD) modeling. In the investigations the emphasis was on the modeling of the influence of the covariates age, severity of illness and organ failure on the pharmacokinetics and pharmacodynamics of the sedatives propofol and midazolam.

Outline of the thesis:

Sedation in pediatrics

Propofol and midazolam were studied in a population of relatively healthy non-ventilated infants aged 3-24 months following craniofacial surgery. **Chapter 2** describes the clinical results obtained with propofol in this patient group and focuses specifically on the evaluation of the safety as the use of propofol is still controversial in the pediatric intensive care. No adverse events in terms of increased triglycerides, creatine phosphokinase or metabolic acidosis were observed, using dosages < 4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}, during a median of 11 h. In **Chapter 3** dosing guidelines are developed for propofol, based on population pharmacokinetic and pharmacodynamic modeling, using the COMFORT-B score and the BIS as pharmacodynamic endpoints. A remarkably high clearance of propofol was found, which was shown to be influenced by bodyweight. Moreover, a very high interindividual variability in the pharmacodynamics (i.e. the brain sensitivity to propofol) was described. The investigations in **Chapter 4** focus on the pharmacokinetic-pharmacodynamic modeling of midazolam. As found for propofol, the clearance of midazolam was relatively high. The interindividual variability in pharmacodynamics on the COMFORT-B was 89%, thereby showing a less predictable effect than propofol (47%).

Sedation in critically ill patients

Propofol was studied in the population of critically ill patients, who are characterized by high variability in dosing requirements between and within patients. In **Chapter 5** we evaluated the implementation of a sedation protocol in the ICU. The findings of our study show, that in practice, on average patients were deeper sedated by the nurses than was intended by the physicians. In **Chapter 6** the influence of the severity of illness (expressed as Sequential Organ Failure Assessment; SOFA score) of the patients was studied on the pharmacokinetics and pharmacodynamics, using the Ramsay and BIS as pharmacodynamic endpoints. It was shown that severity of illness is a major determinant of the response to propofol, with the patients with the highest SOFA score requiring the lowest doses for adequate sedation. In **Chapter 7** the influence of variability in liver blood flow (as determined on the basis of the sorbitol clearance) and cardiac output on the pharmacokinetics of propofol were explored in

a preliminary study. It was shown that the variability in hepatic blood explains a large part of the variability in propofol clearance. It was also shown that in this patient group variability in hepatic blood flow is unrelated to variability in cardiac output.

Discussion and perspectives

The results of the investigations described in this thesis are reviewed and discussed in **Chapter 8.** In addition, prospective use of developed population models were tested for their predicted value in the youngest pediatric age group, namely neonates, using allometric scaling (between species and within children) and the per kg model.

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Sedation in pediatrics

Chapter 2

Propofol 6% as sedative in children under 2 years of age following major craniofacial surgery

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Abstract

Background: After alarming reports concerning deaths after sedation with propofol, infusion of this drug was contraindicated by the US Food and Drug Administration in children <18 yr receiving intensive care. We describe our experiences with propofol 6%, a new formula, during postoperative sedation in nonventilated children following craniofacial surgery.
Methods: In a prospective cohort study, children admitted to the pediatric surgical intensive care unit following major craniofacial surgery were randomly allocated to sedation with propofol 6% or midazolam, if judged necessary on the basis of a COMFORT-Behavior score. Exclusion criteria were respiratory infection, allergy for proteins, propofol or midazolam, hypertriglyceridemia, familial hypercholesterolemia or epilepsy. We assessed the safety of propofol 6% with triglycerides (TG) and creatine phosphokinase (CPK) levels, blood gases and physiological parameters. Efficacy was assessed using the COMFORT-Behavior scale, Visual Analogue Scale and Bispectral index™ monitor.
Results: Twenty-two children were treated with propofol 6%, 23 were treated with midazolam and 10 other children did not need sedation. The median age was 10 ($_{IQR}$ 3-17) months in all groups. Median duration of infusion was 11 (range 6-18) h for propofol 6% and 14 (range 5-17) h for midazolam. TG levels remained normal and no metabolic acidosis or adverse events were observed during propofol or midazolam infusion. Four patients had increased CPK levels.
Conclusion: We did not encounter any problems using propofol 6% as a sedative in children with a median age of 10 ($_{IQR}$ 3-17) months, with dosages < 4 mg kg^{-1} h^{-1}, during a median period of 11 (range 6-18) h.

Introduction

Propofol for sedation in children has become controversial after reports describing the propofol infusion syndrome, which is characterized by increased triglyceride (TG) levels,[1,2] myocardial failure,[1-3] rhabdomyolysis,[2,3] metabolic acidosis,[1-3] hyperthermia[1] and death.[1] Therefore a warning was issued against use of propofol as a sedative in children < 18 years in intensive care.[4]
In Diprivan®-10, propofol is formulated in Intralipid® 10%. Long-term infusions of Diprivan®-10 have been associated with increases in serum lipid levels, notably TG.[3] In order to reduce the volume and amount of lipids, a new formulation of propofol 6% in Lipofundin® MCT/LCT 10% (propofol 6%) was developed and tested in animals,[5] adults[6] and six children.[7]
In contrast with propofol, midazolam is a widely used sedative for children.[8,9] On initial administration, it has a short duration of action.[10] However, paradoxical reactions such as agitation,[11] convulsions, hyperactivity or adverse reactions[12] have been reported in neonates and children.[13] Also, the active metabolites and prolonged effect of midazolam often delay awakening and weaning from mechanical ventilation.[14,15] A new formula for propofol would be an alternative or additional sedative in children receiving intensive care. In view of the existing controver-

sies, we present our experiences with propofol 6% as a postoperative sedative in nonventilated children < 2 yr of age following major craniofacial surgery.

Materials and Methods

With approval from the Erasmus MC research ethics board and written consent from a parent or legal guardian, from July 2002 until September 2003 we studied children aged between 1 month and 2 yr of age admitted to our pediatric surgical intensive care unit (PSICU) during the first 24 h after elective craniofacial surgery. Exclusion criteria for propofol were known allergies for proteins, egg or propofol, respiratory infections, hypertriglyceridemia, epilepsy, familial hypercholesterolemia or weight < 6 kg.
At least 1 day before surgery, the parents of eligible patients were asked to give written informed consent for either propofol or midazolam. If consent for propofol was refused, consent was asked for midazolam, even though midazolam is our standard of care. Four patients were excluded from receiving propofol on the ground of familial hypercholesterolemia, one patient was excluded as his TG level was 2.62 mmol litre^{-1} the day before surgery, probably because he had been fed just before blood sampling, and parents of two patients refused consent for propofol. These seven patients received midazolam for sedation instead of propofol.

Perioperative procedure

Anesthesia was induced with either sevoflurane or i.v. thiopental. An arterial line and a central venous line were placed for clinical purposes and blood was drawn to evaluate liver and kidney function, TG level and creatine phosphokinase (CPK) level. After i.v. administration of vecuronium 0.1 mg kg^{-1} and fentanyl 2.5 µg kg^{-1}, the trachea was intubated and ventilated with air, oxygen and isoflurane. Approximately 2 h before anticipated extubation, acetaminophen 40 mg kg^{-1} was administered rectally as previously described.[16] After surgery, the trachea was extubated and the patient was transferred to the PSICU, where heart rate, arterial pressure, oxygen saturation and central venous pressure were monitored continuously. Body temperature was measured every 2 h. Routine postoperative care included evaluation of haemoglobin, haematocrit, thrombocytes, white blood count and arterial blood gases. The children received no parenteral nutrition during the study period.

Sedation and analgesia protocol

On admission to the PSICU, usually in the early afternoon, sedation and analgesia levels were assessed using the COMFORT-Behavior scale and the Visual Analogue Scale (VAS). At COMFORT-Behavior scores < 17, no sedatives were given. At scores ≥ 17, propofol or midazolam was started. At VAS scores ≥ 4, more analgesia was given. During the first 2 h after start of sedation, sedation and analgesia levels were assessed at least three times using the COMFORT, VAS and Bispectral Index (BIS) values. After the first 2 h, the level of sedation was assessed every 2 h until the next morning. If the COMFORT-Behavior score remained ≥

17 after administration of a sedative, propofol and midazolam dosing were increased by 0.1 ml h^{-1} and 0.025 mg $kg^{-1}h^{-1}$, respectively. If scores remained ≥ 17 during propofol infusion of a maximum of 4 mg $kg^{-1}h^{-1}$, midazolam was added. At scores < 9, propofol and midazolam dosing were decreased by 0.1 ml h^{-1} and 0.025 mg $kg^{-1}h^{-1}$, respectively.
At 8 a.m. the next morning, the sedatives were stopped to allow the patients to wake up and prepare for transfer to medium care. The effects of stopping the infusion were assessed using the COMFORT, VAS and BIS for the next 2 h. At approximately 11 a.m., all children were transferred to medium care.

The COMFORT-Behavior scale

The COMFORT-Behavior scale is an adapted version of the scale that was originally developed by Ambuel *et al*.[17] in 1992 and consists of six behavioural items and two physiological parameters, heart rate and blood pressure. Marx *et al*.[18] showed that this scale was useful to assess sedation. We showed that, leaving out the physiological items, the scale was still valid for both postoperative pain and sedation in children aged 0-3 yr.[19] The COMFORT-Behavior scale assesses six patterns of behaviour: alertness, calmness, muscle tone, body movement, facial tension, crying (nonventilated children) or respiratory response (ventilated children). The total score ranges from 6 to 30: the higher the score, the more uncomfortable the child is. All nurses were trained to use the COMFORT-Behavior scale, as reported in our earlier analgesia study. Inter-observer reliability, represented by linearly weighted κ was satisfactory, with κ > 0.65 for all nurses and principal investigator. A COMFORT-Behavior score < 9 represents oversedation, score between 9 and 17 represents no distress and ≥ 17 represents distress.

Bispectral index monitor

Sedation was assessed continuously using a Bispectral A 2000 version 3.12 monitor (Aspect Medical Systems, Natick, MA, USA) with commercially available pediatric BIS sensors applied according to the manufacturer's instruction manual. We used the impedance limits set in the monitor: if the signal quality index was > 50, the BIS value was recorded.

Visual Analogue Scale

To determine whether restlessness might be induced by pain, analgesia levels were assessed using the VAS. At VAS scores ≥ 4, more analgesia was given. If the VAS score was < 4 and the COMFORT-Behavior ≥ 17, a sedative was given.

Determining safety

Before, during and 2 h after stopping the infusion of propofol or midazolam, we determined TG and CPK levels to evaluate the influence of propofol on these variables. We used an enzymatic and colorimetric in vitro test, with a Hitachi analyser (Roche Diagnostics, GmbH, Mannheim, Germany). TG levels in the range 0-1.6 mmol $litre^{-1}$ and CPK levels < 230 U $litre^{-1}$ were considered normal.[20] We defined desaturation as saturation < 95% for > 5 s and requiring intervention. Hypotension was defined as any period of time when a patient's arterial pressure was 10-15% below the arterial pressure mentioned in Table 1. Bradycardia was defined as any

period of time when a patient's heart rate was <80 beats min^{-1} (see Table 1). Hyperthermia was defined as body temperature > 38.3ºC. Metabolic acidosis was defined as arterial pH < 7.30 with a concomitant $PaCO_2$ < 4.7 kPa. All physiological parameters, except temperature, were screened hourly using a computer-guided patient data management system.

Determining efficacy

To compare efficacy of propofol with that of midazolam, we considered COMFORT-Behavior, VAS scores and BIS values in four groups: children receiving propofol, children receiving propofol with additional midazolam, children receiving midazolam and children who did not need sedation. Additionally, we determined the dose change frequency, i.e. the number of times that dosing of propofol or midazolam was adjusted.

Medication preparation

Propofol 6% was prepared in the Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands.[21] Propofol 6% was given through the central venous line in order to prevent pain from injection. Midazolam hydrochloride was dissolved in glucose 5% to make an i.v. solution.

Statistical analysis

The data were analysed using SPSS for Windows (version 10,0; SPSS, Chicago, IL). The safety parameters of children receiving propofol 6% and those receiving no propofol 6% were compared using the Mann-Whitney *U*-test. Statistical differences were considered significant if $P < 0.05$. A correlation r of 0.10-0.29 was considered small, 0.30-0.49 was considered medium and ≥ 0.50 was considered large.

Table 1 Patient characteristics. Data are median (range). *N/a, not applicable

Total *n*=55	**Propofol *n*=17**	**Propofol + midazolam *n*=5**	**Midazolam *n*=23**	**No sedatives needed *n*=10**
Patients, M/F	11 / 6	4 / 1	17 / 6	5 / 5
Age, months	9 (4-17)	12 (11-17)	11 (3-15)	9 (4-13)
Weight, kg	9 (6-13)	10 (9-10)	10 (5-12)	8 (6-10)
Duration of surgery, h	5 (4-7)	4 (4-5)	5 (3-7)	5 (3-6)
Duration of infusion of sedatives, h	12 (6-17)	10 (7-18)	13 (4-17)	*N/a
Doses, mg kg^{-1} h^{-1}	2.4 (1.8-4.0)	Propofol 3.0 (1.8-3.6) Midazolam 0.1 (0.05-0.10)	0.05 (0.05-0.20)	*N/a
Baseline arterial pressure, mm Hg	55 (35-100)	50 (40-60)	51 (35-82)	52 (45-55)
Baseline heart rate, beats min^{-1}	129 (90-180)	127 (95-150)	113 (80-153)	121 (105-140)

Results

We studied 55 patients, with a median age of 10 ($_{IQR}$ 3-17) months and weight 9 (5-13) kg. Pre-operative diagnoses were scaphocephaly (*n*=26), trigonocephaly (*n*=18), brachycephaly (*n*=2), encephalocele (*n*=1), plagiocephaly (*n*=5) and Saethre-Chotzen syndrome (*n*=3). There was no significant differences between the groups with regard to age, weight, duration of surgery or duration of infusion of sedatives (Table 1).

In one patient the TG level was 2.00 mmol litre^{-1} during propofol infusion without metabolic acidosis, disturbance in physiological parameters or increase of CPK levels (Figure 1). Four patients had raised CPK levels, ranging from 261 to 313 U litre^{-1} during and after the end of infusion (Figure 2). Three patients had received propofol and one patient had no medication. Two patients receiving propofol had elevated CPK levels before the start of infusion and one of these patients had elevated CPK levels during and after infusion. The first patient had CPK levels of 261 U litre^{-1} before infusion. The second patient had CPK levels of 336 U litre^{-1} before infusion, 276 U litre^{-1} during infusion and 240-282 U litre^{-1} after infusion. One patient receiving propofol had a CPK level of 313 U litre^{-1} after infusion. These patients showed no acidosis, no abnormal physiological parameters and no increased TG levels.

There were no respiratory complications. Three patients, one receiving propofol and two receiving midazolam, experienced short periods of desaturation with spontaneous recovery.

Median minimal arterial pressure was 56 mm Hg and 59 mm Hg for propofol 6% and no propofol 6%, respectively (Mann-Whitney *U*-test, 330; *P*=0.57). Median minimal heart rate was 110 beats min^{-1} and 111 beats min^{-1} for propofol 6% and no propofol 6%, respectively (Mann-Whitney *U*-test, 353; *P*=0.86). One episode of bradycardia lasting 90 s (median of 77 beats min^{-1}) was observed in a patient receiving midazolam. The median maximal temperature was 37.8ºC during propofol and 37.7ºC with no propofol (Mann-Whitney *U*-test, 352; *P*=0.84).

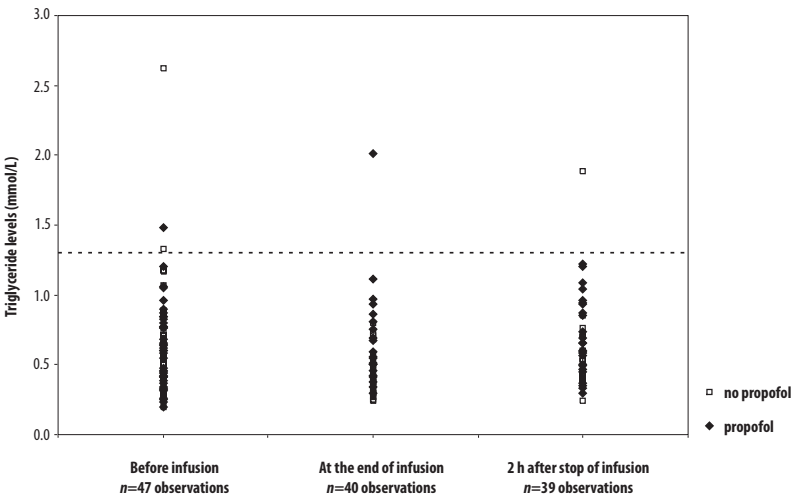

Figure 1 Triglyceride levels

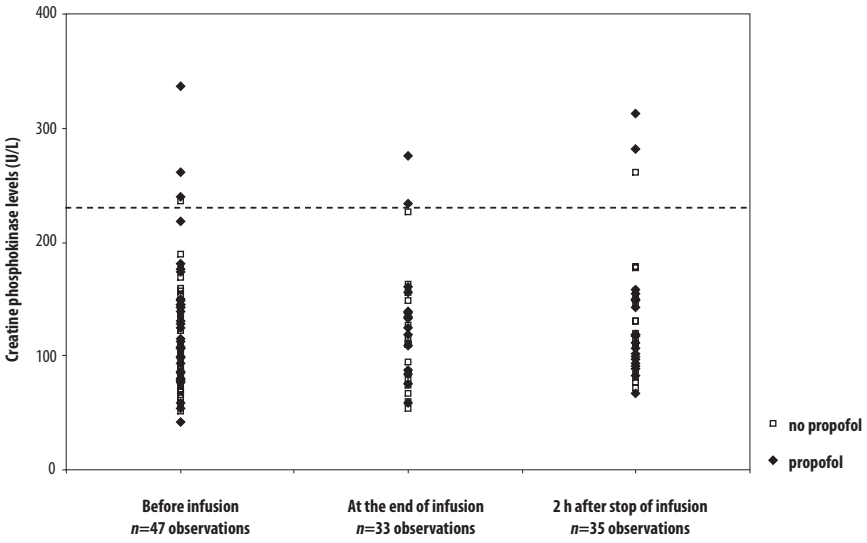

Figure 2 Creatine phosphokinase levels

A total of 915 paired COMFORT-Behavior scores, VAS and BIS values were obtained with a median of 15 ($_{IQR}$ 13-18) observations per patient. During infusion of propofol 6% median COMFORT and BIS values were 11 (9-18) and 78 (65-91), respectively. During infusion of midazolam, median COMFORT and BIS values were 11 (9-15) and 77 (63-91), respectively. VAS was ≥ 4 in only seven observations in seven children (less than 1% of all observations). The starting dose of propofol was sufficient in three children (< 14 %). A propofol infusion of 4 mg kg^{-1} h^{-1} was not sufficient in five cases (~ 23% of the propofol group), and these patients received additional sedation with either a single dose of midazolam (two patients), multiple doses (two patients) or continuous midazolam infusion (one patient) (median rate 0.05 mg $kg^{-1}h^{-1}$).
One of the patients receiving midazolam became agitated and more restless after administration of up to 0.2-mg $kg^{-1}h^{-1}$ maintenance infusion and five doses of midazolam.

Discussion

We did not encounter any problems with propofol 6% in dosages < 4 mg $kg^{-1}h^{-1}$ in children with a median age of 10 ($_{IQR}$ 3-17) months during a median period of 11 (range 6-18) h.
Propofol doses of 2 mg $kg^{-1}h^{-1}$ were insufficient to maintain an adequate sedation level in > 86% of the children. Midazolam was insufficient in only 21% of the children. The TG level was 2.0 mmol $litre^{-1}$ in only one patient, during propofol infusion, without abnormalities in other physiological parameters. This patient had been fed with formula milk Nutrilon 1 (Nutricia, Zoetermeer, The Netherlands), just before blood sampling. Four other patients had increased

CPK levels, without other signs of the propofol infusion syndrome.[22,23] An increase of the CPK level can also be a valid indication of the extent of muscle damage. Muscle damage due to major muscle-cutting surgery, such as craniofacial surgery, has been reported and should be taken into account when interpreting CPK levels postoperatively.[23] CPK levels 10 times higher than normal are regarded as a warning sign for rhabdomyolysis.[23]

A review of the literature yields reports both for and against the use of propofol as a sedative in children. Seventeen publications support propofol use in children at the pediatric intensive care unit (PICU). Pepperman and Macrae[24] found no differences in mortality between propofol and other sedative agents in 198 children. Cornfield *et al*.[25] described continuous infusion of propofol in 142 critically ill children, with a mean age of 5 yr 9 months. Ten showed metabolic acidosis and 10 died during the first week of propofol infusion. These deaths could all be attributed to the primary diagnosis. Martin *et al*.[20] described nine children on mechanical ventilation receiving propofol for sedation and concluded that it was useful and safe. Knibbe *et al*.[7] evaluated propofol for sedation for < 6 h sedation in six children aged 1-5 yr, following cardiac surgery, and found no adverse events. A number of authors have published guides to drug selection and use in the PICU.[8,14,26,27] They acknowledge that propofol infusion may cause problems and therefore suggest avoiding it in patients with sepsis, respiratory infections or underlying metabolic problems,[8] avoiding infusion for > 24 h[8,14] and taking into account the lipid content of propofol when calculating patients' daily caloric intakes.[14,26]

Fourteen publications and one unpublished trial outline adverse events and deaths associated with propofol. Twelve publications pertain to children, four of which are case reports describing a total of eight children, aged from 4 weeks to 13 yr.[1,8,28,29] Parke *et al*.[1] reported five critically ill children who received propofol for > 90 h at a rate of > 5 mg kg h-1 and died. The high doses and long duration may explain these deaths. Regrettably, these case reports reveal no details on use of parenteral feeding. Bray[2] reviewed propofol infusion in a PICU and found a significant association between long-term high-dose propofol infusion and the development of progressive myocardial failure. However, full details on comorbidity and parenteral feeding are lacking. Bray,[22,30,31] Cray *et al*.[29] and Cravero (unpublished data) expressed concerns about propofol as a sedative in children. Strickland *et al*.[32] reported an 11-year-old girl with an astrocytoma who died after long-term propofol infusion. However, a cause-and-effect relationship could not be determined. More recently, Koch *et al*.[33] described a 5-year-old child receiving short-term propofol infusion at a high rate who developed lactic acidosis.

Based on 14 publications, describing 27 patients, and one unpublished trial, the US Food and Drugs Administration contraindicated propofol for sedation of children < 18 yr receiving intensive care.[4] However, 17 other publications appeared in support of propofol, reviewing a total of 395 patients without evidence for a relationship between propofol infusion and death.

This paper describes a prospective cohort study comparing safety and efficacy of propofol and midazolam in children < 2 yr. Clearly, our study has limitations. First, the number of children receiving propofol 6% in this study is too small to allow conclusions to be drawn. Reviewing the total of 422 children, described in the above publications with regards to safety, eight children (< 2%) had evidence of propofol infusion syndrome.[3] Thus, to encounter one child with the propofol infusion syndrome, we would have had to include at least 50 patients

receiving propofol. Secondly, all studied children were healthy, apart from their major craniofacial deformities. Therefore these children are not representative of the general ICU population. Thirdly, the children received low doses of propofol; higher doses might have produced adverse events. Fourthly, blinding was not possible in this study, because of propofol's characteristic consistency. Fifthly, randomization was aimed at but failed due to unforeseen logistic reasons.

Despite the limitations of our study, it is important to note that we did not encounter any problems using propofol 6% as a sedative with dosages less than 4 mg $kg^{-1}h^{-1}$ in children with a median age of 10 ($_{IQR}$ 3-17) months during a median period of 11 (6 to 18) h in postoperative patients without multiple organ failure or critical illness. Based on this study, it is too early to state that propofol is safe for sedation in children. However, we believe that it is important to share our experiences with propofol 6% and call for randomized controlled trials in pediatric patients to establish the safety of propofol as a sedative.

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Chapter 3

Propofol pharmacokinetics and pharmacodynamics for depth of sedation in nonventilated infants after major craniofacial surgery

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Abstract

Background: To support safe and effective use of propofol in nonventilated children after major surgery, a model for propofol pharmacokinetics and pharmacodynamics is described.
Methods: After craniofacial surgery, 22 of the 44 evaluated infants (aged 3-17 months) in the pediatric intensive care unit received propofol (2-4 $mg \cdot kg^{-1} \cdot h^{-1}$) during a median of 12.5 h, based on the COMFORT-Behavior score. COMFORT-Behavior scores and Bispectral index values were recorded simultaneously. Population pharmacokinetic and pharmacodynamic modeling was performed using NONMEM V (GloboMax LLC, Hanover, MD).
Results: In the two-compartment model, body weight (median, 8.9 kg) was a significant covariate. Typical values were $CL = 0.70 \cdot (BW/8.9)^{0.61}$ l/min, $V_c = 18.8$ l, $Q = 0.35$ l/min and $V_{ss} = 146$ l. In infants who received no sedative, depth of sedation was a function of baseline, postanesthesia effect (E_{max} model) and circadian night rhythm. In agitated infants, depth of sedation was best described by baseline, postanesthesia effect, and propofol effect (E_{max} model). The propofol concentration at half maximum effect was 1.76 mg/l (coefficient of variation = 47 %) for the COMFORT-Behavior scale and 3.71 mg/l (coefficient of variation =145%) for the Bispectral index.
Conclusion: Propofol clearance is two times higher in nonventilated healthy children than reported in the literature for ventilated children and adults. Based on the model, we advise a propofol dose of 30 mg/h in a 10 - kg infant to achieve values of 12-14 on the COMFORT-Behavior and 70-75 on the Bispectral index during the night. Wide pharmacodynamic variability emphasizes the importance of dose titration.

Introduction

To correct craniosynostosis, most infants undergo surgery in the first years of life. Because of edematous eyelids, separation from parents and the need to stay at the intensive care unit for control of vital signs, and the possible development of neurological sequelae, these children often experience stress postoperatively. Although propofol is widely used for sedation in the adult intensive care, its use is subject to debate in sedated children in the pediatric intensive care since the report of five deaths in children receiving high doses ($> 5 \text{ mg} \cdot kg^{-1} \cdot h^{-1}$) of propofol.[1] In general, larger doses of propofol are required in children, and it is suggested that this is because of differences in pharmacokinetics,[2] sensitivity,[3] or both.
To date, there are no population models in children investigating the pharmacodynamics to study the variability between and within children. As a pharmacodynamic endpoint, a number of clinical sedation scores have been devised for use in children, in which the COMFORT-Behavior (COMFORT-B) scale[4,5] would be a reliable alternative to the original, most used COMFORT scale.[6] The Bispectral Index (BIS) may have benefits in comparison with clinical sedation scores because it assesses sedation continuously and may provide an objective, quantitative measure of the level of sedation.[7] However, to date, the BIS has only

been validated in children older than 1 yr.
Our clinical experiences regarding the use of propofol evaluated by COMFORT-B in young children in the pediatric surgical intensive care unit (PSICU) have recently been published by Prins *et al*.[8] In the current article, propofol pharmacokinetics and pharmacodynamics characterized by use of the COMFORT-B and BIS on the postoperative sleep pattern in nonventilated infants are described using population modeling, to select appropriate doses in infants and to support the safe and effective use of propofol.

Materials and Methods

The study was performed in the PSICU of the Erasmus Medical Center – Sophia Children's Hospital, Rotterdam, The Netherlands. The study protocol was approved by the ethics committee of the Erasmus Medical Center – Sophia Children's Hospital. Written informed consent was obtained from the parents. The studied infants, the design, sedative and analgesic regimen, and safety parameters are presented in detail in the article of Prins *et al*.[8] and shortly repeated as relevant to this article.

Patients

Eligibility criteria included major craniofacial surgery, age between 1 month and 2 yr, and postoperative admitted to the PSICU. The children were randomly allocated to receive propofol or midazolam if sedative medication was judged necessary on the basis of the COMFORT-B score (score $\geq$ 17). Infants were excluded when they had respiratory infections, epilepsy, hypertriglyceridemia or family histories of hypercholesterolemia, or history of allergy to propofol, eggs or soybean oil.
Patient characteristics of the group in which no sedation was necessary (nonagitated group) and the group in which sedation was needed (agitated group) are presented in Table 1. Infants who received midazolam could be used for pharmacokinetic and pharmacodynamic analysis before midazolam administration if more than two COMFORT-B observations were available for the description of the postoperative sleep pattern in the agitated group. These infants are represented in table 1 as the agitated, no sedative group. All patients had normal hepatic and renal functions.

Table 1 Patient characteristics of agitated infants and nonagitated infants.

	Agitated		Nonagitated
	Propofol	No sedative	No sedative
Sex, M/F	15 / 7	8 / 5	5 / 4
Age, months	10 (3.8-17.3)	10.9 (3.2-18.5)	8.8 (4.0 – 12.4)
Weight, kg	8.9 (4.8-12.5)	9.3 (5.1-11)	8.3 (5.5 – 9.6)
Height, cm	71 (60-76)	72 (58-80)	70 (61.5-77)
CYP genotype mutant frequencies			
2B6*1/*5	2		
2B6*1/*6	5		
2B6*6/*6	1		
2B6*1/*7	1		
2C9*1/*2	4		
2C9*1/*3	3		
2C19*1/*2	7		
2C19*2/*2	1		
Infusion duration, h	12.5 (6.0-18.1)	-	-

Data are median (minimum-maximum).

Anesthesia

Standardized anesthesia was induced with thiopental (5 mg/kg) or sevoflurane and fentanyl (2.5 μg/kg) and the infants were paralyzed with vecuronium (0.1 mg/kg). Thereafter, the infants underwent intubation and mechanical ventilation. Anesthesia was maintained with isoflurane, oxygen, and air, and fentanyl was given as needed. A median total dose of 17.9 (10.0-32.9) μg/kg fentanyl was administrated during surgery. Approximately 2 h before extubation, a loading dose of acetaminophen (40 mg/kg) was administered rectally. After the operation, the patients were admitted to the PSICU for a minimum of 24 h, depending on the clinical condition.

Sedative and Analgesic regimen

Pharmacodynamic data collection was started at arrival at the PSICU. The COMFORT-B score, which has been validated in pediatric intensive care, was used as a pharmacodynamic endpoint.[4,5] The COMFORT-B scale assesses six behavioral items: alertness, calmness, muscle tone, body movement, facial tension, crying (nonventilated children) or respiratory response (ventilated children). All items range from 1 (no distress) to 5 (severe distress), resulting in a total score varying from 6 to 30. The interobserver reliability represented by linearly weighted κ was greater than 0.65 for all nurses and the principal investigator. In addition, the BIS was recorded continuously and noted at 15-min intervals (BIS® A 2000 version 3.12, Aspect Medical Systems, Natick, MA; with pediatric BIS® sensors). The BIS

ranges from 100 (awake) to 0 (isoelectric electroencephalogram). Propofol 6% (Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands[9,10]) was given by a central venous line into a running saline infusion by a B.Braun Medical infusion pump (Melsungen, Germany) to a summed rate of 3 ml/h. For propofol, the doses were increased or decreased as needed up to a maximum of 4 mg · kg^{-1} · h^{-1}. When patients were inadequately sedated with 4 mg · kg^{-1} · h^{-1} propofol, midazolam was added. One patient received an additional dose of 0.1 mg/kg followed by 0.05 mg/kg midazolam, one patient received two doses of 0.1 mg/kg, and two patients a single bolus of midazolam. These responses were excluded from the analysis. To determine whether restlessness was induced by pain, the trained nurses also obtained the visual analog scale score. Patients received standard four daily doses of 120-240 mg acetaminophen rectally.[11] In more than 99% of the observations, the visual analog scale score was less than 4.

Blood sampling

Arterial samples (250 µl) were taken before the start of the propofol infusion; at approximately 30 or 45, 60 or 90, and 120 min after the start of the propofol infusion; three times in steady state, just before and 1 h after dose adjustment; just before stopping; and 15 or 30, 45 or 60, 120, and 150 min after the end of the infusion.

Analytical methods

Propofol concentrations were measured in whole blood using high-performance liquid chromatography with fluorescence detection as described in a previous study from our laboratory.[3,12] Blood samples were collected in oxalate tubes and stored at 4ºC until analysis (within 1 week). The limit of quantification was 0.035 mg/l, and the between-day coefficients of variation were less than or equal to 6.0%.

Genomic DNA was isolated from EDTA blood (MasterAmp; Epicenter Technologies, Madison, WI). Cytochrome P450 (CYP) 2B6 mutations 516G>T, 785A>G and 1459C>T were analyzed (alleles *4, *5, *6, *7 and *9). Polymerase chain reaction-restriction fragment length polymorphism analyses were performed as described previously[13] with the exception of using *Bst*NI as restriction enzyme instead of *Sty*I. Analysis for the 1459C>T polymorphism was performed using primers 5'-CTGTTGCAGTGGACATTTG-3' and 5'-ATCTCACTCCTGCACTCAC-3' in a polymerase chain reaction with an initial step of 7 min 94ºC, followed by 30 cycles of (1 min at 94ºC, 1 min at 57ºC, 1 min at 72ºC) and concluded by a final extension step of 6 min at 72°C. The polymerase chain reaction product was digested with *Bgl*II. CYP2C9*2, *3 and CYP2C19*2 and *3 analyses were performed on the LightCycler® (Roche Diagnostics, Mannheim, Germany), using the CYP2C9 and CYP2C19 kits (Roche Diagnostics), respectively.

Data analysis

The Non-Linear Mixed effect Modeling (NONMEM) program (version V; GloboMax LLC, Hanover, MD)[14] was used for population analysis. S-plus (version 6.2; Insightful software, Seattle, WA) was used to visualize the data. NONMEM estimates the mean pharmacokinetic

and pharmacodynamic parameters of the population and the interindividual variability and the residual error, minimizing the objective function (-2 log likelihood). The NONMEM option of the first-order conditional estimation (method 1) with η-ε interaction was used. Model development was performed in four steps: (1) choice of the structural pharmacokinetic or pharmacodynamic model, (2) choice of the residual model, (3) covariate analysis, and (4) internal validation of the model. Discrimination between different models was made by comparison of the objective function. A value of $P < 0.005$, representing a decrease of 7.8 in the objective function, was considered statistically significant. In addition, the diagnostic plots (observed *vs*. individually predicted, observed *vs*. population predicted, time *vs*. weighted residuals, and population predictions *vs*. weighted residuals) for examining bias and precision, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the model.

Covariate analysis

Covariates were plotted independently against the individual *post hoc* parameter estimates and the weighted residuals to identify their influence. Tested covariates were body weight, age, body surface area, body mass index (if height was known), and sex. The pharmacokinetic parameters were also tested for correlation with heart frequency, blood pressure, triglycerides, and the CYP isoforms (2B6*4, *5, *6, *7, *9, 2C9*2, 2C9*3, 2C19*2, 2C19*3). In addition, the influence of the total dose of fentanyl administration during surgery on the pharmacodynamics was assessed.

Potential covariates were separately incorporated, and a significant covariate that most reduces the objective function was left in the model. Additional covariates had to reduce this objective function further to be retained in the model. The choice of the model was further evaluated as discussed above.

Validation

Bootstrap resampling method was used to assess the stability of the parameter estimates and the robustness of the final model.[15] A bootstrap involves repeated random sampling to produce another data set of the same size but with a different combination of individuals. The mean parameter values and coefficients of variation (CVs) of the bootstrap replicates were compared with the estimates of the original data set.

Pharmacokinetic model

The parameters of a two-compartment model were fitted to the log-transformed data, parameterized in terms of volume of steady state (V_{ss}), volume of the central compartment (V_c), clearance (CL), and intercompartmental clearance (Q) using subroutine ADVAN 5. The central volume was related to the volume of distribution at steady state as

$$V_c = \frac{V_{ss}}{(1+\vartheta)} \quad (1)$$

The individual value of the parameters of the *i*th subject was modeled by

$$\theta_i = \theta_{mean} \cdot e^{\eta_i} \quad (2)$$

where θ_{mean} is the population mean and η_i is assumed to be a Gaussian random variable with zero mean and variance ω^2. The residual error was described with a proportional error model. This means for the *j*th observed log-transformed concentration of the *i*th individual the relation (Y_{ij}):

$$Y_{ij} = \log c_{pred,ij} + \varepsilon_{ij} \quad (3)$$

where c_{pred} is predicted transformed propofol concentration and ε_{ij} is a random variable with mean zero and variance σ^2.

Simulation

To compare the pharmacokinetic results with previously published pharmacokinetic models, simulations were performed using the model developed by Knibbe *et al*.,[3] Rigby-Jones *et al*.,[16] and Schüttler and Ihmsen.[17]

Pharmacodynamic model

Depth of sedation was characterized with postoperative natural sleep pattern (PNSP) and propofol effect (PEF).

$$S_{ij} = PNSP_{ij} - PEF_{ij} \quad (4)$$

where S_{ij} is the *j*th observed sedation level in the *i*th subject.
The postoperative natural sleep pattern (PNSP) was described as a function of three equations allowing the depth of sedation to increase and decrease during the first postoperative night in the absence of a sedative.

$$PNSP_{ij} = BSL_i + PAEFF_{ij} - CNR_{ij} \quad (5)$$

In which BSL represents the level of sedation at arrival at the PSICU, PAEFF represents the postanesthesia effect, and CNR the circadian night rhythm.
For estimation of the interindividual variability of the baseline, log-normal distributions were assumed. This means for the *i*th individual:

$$BSL_i = BSL_{mean} \cdot e^{\eta_i} \quad (6)$$

where BSL_{mean} is the population mean and η_i is a Gaussian random variable with zero mean and variance ω^2.
Postanesthesia effect (PAEFF) was assumed to wash out in time postoperatively by an E_{max}

model, resulting in an decrease of the depth of sedation to a maximum estimated score (S_{max}) for the COMFORT-B and 100 (awake) for the BIS.

$$PAEFF_{ij} = \frac{PAE_{\max,i} \cdot T_{PS,ij}^{\gamma}}{(T_{50,PS,i} + T_{PS,ij})^{\gamma}} \tag{7}$$

where PAE_{max} is the maximal effect from BSL to the maximal score S_{max}. T_{PS} is the time (minutes) postsurgery, $T_{50, PS}$ is the time (minutes) postsurgery at half maximum postanesthesia effect, and γ is the steepness of the time-*versus*-response relation. Interindividual variability of $T_{50, PS}$ and γ were assumed to be log-normally distributed.
Circadian night rhythm (CNR) was modeled by

$$CNR = A \cdot SIN((TIME - O) \cdot (\frac{2\pi}{Fr})) \tag{8}$$

where O denotes the onset of the natural night dip in minutes from 12.00 h. The end of the circadian night dip (wake-up time) was assumed at 7.00 h, because at this time point, the light is turned on, nursing care is optimized, and parents arrive at the PSICU. A (COMFORT-B or BIS units) is the amplitude of the night dip, and 2 π / Fr (minutes) is frequency of the oscillations.
Propofol effect (PEF) was related to the pharmacokinetic model-predicted individual propofol concentration (C_{ij}) by a simple E_{max} model:

$$PEF_{ij} = \frac{E_{\max,i} \cdot C_{ij}}{EC_{50,i} + C_{ij}} \tag{9}$$

where $E_{max,i}$ is the maximum possible propofol effect (equal to S_{max} -6 on the COMFORT-B scale and 100 on the BIS scale) in the *i*th subject, assuming that the response will reach the maximum effect at doses sufficiently higher than 4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} propofol. EC_{50} is the propofol concentration (mg/l) at half maximum effect, in which the interindividual variability was assumed to be log-normally distributed. The residual error in the COMFORT-B score and BIS was best characterized by a proportional and an additive error model, respectively.

$$Y_{ij} = COMFORT - B_{pred,ij} \cdot (1 + \varepsilon_{1,ij}) \tag{10}$$

$$Y_{ij} = BIS_{pred,ij} + \varepsilon_{2,ij} \tag{11}$$

where Y_{ij} represents the observed effect in the *i*th subject at the *j*th time point.

Results

A median of 11 blood samples per infant were collected from 22 evaluable propofol patients. The pharmacokinetics of propofol were best described with a two-compartment model. In some of the patients, the central line had not been primed, for which we added a lag time (ALAG) for a subpopulation to the model to describe the delay of delivery. Body weight (median, 8.9 kg) incorporated as a power function was found to be a significant covariate for elimination clearance, thereby reducing the interindividual variability (CV%) in clearance from 27% to 20%. A slope-intercept model or a weight-proportional model resulted in the

Table 2 Parameter estimates of the basic pharmacokinetic model, the bodyweight power model and the stability of the parameters using the bootstrap validation.

Parameter	Basic model, Mean (CV%)	Bodyweight power model, Mean (CV%)	BS Bodyweight power model, BS Mean (CV%)
Fixed effects			
CL, l/min	0.69 (6.9)	$= CL_{std} \cdot (BW/8.9)^{b}$	
CL_{std}, l/min	-	0.70 (5.3)	0.71 (6.6)
b	-	0.61 (19.7)	0.59 (33.8)
V_{SS}, l	144 (32.1)	146 (31.2)	148 (32.0)
Q, l/min	0.34 (11.9)	0.35 (11.0)	0.35 (11.1)
V_c, l	20.3 (27.9)	18.8 (30.0)	16.8 (46.0)
$ALAG_1$, min	0	0	-
$ALAG_2$, min	40.20 (3.1)	40.20 (3.0)	38.10 (16.3)
Fraction (ALAG)	0.52 (24.1)	0.52 (24.3)	0.47 (31.1)
Interindividual variability, %			
CL	27 (44.9)	20 (40.0)	20 (48.3)
V_{SS}	136 (34.6)	145 (38.4)	126 (44.8)
CLV_{SS}	49 (34.0)	49 (29.3)	43 (33.4)
Residual error, %			
ε	37 (21.0)	37 (20.7)	36 (20.4)
Performance measures			
-2LL	-141.5	-155.8	-176.2

CV, coefficient of variation of the parameter values; BS, bootstrap validation; CL, clearance in an individual; CL_{std}, clearance in a standardized individual of 8.9 kg; b, power scaling parameter; V_{ss}, volume of steady state; Q, intercompartmental clearance; V_c, central volume (related to V_{ss}); ALAG, lag time of delivery; Fraction, fraction of the population with ALAG=0; interindividual variability, square root of the exponential variance of η minus 1; ε, residual error proportional calculated as square root of the variance; -2LL, objective function.

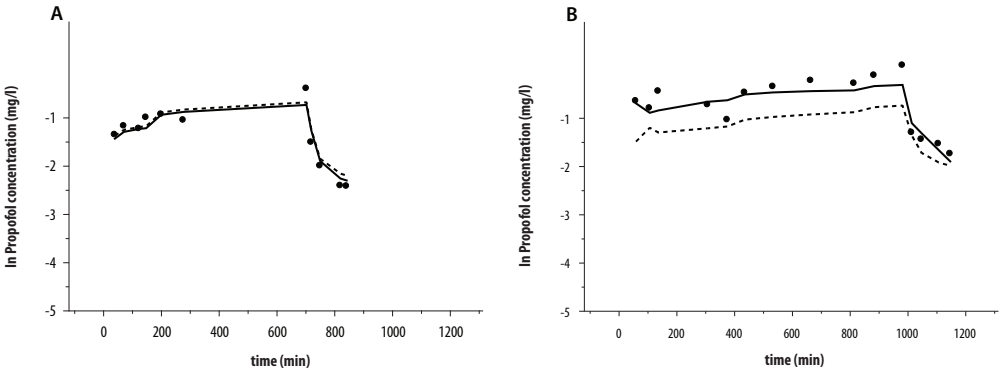

Figure 1 Log-transformed propofol concentration *versus* time for a median (A) and the worst (B) performance of the final pharmacokinetic bodyweight power model. The solid circles represent measured propofol concentrations, the solid lines represent the individual predicted concentrations, and the dashed lines represent the population predicted concentrations.

same decrease in objective function. The addition of other covariates (arterial blood pressure, heart frequency, triglycerides, CYP isoforms [2B6 *5, *6, *7, 2C9*2, 2C9*3, 2C19*2], age, body mass index, body surface area and sex) to the model did not improve the quality of fit. The pharmacokinetic parameter values and precision of the basic model, the bodyweight power-adjusted model, and the values obtained from the bootstrapping are shown in Table 2. The fits of 250 bootstrap replicates of the data set demonstrated the stability of the model. Individual fits of the model for a median situation and the most biased situation of the final model (bodyweight power model) to the observed data are shown in Figure 1.

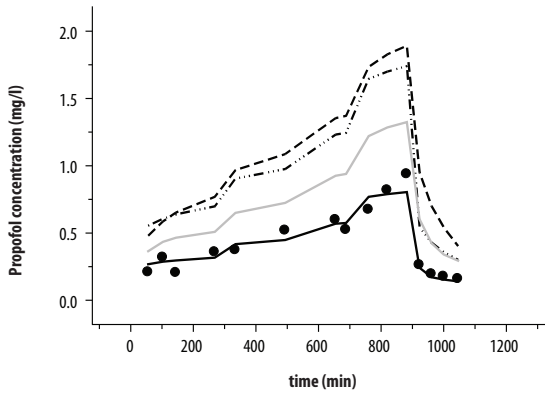

Figure 2 Simulated population propofol concentrations (line) *versus* observed concentrations (solid circles) in an infant aged 10 months and weighting 10 kg, after continuous infusion of 18, 24, 30 and eventually up to 42 mg/h. The simulations were based on the current study (solid black line) and published pharmacokinetic models in ventilated children after cardiac surgery (dashed line)[3] (dashed and dotted line)[16] and during anesthesia (solid gray line).[17]

Simulations

The simulations using the pharmacokinetic model previously developed by Knibbe *et al*.,[3] Rigby-Jones *et al*.,[16] Schüttler and Ihmsen[17] overestimated the observed propofol concentrations in our patients (Figure 2), indicating that the pharmacokinetics in our study population of awake children are distinctly different.

Pharmacodynamics

The total data set included a median of 15 (3-25) COMFORT-B scores and 73 (3-101) BIS observations per infant from 21 propofol patients, 9 natural sleep patients who received no sedative, and 13 natural sleep patients until midazolam administration. Table 3 summarizes the estimated pharmacodynamic parameters for the full model (postoperative natural sleep pattern and propofol effect) for the COMFORT-B and the BIS. All infants arrived comfortable and lightly sedated at the PSICU (BSL), starting with a COMFORT-B score of 10.4 (CV 16%) and a BIS value of 79 (CV 7%). In the agitated infants during the postoperative night, the narcotic effect washed out earlier, indicated by a smaller $T_{50,PS}$ (518 *vs*. 1580 minutes for the COMFORT-B and 1044 *vs*. 2052 min for the BIS). The steepness value of the washout effect (γ) for the BIS was 8, whereas the steepness for the COMFORT-B was not found to be significantly different from 1. During the night, the infants were "deeper" asleep, which was implemented in the model using the dip of a circadian rhythm. The start of the dip was estimated at 20.00 h (equal to 480 min from 12.00 h) on the COMFORT-B with an amplitude of 3.5 units and 17.30 h (equal to 330 min) on the BIS with an amplitude of 14.5. For the agitated infants receiving propofol during the night, a night dip could not be estimated. Propofol was started at a median time of 19.00 h, which is equal to 5.5 h after surgery. The induced BIS depression as a function of the propofol concentration showed considerable intersubject variability (CV 145%). The bootstrap validation (100 times) confirmed the precision of the parameters. Figure 3A shows a median fit of a nonagitated infant who received no sedative, with a reduction in response during the night. Figure 3B and C show a median and a worse fit of the sleep pattern of an agitated infant and the influence of propofol. Figure 4 illustrates the simulated relation among time, propofol infusion rate, propofol concentration, and predicted population response in terms of depth of sedation using COMFORT-B and BIS. The difference between a 10-kg infant and a 5-kg infant is shown at the infusion rate of 18 mg/h. The difference in postoperative natural sleep pattern between infants who did or did not become agitated is shown at the propofol infusion rate of 0 mg/h.

There was not enough evidence to support sex, age, bodyweight, and total dose of fentanyl during surgery as covariates on the pharmacodynamic parameters.

Table 3 Pharmacodynamic parameter estimates of the depth of sedation postoperatively using COMFORT-B and BIS and the stability of the parameters using the bootstrap validation.

parameter		**COMFORT-B, Mean (%CV)**	**BS COMFORT-B, Mean (%CV)**	**BIS, Mean (%CV)**	**BS BIS, Mean (%CV)**
		Fixed effects			
BSL		10.4 (5.1)	10.4 (5.6)	79.2 (1.2)	78.9 (1.1)
PAEFF	$T_{50,PS}$, min, agitated	518 (44.2)	548 (49.7)	1044 (7.1)	1048 (10.8)
	$T_{50,PS}$, min, nonagitated	1580 (46.3)	1694 (49.9)	2052 (24.3)	2106 (41.5)
	γ	1 Fixed	-	8.3 (27.3)	9.7 (46.3)
	Maximal score S_{max}	20.0 (25.1)	19.7 (28.5)	100 Fixed	-
CNR	Onset, min	480 (1.2)	376 (42)	330 (0.8)	323 (11.8)
	Frequency, min	1390 (8.6)	1752 (38.4)	2440 (20.3)	2796 (31.1)
	Amplitude, response units	3.5 (36.7)	3.7 (33.7)	14.5 (16.2)	16.8 (18.7)
PEF	EC_{50}, mg/l	1.76 (28.4)	2.01 (38.7)	3.71 (31.3)	4.01 (38.0)
		Interindividual variability, %			
BSL		16 (33.6)	15 (37.1)	7 (22.7)	7 (18.9)
$T_{50,PS}$		-	-	23 (48.0)	29 (55.0)
γ		-	-	115 (48.3)	103 (65.9)
EC_{50}		47 (70.2)	47 (80.7)	145 (43.2)	135 (59.3)
		Residual error			
ε_1, %		32 (8.1)	32 (8.1)	-	-
ε_2, BIS units		-	-	13 (6.0)	13 (6.5)
		Performance measures			
-2LL		2470.9	2446	16497	16430

CV, coefficient of variation of the parameter values; COMFORT-B, COMFORT-Behavior score; BIS, Bispectral index; BS, bootstrap validation; BSL, level of sedation at arrival; PAEFF, postanesthesia effect; $T_{50,PS}$, time post surgery at half maximum postanaesthesia effect; γ, steepness; CNR, circadian night rhythm; PEF, propofol effect; EC_{50}, propofol concentration at half maximum effect; interindividual variability, square root of the exponential variance of η minus 1; ε_1, residual error proportional; ε_2, residual error additive; -2LL, objective function.

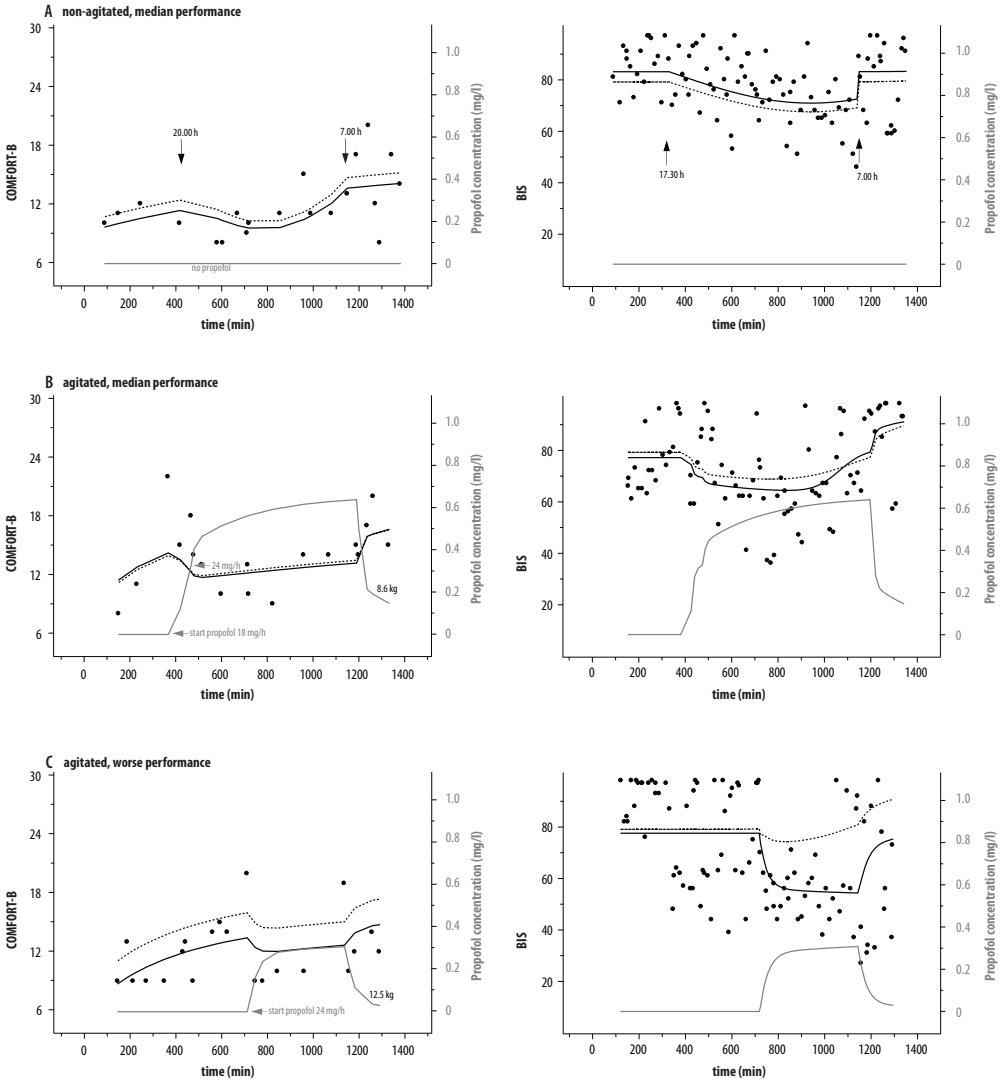

Figure 3 COMFORT-Behavior score (COMFORT-B; left column) and Bispectral index (BIS; right column) *versus* time (minutes) from 12.00 h for a median performance in the nonagitated group (A) and a median (B) and worse (C) performance in the agitated group receiving propofol. The solid circles represent the observations, the solid lines represent the individual predicted observations, and the dashed lines represent the population predicted observations. The gray line represents the individual predicted propofol concentrations.

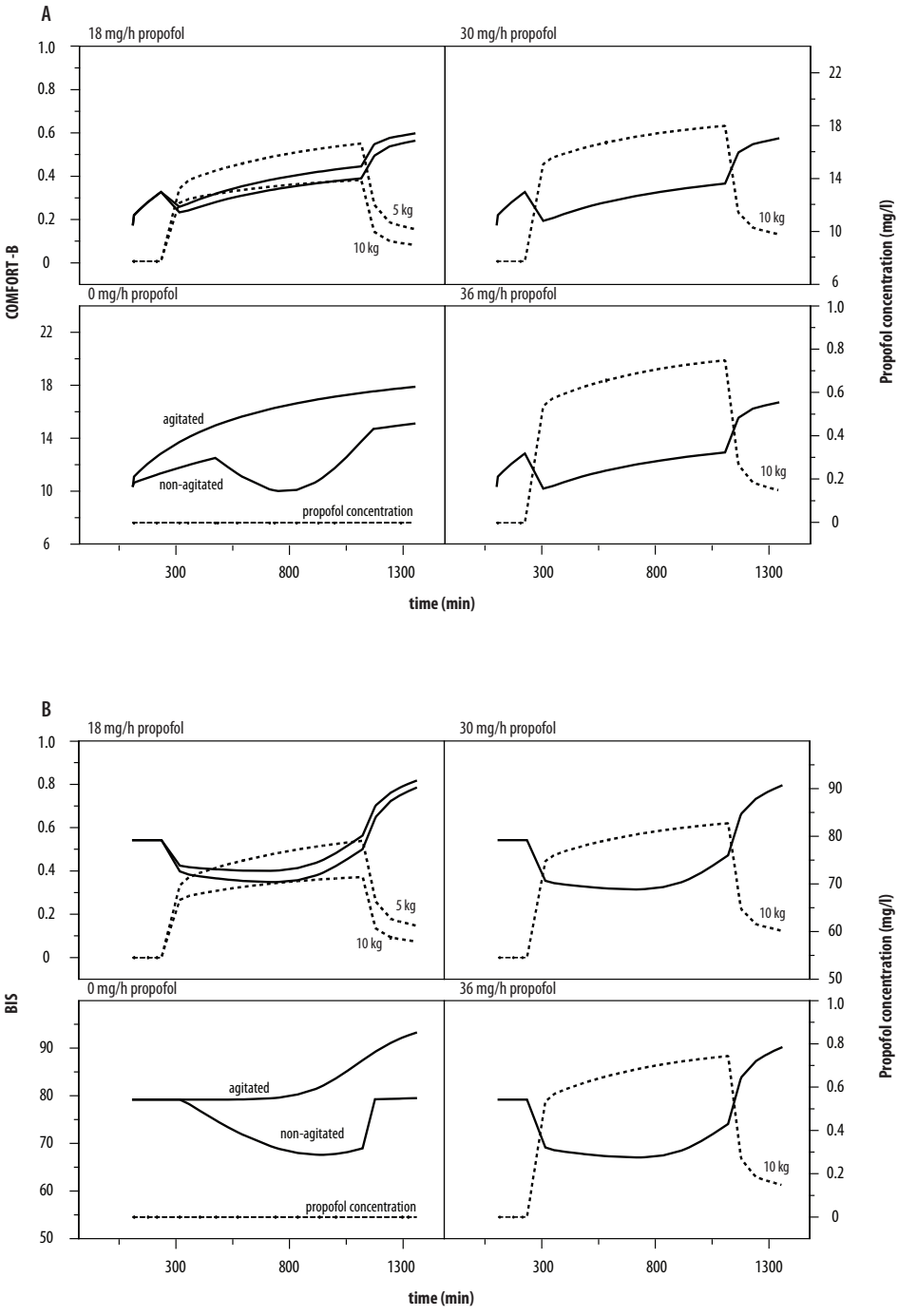

Figure 4 Simulated representation of the relation between time (minutes) from 12.00 h, propofol administration (0, 18, 30, and 36 mg/h), population predicted propofol concentration (dashed line) and population predicted response COMFORT-Behavior score (COMFORT-B; A) and Bispectral index (BIS; B) (solid lines) in a 10-kg and 5-kg infant.

Discussion

To support safe and effective use of propofol during the first night after major surgery in nonventilated infants younger than 1.5 yr, a population model for the influence of propofol pharmacokinetics and pharmacodynamics on the depth of sedation was described, assessed using COMFORT-B and BIS.

Clearance in postsurgical healthy nonventilated infants was found to be two times higher than reported in the literature for ventilated children and adults.[3,16,17] Based on the pharmacokinetic model, propofol doses must be doubled in this pediatric group to obtain similar blood concentrations. We believe that the higher estimate of the CL (0.70 l/min) in an infant with a bodyweight of 8.9 kg (2.64 l/min standardized to an adult of 70 kg) in our study compared with 0.27 l/min (0.030 $l \cdot kg^{-1} \cdot min^{-1}$) reported in the literature can partly be explained by the effect of the surgery and the condition of the patients. Rigby-Jones *et al*.[16] found that patients aged 1 week to 12 yr undergoing cardiac surgery had reduced values for metabolic clearance (-26%). Cardiac patients in general show a reduced cardiac output, which may effect the propofol elimination because the clearance of propofol (a high-extraction drug) is dependent on liver blood flow. In addition, mechanical ventilation may be of influence on the clearance of propofol. In patients with trauma and those in the surgical intensive care unit, increasing the positive end-expiratory pressure during mechanical ventilation has been shown to decrease total hepatic blood flow[18]. Murat *et al*.[2] reported a large clearance of 0.44 l/min (0.049 $l \cdot kg^{-1} \cdot min^{-1}$) in spontaneously breathing children aged 1-3 yr with minor burns after a single dose of 4 mg/kg. Healthy ventilated children undergoing anesthesia did show a lower estimate of the clearance.[17,19] The model developed by Schüttler and Ihmsen[17] for healthy ventilated children undergoing anesthesia from 2 yr of age showed less overprediction of the blood concentration than the model developed by Knibbe *et al*.[3] and Rigby-Jones *et al*.[16] for ventilated children after cardiac surgery. They also found a smaller value of the central volume compared to our model (5-12 l *vs*. 19 l), which may be a consequence of the relation of the central volume to the volume of distribution of steady state. Bodyweight partially explained the interpatient variability in CL. The influence of a slope-intercept model, a proportional model, or a power model with a power scaling parameter of 0.61 on the clearance was comparable in the range of 4.8-12.5 kg. We choose for the power model because an allometric three-fourths power model has been used with success for interspecies scaling.[20] As with other studies, age was not found to be a significant covariate.[16,21] In addition, the genetic expression of the investigated CYP isoforms did not explain the interindividual differences in the clearance. 2B6 would be predominantly involved and, at a lower rate, 2C9 and 2C19 in the minor metabolic hydroxylation pathway.[22] The homogeneous patient characteristics and the relatively small number of patients may account for the unexplained interpatient variability.

The large pharmacodynamic interindividual variability and residual error in BIS and COMFORT-B emphasize the complexity of depth of sedation in infants. Young children can vary in depth of sedation in the absence of sedatives as a result of day-night rhythm, the presence of parents and medical staff, hunger, light and noise.[5,23] Especially at lighter

sedation levels, noise has a greater effect on the BIS.[24] To account for natural variation, data of infants not receiving a sedative and until sedative administration were used to describe a postanesthesia effect (PAEFF) and a night dip (CNR). For adults, a similar PAEFF has been described after coronary artery bypass grafting by assuming a virtual drug that washes out over time.[25] Because stress and severe discomfort entail risks, a complete natural sleep pattern of agitated infants could not be described. The administration of the sedative may cover the night dip, which could not been estimated in the agitated children. The EC_{50} of propofol for the reduction of the BIS was different from that of the COMFORT-B, indicating that the two measurements are not interchangeable measures of the propofol effect in a spontaneously breathing child. Courtman *et al*.[26] and Crain *et al*.[27] also suggest that BIS and COMFORT are only moderately correlated: A child can be comfortable, but fully awake. The use of the BIS has the advantage that it assesses sedation continuously and may allow more objective assessment of sedation. It gives additive information and can be useful for patients who are difficult to assess clinically. The use of the maximal estimated score of 20 on the COMFORT-B scale and a smaller number of observations make it difficult to determine which sedation scale is more sensitive in this population based on the EC_{50}, but in lightly sedated children, the COMFORT-B seems more advantageous. The COMFORT-B has never been used before as a pharmacodynamic instrument in a pharmacokinetic-pharmacodynamic propofol analysis, but the effect of propofol on BIS in adults has been described. Interestingly, the sensitivity of infants to propofol, defined as EC_{50}, seems comparable to that in adults. Defining the E_{max} as the maximum effect seen on the BIS, Bouillon *et al*.[28] estimated an EC_{50} of 3.07 mg/l (CV 12.1%) and Doufas *et al*.[29] estimated a value of 2.4 mg/l (CV 30%). By fixing the E_{max} to 100, Calvo *et al*.[30] estimated the EC_{50} on 3.91 mg/l (41%), which may suggest that infants only require higher doses because of differences in pharmacokinetics rather than pharmacodynamics. In general, the sensitivity to propofol between infants is quite variable. Unfortunately, no explanation could be found based on patient characteristics as age, bodyweight and sex. In this narrow age group, the potential stressful environment resulting from inability to see, separation from parents, and unknown voices may play a major role.

Based on the population pharmacodynamic model, we advise a propofol infusion rate of 30 mg/h for a 10-kg nonventilated infant to achieve a COMFORT-B score between 12 and 14, 6 h after surgery during the night, which corresponds to BIS values of 70-75 (Figure 4). The considerable variability emphasizes the importance of drug titration to a maximum of 4 $mg \cdot kg^{-1} \cdot h^{-1}$. Further pharmacodynamic studies in larger groups of children are needed to explain the variability in response and help clinicians to improve individualization. For drugs such as propofol, this is especially important because of the troublesome reports in the literature regarding the safety of the use of propofol in children beyond procedures.

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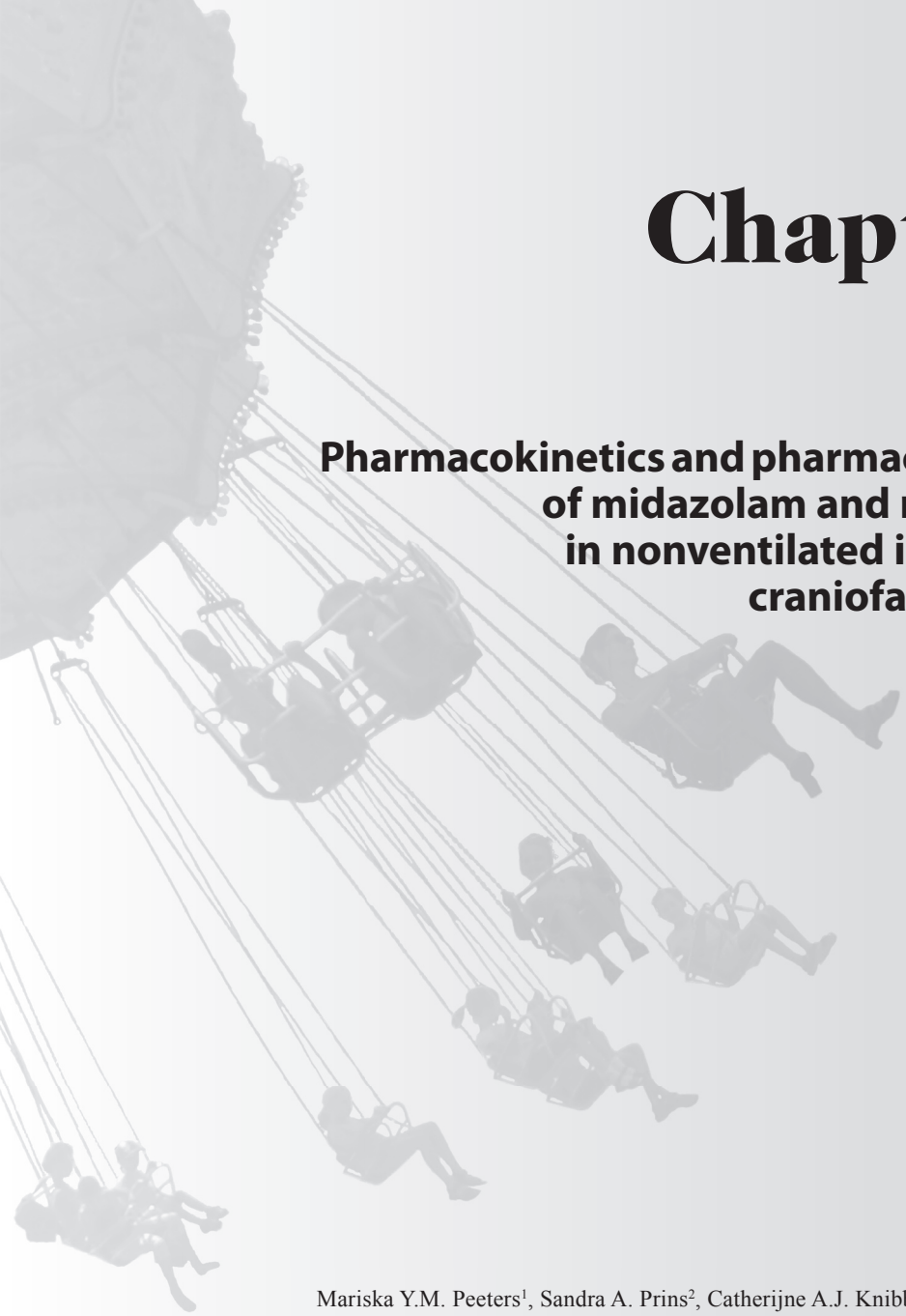

Chapter 4

Pharmacokinetics and pharmacodynamics of midazolam and metabolites in nonventilated infants after craniofacial surgery

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Abstract

Background: Because information on the optimal dose of midazolam for sedation of nonventilated infants after major surgery is scant, a population pharmacokinetic and pharmacodynamic model is developed for this specific group.

Methods: Twenty-four of the 53 evaluated infants (aged 3-24 months) admitted to the Pediatric Surgery Intensive Care Unit, who required sedation judged necessary on the basis of the COMFORT-Behavior score and were randomly assigned to receive midazolam, were included in the analysis. Bispectral index values were recorded concordantly. Population pharmacokinetic and pharmacodynamic modeling was performed using NONMEM V (GloboMax LLC, Hanover, MD).

Results: For midazolam, total clearance was 0.157 l/min, central volume was 3.8 l, peripheral volume was 30.2 l, and intercompartmental clearance 0.30 l/min. Assuming 60% conversion of midazolam to 1-OH-midazolam, the volume of distribution for 1-OH-midazolam and 1-OH-midazolamglucuronide was 6.7 and 1.7 l, and clearance was 0.21 and 0.047 l/min, respectively. Depth of sedation using COMFORT-Behavior could adequately be described by a baseline, postanesthesia effect (E_{max} model) and midazolam effect (E_{max} model).The midazolam concentration at half maximum effect was 0.58 µmol/l with a high interindividual variability of 89 %. Using the Bispectral index, in 57% of the infants the effect of midazolam could not be characterized.

Conclusion: In nonventilated infants after major surgery, midazolam clearance is two to five times higher than in ventilated children. From the model presented, the recommended initial dosage is a loading dose of 1 mg followed by a continuous infusion of 0.5 mg/h during the night for a COMFORT-Behavior of 12-14 in infants aged 1 yr. Large interindividual variability warrants individual titration of midazolam in these children.

Introduction

Midazolam is one of the most commonly used agents for sedation in the pediatric intensive care unit (PICU) and has been studied in children and neonates requiring mechanical ventilation[1,2,3] and in children when given as oral premedication.[4,5] Moreover, midazolam can also be an adjuvant in the care of nonventilated infants admitted to the PICU, *e.g.*, after craniosynostosis when the development of edematous eyelids postoperatively adds an extra stressful stimulus to the physical and emotional distress and discomfort that young children often encounter in the PICU.[6] However, in this postoperative population of nonventilated infants aged younger than 1 yr, information about pharmacokinetics and pharmacodynamics of intravenous continuous infusion is scant. According to the literature, the optimal dose of midazolam may vary depending on hepatic blood flow, which is affected by mechanical ventilation, hepatic and renal function, or change in enzyme activity of the cytochrome P450 3A subfamily during the first year of age.[7,3,8,9] Midazolam is hydroxylated by CYP3A4/5 and, to

a lesser extent, by CYP3A7 in the major metabolite 1-OH-midazolam,[10] which is as potent as the parent drug,[11,12] and the minor metabolites 4-OH-midazolam and 1,4-OH-midazolam. The metabolites are rapidly converted to their glucuronide conjugates and excreted in the urine.

To date, the pharmacokinetic and pharmacodynamic relation of midazolam in infants has not been fully characterized.[13]

In this study, we describe a population pharmacokinetic and pharmacodynamic model for midazolam in nonventilated children after major craniofacial surgery using the validated pediatric clinical sedation score COMFORT-Behavior (COMFORT-B).[14,15] Secondly, the Bispectral Index (BIS)[16,17] is explored as a pharmacodynamic endpoint whose value in children in the PICU is still unclear. In the models, intraindividual and interindividual variabilities in concentration and effect are characterized, and the effect of covariates influencing interpatient variability is explored to develop an optimal dose scheme for midazolam in nonventilated postoperative infants.

Materials and methods

The study was performed in the Pediatric Surgery Intensive Care Unit (PSICU) of the Erasmus Medical Center – Sophia Children's Hospital, Rotterdam, the Netherlands. The study protocol was approved by the ethics committee of the Erasmus Medical Center – Sophia Children's Hospital. Written informed consent was obtained from the parents. The studied patients and the design of the randomized study are presented in detail in the article of Prins *et al*.,[18] in which the safety assessments in the patients receiving midazolam and propofol are described and shortly repeated in the article of Peeters *et al*.,[19] in which the population pharmacokinetic and pharmacodynamic model for the children allocated to receive propofol is described. For brevity, parts of the methods are mentioned in this article when relevant.

Patients

Data of children who required sedative medication (agitated group) according to the COMFORT-B score (score $\geq$ 17) and who were randomly allocated to receive midazolam were included in the analysis. Criteria for eligibility in the study included age between 1 month and 2 yr; admission to the PSICU after major craniofacial surgery; and no respiratory infections, epilepsy, hypertriglyceridemia or family histories of hypercholesterolemia, or allergic history to midazolam, propofol, eggs or soybean oil. Characteristics of patients in the midazolam group are shown in Table 1. The median age was 11.1 (3.2-24.7) months, and the median weight was 9.4 (5.1-12) kg. For the description of the postoperative sleep pattern of the agitated group, we also included in the analysis data from 20 infants (14 male, 6 female; age, 9.4 [3.8-17.3] months; weight, 8.8 [4.8-12.5] kg) who were randomly assigned to receive propofol for whom more than two COMFORT-B observations before

Table 1 Patient characteristics of agitated infants who received midazolam.

Patient	Sex, M/F	Age, months	Weight, kg	Height, cm	Infusion duration, h
1	M	12.3	10	-	12.2
2	M	11.2	10.5	-	16.7
3	M	11.7	9.4	71	12.0
4	F	11.5	9.5	72	11.9
5	M	18.5	8.4	-	10.9
6	M	4.8	6.3	-	10.3
7	F	24.7	12	92	14.8
8	M	12.6	12	-	16.3
9	M	10.5	11	-	14.6
10	M	15.4	10	-	11.8
11	M	4.2	6.7	-	16.0
12	F	12.1	9.3	78	14.9
13	M	9.3	8.1	68	16.2
14	F	3.2	5.1	-	13.9
15	F	3.4	6.5	58	14.9
16	F	14	11.5	78	14.8
17	F	10.2	7	67	0.0
18	M	10.9	8	-	4.5
19	F	4.9	7.5	61.5	13.3
20	M	6.5	7.6	69	4.0
21	M	11.0	9.6	75	10.9
22	M	9.2	9.8	73.5	10.6
23	M	11.7	11	-	16.0
24	M	15.0	10.6	80	4.9
Median		11.1	9.4	72	12.7
Minimum		3.2	5.1	58	0.0
Maximum		24.7	12	92	16.7

propofol administration were available. In 9 infants (5 male, 4 female; age, 8.8 [4.0 – 12.4] months; weight, 8.3 [5.5 – 9.6] kg), no sedation was necessary (nonagitated group). One infant received a bolus of midazolam at the end of the operation, before entering the PSICU. During the stay in the PSICU, no sedation was needed. In contrast to Prins *et al*.,[18] this particular infant was included in the midazolam group in stead of the group in which no sedation needed. All were full-term babies without overt growth retardation. All patients had normal hepatic and renal functions. Genotype analysis identified 22 carriers of the CYP3A5 allele among the 24 infants who received midazolam (2 heterozygous CYP3A5*1/*3, classified as extensive metabolizers, and 20 homozygous CYP3A5*3/*3, classified as poor metabolizers), and in 2 infants, no result was obtained. Three carriers of the CYP3A7*1C were identified (3 heterozygous). The allele CYP3A4*1B was not detected.

Sedative and analgesic regimen

From arrival at the PSICU, depth of sedation was evaluated using the COMFORT-B score, which rates six behavioral items.[20,14] Alertness, calmness, muscle tone, body movement, facial tension, crying (nonventilated children), or respiratory response (ventilated children) are scored on a five-point scale, resulting in a total score varying from 6 (no distress) to 30 (severe distress). The interobserver reliability proved to be good for all nurses and the principal investigator ($\kappa > 0.65$). In addition, the BIS was recorded continuously and noted at 15-min intervals (Bispectral® A 2000 version 3.12; Aspect Medical Systems, Natick MA, with pediatric BIS® sensors). The BIS ranges from 100 (awake) to 0 (isoelectric electroencephalogram). Midazolam was initially given as 0.1 mg/kg bolus followed by a continuous infusion of 0.05 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}, titrated up after an additional bolus or down by 0.025 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}. In 21% of the infants, the starting dose was insufficient. To determine whether restlessness was induced by pain, the trained nurses also obtained the visual analog scale. Patients received standard four daily doses of 120-240 mg acetaminophen rectally in the PSICU after a loading dose of 40 mg/kg rectally 2 h before extubation during the operation.[21]

Blood sampling

Arterial blood samples (500-1000 µl) were collected in each infant at the following times: at baseline before the start of the midazolam bolus, approximately 45 or 30 min, 90 or 60 min, 120 min, 4 h, 6 or 8 h, and 10 h after the start of the midazolam infusion, just before and 1 h after dose adjustment, just before discontinuation of the midazolam infusion, and 30 or 45, 60 or 90, 120 and 180-240 min after the end of the infusion (median of 11 samples per child). If the arterial line was no longer available (dislocation, obstruction), venous samples were collected from a central line, routinely present in the superior caval vein. In five infants, venous blood samples were obtained with three, three, five, eight, and nine venous samples taken per infant, respectively. After collection, the samples were centrifuged and stored at -80ºC until analysis.

Analytical methods

Midazolam, 1-OH-midazolam and 1-OH-midazolamglucuronide concentrations were measured in serum using high performance liquid chromatography with ultraviolet detection at 230 nm. The mobile phase was prepared as follows: 400 µl phosphoric acid, 85%, and 146 µl triethylamine were added to 530 ml water. The pH was adjusted to 3.2 with 10% potassium hydroxide, and 470 ml acetonitrile was added. Temazepam was used as an internal standard. Borate buffer, 500 µl, 0.05 M (pH 9.2), was added to 200 µL serum. Following liquid-liquid extraction with 6 ml dichloromethane, the organic layer was evaporated to dryness at 37ºC. The residue was reconstituted in 200 µl of mobile phase, and 75 µl was injected onto the analytical column (Lichrosphere 100RP-18 encapped 5 µm; Merck, Darmstadt, Germany). Total (conjugated and unconjugated) drug concentrations of 1-OH-midazolam were measured after enzymatic hydrolysis of 200 µl serum with 100 UI β-glucuronidase (Roche Diagnostics, Almere, The Netherlands) for 24 h at 37ºC. The differences between total and unconjugated 1-OH-midazolam concentration was taken as the 1-OH-midazolam-glucuronide concentration. The limits of quantification were 11 µg/l for midazolam and 6 µg/l for 1-OH-midazolam using 200 µl of serum. Interassay and intraassay coefficients of variation were less than 8 % and 13 %, respectively. Total recovery was larger than 90% for both compounds.

Providing data for a large genomic study, DNA was isolated from EDTA blood (MasterAmp; Epicenter Technologies, Madison, WI). CYP3A4*1B, CYP3A5*3, and CYP3A7*1C analyses were performed, using polymerase chain reaction restriction fragment length polymorphism assays, as described previously.[22,23,24]

Data analysis

The analysis was performed in NONMEM (Non-Linear Mixed effect Modeling; version V, release 1.1; GloboMax LLC, Hanover, MD)[25] by use of the first-order conditional estimation (method 1) with η-ε interaction. S-plus (version 6.2; Insightful software, Seattle, WA) was used to visualize the data. Population pharmacokinetic and pharmacodynamic data were sequentially analyzed. Discrimination between different models was made by comparison of the objective function. A value of $P < 0.005$, representing a decrease of 7.8 in the objective function, was considered statistically significant. In addition, goodness-of-fit plots (observed *vs*. individually predicted, observed *vs*. population predicted, time *vs*. weighted residuals, and population predictions *vs*. weighted residuals) were used for diagnostic purposes. Furthermore, the confidence interval of the parameter estimates, the correlation matrix, and visual improvement of the individual plots were used to evaluate the model.

Covariate analysis

Covariates were plotted independently against the individual *post hoc* parameter estimates and the weighted residuals to visualize potential relations. The following covariates were tested: body weight, age, body surface area, body mass index, sex, and sampling (venous or arterial). The pharmacokinetic parameters were also tested for correlation with heart frequency, blood pressure, and the genotypes (CYP3A4*1B, 3A5*3, 3A7*1C). Potential co-

variates were separately entered into the model and statistically tested by use of the objective function. A significant covariate that most reduces the objective function was left in the model. Additional covariates had to reduce this objective function further to be retained in the model. The choice of the model was further evaluated as discussed previously.

Validation

The internal validity of the population pharmacokinetic and pharmacodynamic models was assessed by the bootstrap resampling method (repeated random sampling to produce another data set of the same size but with a different combination of individuals). Parameters obtained with the bootstrap replicates were compared with the estimates obtained from the original data set.

Pharmacokinetic model

Midazolam and metabolite data were fitted simultaneously, and concentrations were expressed as μmol/l. The molecular weights of midazolam, 1-OH-midazolam, and 1-OH-midazolamglucuronide are 325.77, 341.77, and 517.9, respectively. The pharmacokinetic model used is schematically depicted in Figure 1. The midazolam data were described with a two-compartment model, parameterized in terms of volume of the central compartment (V_1), volume of the peripheral volume (V_2), intercompartmental clearance (Q), and clearances to 1-OH-midazolam (CL_1) and other metabolites (CL_0). In the absence of information on the ratio of metabolite formation in children, CL_1 was assumed to be 60% of the elimina-

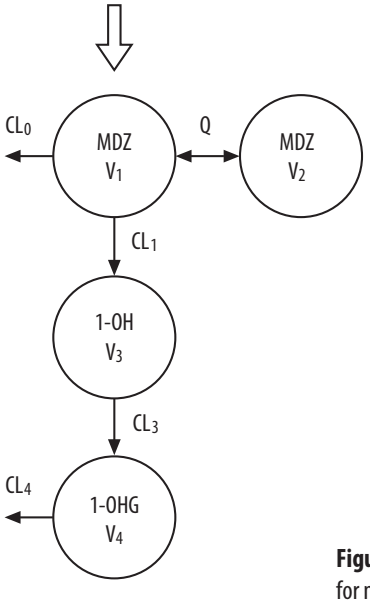

Figure 1 Schematic representation of the pharmacokinetic model for midazolam (MDZ) and its metabolites 1-OH-midazolam (1-OH) and 1-OH-midazolamglucuronide (1-OHG).

tion clearance of midazolam CL_e (the sum of CL_0 and CL_1) as reported in the literature for adults.[1,10,26] The formation of 1-OH-midazolam and 1-OH-midazolamglucuronide was best described with a one-compartment model. CL_3 is the clearance of 1-OH-midazolam, and CL_4 the clearance of 1-OH-midazolamglucuronide. The volume of distribution of 1-OH-midazolam (V_3) was modeled as a fraction of the sum of V_1 and V_2 of midazolam, because estimation of this parameter was found to be unstable by the bootstrap resampling. The individual value (*post hoc* value) of the parameters of the *i*th subject was modeled by

$$\theta_i = \theta_{mean} \cdot e^{\eta_i} \quad (1)$$

where θ_{mean} is the population mean and η_i is assumed to be a gaussian random variable with zero mean and variance ω^2. The intraindividual variability was best described with a combined additive and proportional error model for midazolam assuming a constant coefficient of variation over the complete concentration range superimposed on a constant absolute error (equation 2) and a proportional error model for the metabolites (equation 3), respectively. This means for the *j*th observed concentration of the *i*th individual, the relation (Y_{ij}):

$$Y_{ij} = c_{pred,ij} \cdot (1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \quad (2)$$

$$Y_{ij} = c_{pred,ij} \cdot (1 + \varepsilon_{3ij}) \quad (3)$$

where c_{pred} is predicted midazolam or metabolite concentration and $\varepsilon_{1,2,3,ij}$ are random variables with mean zero and variance σ^2.

Pharmacodynamic model

Depth of sedation (S) was characterized as a function of postoperative natural sleep pattern (PNSP) and midazolam effect (MEF):

$$S_{ij} = PNSP_{ij} - MEF_{ij} \quad (4)$$

The PNSP was described as a function of three equations:

$$PNSP_{ij} = BSL_i + PAEFF_{ij} - CNR_{ij} \quad (5)$$

In which BSL is the level of sedation at arrival at the PSICU, PAEFF the postanesthesia effect, and CNR is the circadian night rhythm.

The postanesthesia effect was assumed to wash out in time postoperatively by an E_{max} model, resulting in a more awake sedation level to a maximum estimated score (S_{max}) for the COMFORT-B and 100 (fully awake) for the BIS.

$$PAEFF_{ij} = \frac{PAE_{\max,i} \cdot T_{PS,ij}}{(T_{50,PS,i} + T_{PS,ij})} \quad (6)$$

where PAE_{max} is the maximal effect from BSL to the maximal score S_{max}. T_{PS} is the time (minutes) postsurgery, and $T_{50, PS}$ is the time (minutes) postsurgery at half maximum postanesthesia effect. Incorporation of the postanesthesia effect of the COMFORT-B score resulted in a reduction of the objective function by 80.1 points, which was highly significant.
Circadian night rhythm was modeled by

$$CNR = A \cdot SIN((TIME - O) \cdot (\frac{2\pi}{Fr})) \quad (7)$$

in which O denotes the onset of the natural night dip in minutes from 12.00 h. The end of the circadian night dip (wake-up time) was assumed at 7.00 h, because at this time point, the light is turned on, nursing care is optimized,and the parents arrive at the PSICU. A is amplitude of the night dip (units COMFORT-B or BIS), and 2 π / Fr is frequency of the oscillations (minutes). Introduction of the CNR improved the goodness of fit as reflected in a decrease in objective function of 18.9 points for the COMFORT-B and 119.3 points for the BIS.
Midazolam effect (MEF) was related to the pharmacokinetic model-predicted individual midazolam concentration ($C_{1,ij}$) by a simple E_{max} model:

$$MEF_{ij} = \frac{E_{\max,i} \cdot C_{1,ij}}{EC_{50,i} + C_{1,ij}} \quad (8)$$

where $E_{max,i}$ is the maximum possible midazolam effect (equal to S_{max} -6 on the COMFORT-B scale and 100 on the BIS scale) in the *i*th subject. EC_{50} is the concentration (μmol/l) at half maximum effect, in which the interindividual variability was assumed to be log-normally distributed. The significant increase in objective function when the midazolam effect is eliminated from the COMFORT-B and BIS model (50.3 and 119 points, respectively) demonstrated the effect of midazolam.
Using the BIS, EC_{50} was modeled with the MIXTURE subroutine in NONMEM ($P < 0.005$). A mixture model assumes that the population consists of two or more subpopulations, each approximating a normal distribution, where each subpopulation may have its own model. The ratio of the fraction and the corresponding typical EC_{50} are estimated, and NONMEM assigned patients to one of the subpopulations.
For the influence of the active metabolite 1-OH-midazolam ($C_{2,ij}$) in the presence of the midazolam concentrations ($C_{1,ij}$), an additive interaction model was tested, in which the maximal effect (E_{max}) of midazolam and 1-OH-midazolam was assumed to be equal and the Hill factor was 1 for the two compounds:

$$MEF_{ij} = \frac{E_{\max 1,2,i} \cdot \left(\frac{C_{1,ij}}{EC_{50,1,i}} + \frac{C_{2,ij}}{EC_{50,2,i}}\right)}{1 + \left(\frac{C_{1,ij}}{EC_{50,1,i}} + \frac{C_{2,ij}}{EC_{50,2,i}}\right)} \quad (9)$$

Because all infants had a normal renal function, the metabolite 1-OH-midazolamglucuronide, which is only of clinical relevance in renal failure when accumulation occurs,[27] was assumed to be without effect. The interindividual variabilities (η_is) were symmetrically distributed zero-mean random variables with a variance ω^2. The intraindividual variabilities in the COMFORT-B (equation 10) and BIS (equation 11) were best characterized by a proportional and an additive error model, respectively.

$$Y_{ij} = COMFORT - B_{pred,ij} \cdot (1 + \varepsilon_{1,ij}) \quad (10)$$

$$Y_{ij} = BIS_{pred,ij} + \varepsilon_{2,ij} \quad (11)$$

where Y_{ij} represents the observed effect in the *i*th subject at the *j*th time point.

Results

Pharmacokinetics

The pharmacokinetic model was derived from a median of 9 midazolam, 8 1-OH-midazolam, and 8 1-OH-midazolamglucuronide observations obtained per infant. Median 1-OH-midazolam/midazolam and (1-OH-midazolam + 1-OH-midazolamglucuronide)/midazolam ratios were 0.37 in 158 samples and 2.3 in 144 samples, respectively. The pharmacokinetic parameter values and their confidence interval and the values obtained from the bootstrapping are shown in Table 2. The fits of 250 bootstrap replicates of the data set demonstrated the stability of the model. These mean parameter estimates were within 17% of those obtained with the original data set. However, it should be noted that the estimated volume of distribution of the metabolites must be taken with caution, because accurate estimates can only be obtained by separate administration and are affected by the assumed fraction of midazolam metabolized to 1-OH-midazolam. One individual who needed up to 0.2 mg · kg^{-1} · h^{-1} midazolam showed very low midazolam and 1-OH-midazolam concentrations (two and five times lower, respectively, as compared with the population mean), indicated by a high individual CL_1 (0.18 l/min) and CL_3 (0.59 l/min) and a low 1-OH-midazolam/midazolam ratio of 0.18. Considering the large effect of this individual on the variability, an extra factor (fa) was estimated for this infant, which resulted in a significant decrease in objective function ($P < 0.001$). This infant was heterozygous for the allele CYP3A7*1C. Figure 2 shows the

Table 2 Population parameter estimates of the pharmacokinetic model and the stability of the parameters using the bootstrap validation.

Parameter	PK model, Mean (CV%)	Bootstrap, Mean (CV%)	Bootstrap Mean/Final estimate ratio, %
		Fixed effects	
midazolam			
CL_e, l/min	0.157 (11.2)	0.157 (11.7)	100
fCL_1, l/min	0.6 Fixed	0.6 Fixed	-
V_1, l	3.80 (30.5)	3.58 (49.8)	94
V_2, l	30.2 (17.3)	30.4 (17.8)	101
Q, l/min	0.30 (17.2)	0.30 (22.9)	100
fa	2.48 (8.9)	2.59 (13.2)	104
1-OH-midazolam			
fV_3, l	0.197 (35.1)	0.195 (45.5)	99
V_3, l	6.69	6.63	
CL_3, l/min	0.21 (7.8)	0.21 (8.3)	100
1-OH-midazolamglucuronide			
V_4, l	1.69 (42.5)	1.98 (45.9)	117
CL_4, l/min	0.047 (8.9)	0.047 (9.3)	100
		Interindividual variability, %	
CL_1	54 (31.1)	51 (31.1)	94
$V_2 = V_3$	82 (31.8)	81 (50.8)	99
CL_3	26 (33.9)	25 (41.3)	96
V_4	135 (50.4)	136 (62.5)	101
CL_4	42 (22.3)	40 (21.1)	95
CL_1CL_4	44 (29.0)	42 (28.0)	95
		Residual error	
$\varepsilon_{1\ midazolam}$, %	23 (24.8)	22 (25.9)	96
$\varepsilon_{2\ midazolam}$, µmol/l	0.016 (37.1)	0.016 (40.9)	100
$\varepsilon_{1,\ 1\text{-}OH\text{-}midazolam}$, %	53 (12.2)	54 (12.1)	102
$\varepsilon_{1,\ 1\text{-}OH\text{-}midazolamglucuronide}$, %	26 (13.8)	26 (13.8)	100
		Performance measures	
-2LL	-2809	-2828	

PK, pharmacokinetic; CL_e, elimination clearance of midazolam; fCL_1, assumed fraction of the elimination clearance converted to 1-OH-midazolam; V_1, central volume; V_2, peripheral volume; Q, intercompartmental clearance; fa, multiplication factor for CL_1 and CL_3 for one particular infant; V_3, volume of distribution of 1-OH-midazolam modeled as a fraction of $V_1 + V_2$ (fV_3); CL_3, clearance of 1-OH-midazolam; V_4, volume of distribution of 1-OH-midazolamglucuronide; CL_4, clearance of 1-OH-midazolamglucuronide; interindividual variability, square root of the exponential variance of η minus 1; ε_1, residual error proportional; ε_2, residual error additive; CV, coefficient of variation of the parameter values; -2LL, objective function.

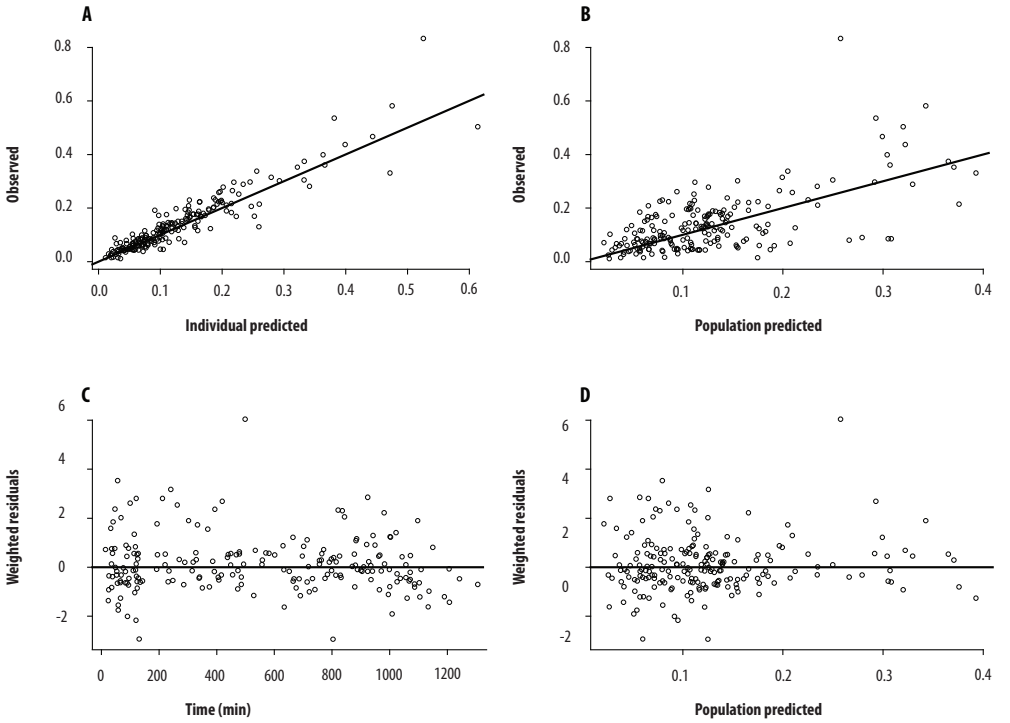

Figure 2 Diagnostic plots for parent midazolam pharmacokinetic model, allowing the evaluation of the optimal model to the data. (A) Observed *versus* individually predicted midazolam concentrations. (B) Observed *versus* population predicted concentrations. (C) Weighted residuals *versus* time. (D) Weighted residuals *versus* population predictions. Solid lines represent the line of unity.

diagnostic plots for parent midazolam pharmacokinetic data. A representative example of measured and predicted serum concentrations of midazolam and its two metabolites for a median fit are shown in Figure 3. None of the explored covariates (body weight, age, body surface area, body mass index, sex, heart frequency, blood pressure, sampling [venous or arterial] and the genotypes [CYP3A4*1B, 3A5*3, 3A7*1C]) were identified as significant, although there was a trend towards a positive linear correlation between age and elimination clearance (Figure 4). In this figure, the appearance of the allele expression is also given.

Pharmacodynamics

The data set included 632 COMFORT-B observations from 53 infants, yielding a median of 13 (3-25) observations per infant and a total of 3570 BIS observations, 75 (4-496) per infant. The population parameters of the pharmacodynamic model are reported in Table 3. The bootstrap validation (100 times) confirmed the precision of the parameters. Age was found to be a significant covariate for the baseline BSL (state of comfort at arrival) in the PSICU, according to a slope-intercept model centered to the median value. Nonagitated

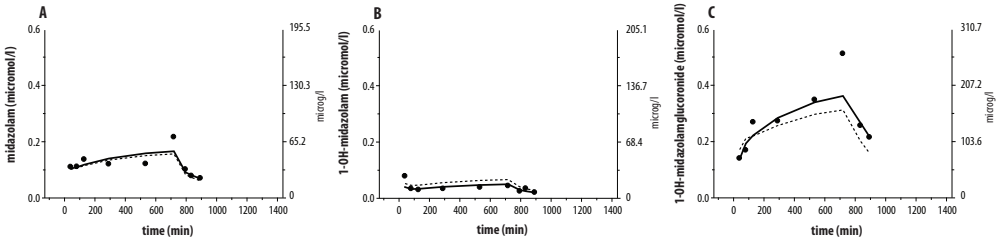

Figure 3 Serum concentration – time observations and predictions of midazolam (A), 1-OH-midazolam (B), and 1-OH-midazolamglucuronide (C) for a median performance after a loading dose of 1 mg, followed by a continuous infusion of 0.5 mg/h. The solid circles represent measured midazolam and metabolite concentrations; the solid lines represent the individual predicted concentrations, and the dashed lines represent the population predicted concentrations.

infants, in whom sedative administration was not necessary (COMFORT-B < 17), displayed a delayed postanesthesia washout ($T_{50,PS}$ 1794 *vs*. 537 min). In addition, they showed a night dip (CNR), which was implemented in the model using the dip of a circadian rhythm. The nighttime observations decreased a maximum of 3.5 units on the COMFORT-B (amplitude) from 20.00 h onward (equal to 478 min from 12.00 h) and 14.7 values on the BIS from 17.30 h onward. In the agitated infants, no night dip (CNR) could be identified. Using the BIS as a pharmacodynamic endpoint, the postanesthesia effect could not be described because of the large observed interindividual and intraindividual variability in response (Table 3). The effect of midazolam on the COMFORT-B was highly variable, with an interindividual coefficient of variation in EC_{50} of 89%. Using the BIS, an estimated 57% of the infants did not display a significant response on midazolam ("nonresponders"). The EC_{50} for the subpopulation "responders" was 0.63 µmol/l, with an interindividual variability of 66%. No covariates, age included, could be detected. Splitting the patients in two age groups, ≥ 1 yr and < 1 yr, according to the age for which the BIS was validated, the EC_{50} was 0.34 µmol/l for two responders in the age group ≥ 1 yr. The other eight patients did not display a response on the BIS. For the age group < 1 yr, 61% displayed a response on the BIS. The EC_{50} was 0.69 µmol/l with an interindividual variability of 70%.

For the influence of 1-OH-midazolam on the pharmacodynamics, an additive interaction

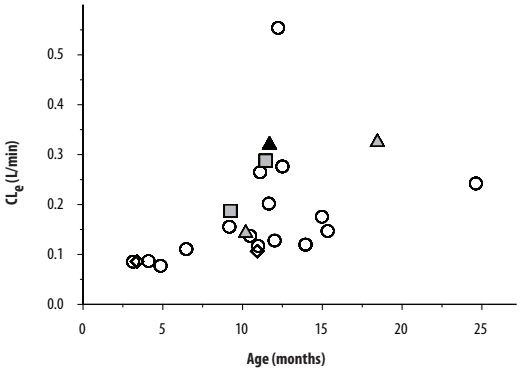

Figure 4 Scatter plot showing relation between age and elimination clearance (CL_e) and the identification of the genotype analysis. The two CYP3A5*1/*3 heterozygotes are represented by squares, the two infants with no result for CYP3A5*3 are represented by diamonds. The three carriers of CYP3A7*1C allele are represented by gray triangles, and a black triangle represents the infant in which an extra factor was estimated.

Table 3 Population pharmacodynamic parameter estimates of the postoperative depth of sedation using COMFORT-B and BIS and the stability of the parameters using the bootstrap validation.

Parameter		COMFORT-B, Mean (%CV)	Bootstrap COMFORT-B, Mean (%CV)	BIS, Mean (%CV)	Bootstrap BIS, Mean (%CV)
Fixed effects					
Postoperative natural sleep pattern					
agitated and nonagitated infants					
BSL		10.2 (5.5) – (age-11.1) • 0.25 (6.7)	10.1 (6.1) – (age-11.1) • 0.24 (25.9)	78.9 (1.2)	79.0 (1.4)
PAEFF	$T_{50,PS}$, min, agitated	537 (48.6)	595 (49.5)	-	-
	$T_{50,PS}$, min, non-agitated	1794 (44.8)	1936 (49.0)	-	-
	Maximal score S_{max}	20 (19.6)	21 (25.7)	-	-
nonagitated infants					
CNR	Onset, min	478 (13.0)	356 (49.4)	330 (1.3)	345 (15.0)
	Frequency, min	1430 (15.0)	1934 (41.4)	2550 (21.9)	2988 (40.8)
	Amplitude, response units	3.5 (33.4)	3.6 (33.4)	14.7 (14.4)	16.7 (20.5)
Midazolam effect					
agitated infants					
MEF	EC_{50}, µmol/l	0.58 (28.7)	0.58 (30.5)		
	EC_{50}, µmol/l, responders	-	-	0.63 (50.3)	0.68 (48.8)
	EC_{50}, µmol/l, nonresponders	-	-	99 FIXED	99 FIXED
	% Responders	-	-	43 (40.2)	46 (41.5)
Interindividual variability, %					
BSL		17 (34.3)	17 (29.2)	8 (21.9)	8 (23.6)
EC_{50}		89 (59.1)	77 (58.7)	-	-
EC_{50} subgroup responders		-	-	66 (108)	61 (103)
Residual error					
ε_1, %		31 (7.2)	30 (8.0)	-	-
ε_2, BIS units		-	-	13 (6.1)	13 (5.7)
Performance measures					
-2LL		2426.7	2402.7	21915.8	21806

BIS, Bispectral index; COMFORT-B, COMFORT-Behavior score; values in parentheses are CV, coefficient of variation of the parameter values; BSL, level of sedation at arrival; PAEFF, postanesthesia effect; $T_{50,PS}$, time postsurgery at half maximum postanesthesia effect; CNR, circadian night rhythm; MEF, midazolam effect; EC_{50}, midazolam concentration at half maximum effect; interindividual variability, square root of the exponential variance of η minus 1; ε_1, residual error proportional; ε_2, residual error additive; -2LL, objective function.

model was tested according to the Materials and Methods section. However, this model was unable to estimate the values of the EC_{50} of midazolam and 1-OH-midazolam separately. Further simplification of this model, assuming equal values for EC_{50} for both components, did not result in a significant decrease in objective function or interindividual variability but only a shift of EC_{50} from 0.58 to 0.81 μmol/l.

The observed and predicted depth of sedation characterized by COMFORT-B and BIS for a responder (A) and a nonresponder (B) and their corresponding midazolam concentrations are shown in Figure 5. In Figure 6A and B, the simulated relation between time, two different dose regimens of midazolam, midazolam concentration, and predicted population response is demonstrated in terms of depth of sedation using COMFORT-B, based on the derived pharmacodynamic model. The influence of the covariate age on the baseline using the COMFORT-B is shown in 6B. Figure 6C shows the postoperative natural sleep pattern of the nonagitated infants who did not need sedative medication.

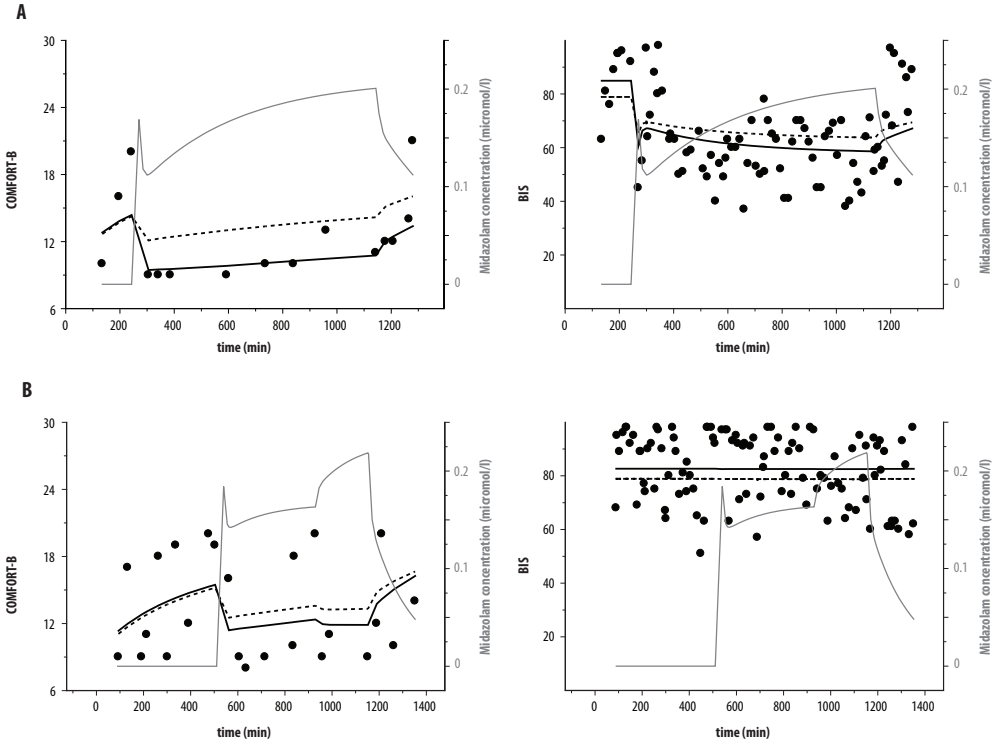

Figure 5 COMFORT-Behavior score (COMFORT-B; left column) and Bispectral Index (BIS; right column) *versus* time (minutes) from 12.00 h in a representative infant of the responder group (A) and the nonresponder group (B). The solid circles represent the observations, the solid lines represent the individual predicted depth of sedation, and the dashed lines represent the population predicted depth of sedation. The gray line represents the individual predicted midazolam concentrations

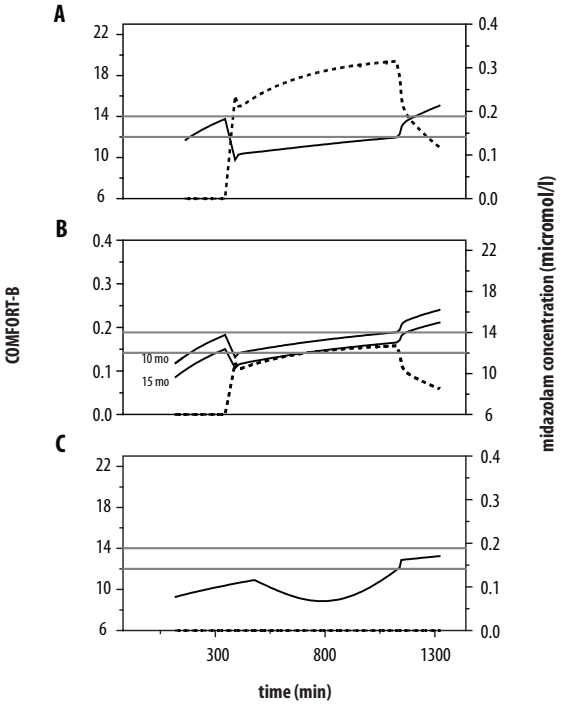

Figure 6 Simulation of the relation between time (minutes) from 12.00 h, midazolam administration, population predicted midazolam concentration (dashed line), and population predicted COMFORT-Behavior score (COMFORT-B; solid lines). A shows the simulation of 2 mg midazolam followed by a continuous infusion of 1 mg/h in a 10-months-old infant. B shows the simulation of 1 mg midazolam followed by a continuous infusion of 0.5 mg/h in a 10- and a 15-month-old infant. C represents the natural sleep pattern of a nonagitated infant. The horizontal reference line ranges from the desired COMFORT-B 12 to14.

Discussion

A population pharmacokinetic and pharmacodynamic model of midazolam and its metabolites 1-OH-midazolam and 1-OH-midazolamglucuronide based on the validated COMFORT-B scale is described to refine postoperative sedative treatment in nonventilated infants aged 3 months to 2 yr after surgery in the PICU.

In defining the optimal dose for children, population pharmacokinetic and pharmacodynamic modeling is useful. Key factors in this respect are that the pharmacokinetic-pharmacodynamic correlation can be established in the clinical situation at the basis of sparse sampling. Furthermore, application of the population approach enables the characterization of interindividual variability as well as the source of this variability on the basis of covariate analysis.

The pharmacokinetic model derived in this study estimated a total clearance of midazolam of 157 ml/min (16.7 ml · kg^{-1} · min^{-1}) in nonventilated children, which is two to five times

higher than clearance described in ventilated critically ill children or in ventilated children after cardiac surgery. Hughes *et al*.[28] estimated a median clearance of 3.1 ml·kg^{-1}·min^{-1} from steady state concentrations in critically ill infants aged 1 month to 1 yr. De Wildt[3] found a mean clearance of 5.0 ml·kg^{-1}·min^{-1} in intensive care patients aged 2 days to 17 yr. In addition, they found a 2.5 times lower ratio for 1-OH-midazolam/midazolam concentrations. Mathews *et al*.[29] reported a clearance of 9.6 ml·kg^{-1}·min^{-1}in children aged 2-8 yr as continuous infusion after cardiac surgery. Compared with nonventilated children aged 6 months to 2 yr after a single dose before minor in-hospital or day-stay procedures, the clearance found in our population was slightly higher (16.7 ml · kg^{-1} · min^{-1} *vs*. 11.3 ml · kg^{-1} · min^{-1})[5] but was comparable to clearance described in nonventilated healthy adults after a bolus injection (16.1 ml · kg^{-1} · min^{-1}).[30] Our pharmacokinetic analysis demonstrates that nonventilated infants after major surgery may require relatively high doses of midazolam. Because midazolam is an intermediate extraction ratio drug, this may be attributable to the relatively healthy state of the children and to the absence of mechanical ventilation, which affects the hepatic blood flow.

A high degree of interindividual variability in clearance (coefficient of variation, 54%) was seen, which could not be attributed to body weight, venous or arterial sampling, frequencies of CYP3A4, 5 or 7 variant alleles, or hemodynamic parameters, probably because of the narrow variability in patient characteristics and condition. The clearance tended to be related to age, but the relatively small number of infants older than 15 months may be the cause that the trend did not reach statistical significance. As a consequence, dose recommendations may be less appropriate for infants aged 15-24 months. Regarding arterial and venous sampling, there is evidence that differences are only relevant during the rapid distribution phase,[31] and this does not seems to be of clinical relevance when midazolam is used as continuous infusion in sedated children. In one heterozygous CYP3A7*1C infant who needed high doses of midazolam, the incorporation in the model of a multiplication factor of CL_1 and CL_3 resulted in a significantly better fit, which means that the oxidation and glucuronidation was between two and three times faster than in the other infants. The allele CYP3A7*1C is associated with continued high hepatic and intestinal CYP3A7 expression.[32] The clinical relevance of the finding is yet unclear because it is limited by the frequency of the alleles as relates to the number of patients because it has been analyzed as part of a large DNA data study. Large studies may answer the question of whether this investigated allele plays a significant role.

Depth of sedation may be difficult to assess in children. The COMFORT scale is validated in the PICU and measures six behavioral items as well as two physiological items (mean arterial pressure and heart rate).[33] Because the physiological items are controlled in the intensive care unit, the COMFORT-B score was developed in Canada by Carnevale and Razack[15] and is routinely used in most PICUs in The Netherlands.[14] The BIS is a processed electroencephalographic parameter developed using adult data and is objective and easy to use, but is not yet validated for children below the age of 1 yr. The impact of age on the BIS is still debated, with divergent findings.[34,17]

Using the COMFORT-B as pharmacodynamic endpoint, depth of sedation was described

as a function of a baseline, a postanesthesia effect, a CNR, and the midazolam effect. Age was found to be a significant covariate for the baseline (the state of comfort at arrival) in the PSICU. This indicates that young children may be more sensitive to the environment and emotional distress than older infants. Non-agitated children displayed on the COMFORT-B a night dip starting at 20.00 h and a slower washout period of the postanesthesia effect (1794 *vs*. 537 min, respectively) compared with agitated infants. In agitated children, no night dip was observed. In these infants, the midazolam effect was implemented using an E_{max} model. Using the BIS, a large residual error and a large interindividual variability were found, resulting in the inability to detect the postanesthesia effect. This confirms the clinical observation that the BIS highly fluctuates in particular in lightly sedated children. This may be explained by the fact that light sedation may be influenced more by the environment.[35] Fifty-six percent of the infants did not show a response of midazolam on the BIS, whereas midazolam influenced the COMFORT-B in all infants, although the interindividual variability in EC_{50} was large (89%) and no patient characteristics (covariates) could increase the predictability. Taking into account the age for which the BIS is validated, 8 of the 10 patients $\geq$ 1 yr did not show a response of midazolam on the BIS. Therefore, the BIS seems less sensitive and less specific for the effect of midazolam than the COMFORT-B score.

In this study, no separate EC_{50} could be identified for midazolam parent and metabolite, because the concentration profiles ran parallel in time while the concentration of the metabolite 1-OH-midazolam was low throughout the entire treatment period (ratio 1-OH-midazolam/midazolam is 0.37). Therefore, the observed effect was only ascribed to midazolam, using a simple E_{max} model. Sampling immediately after the bolus may have provided a different ratio of metabolite and parent drug, which would enable identification of contribution of 1-OH-midazolam to the effect. It has been shown before in a study after oral or separate intravenous administration that 1-OH-midazolam has pharmacological activity.[4,12] However, after intravenous administration, the concentration of the metabolite is relatively low compared with oral use. Also in adults after coronary artery bypass grafting, no effect of 1-OH-midazolam could be detected,[36] whereas 1-OH-midazolam levels were above 10 μg/l in only 11% of the patients and the ratio was at most 0.20.[37]

Currently, no population pharmacodynamic studies in adults are available for comparison of the sensitivity of infants to adults using these sedation scales. In adults, the Ramsay score is often used to assess the level of sedation. Using the Ramsay scale, the midazolam concentrations in adults associated with 50% probability of a level of sedation 2 (cooperative), 3 (drowsy or asleep, easily responded to commands), and 4 (asleep, brisk response to a glabellar tap) were 0.017, 0.22, and 0.52 μmol/l, respectively.[36] In the present study, after a bolus of 1 mg and a continuous infusion of 0.5 mg/h, the predicted concentration in the infants is 0.16 μmol/l, corresponding to values between 12 and 14 on the COMFORT-B (lightly sedated). Although comparison is difficult, it seems that the midazolam concentration to achieve light sedation in infants is comparable to that in adults.

In a previous article, we described a pharmacokinetic and pharmacodynamic model for propofol in this population group[19] and discussed the safety of propofol compared with midazolam.[18] As found for midazolam, clearance of propofol was also higher than the values

reported in the literature. The results of the current analysis demonstrate that midazolam shows a less predictable effect than propofol, because the interindividual variability in EC_{50} (89% *vs*. 47%) on the COMFORT-B is higher, whereas the residual (intraindividual) variability and elimination half-life are comparable (30% *vs*. 32% and 16.8 *vs*. 18.6 min, respectively). The results indicate that propofol may be preferred over midazolam as a sedative in intensive care, which should be further studied taking into account the safety recommendations.

The pharmacokinetic and pharmacodynamic population model shows that a loading dose of 1 mg followed by a continuous infusion of 0.5 mg/h midazolam is the optimal initial dose for a desired COMFORT-B score of 12-14 during the first night after major surgery in non-ventilated infants aged 1 yr. Because of large interindividual variability, further individual titration is important for midazolam. Although no significant effect of age on the clearance could be detected, the initial dose recommendation may be less suitable for application in infants older than 15 months.

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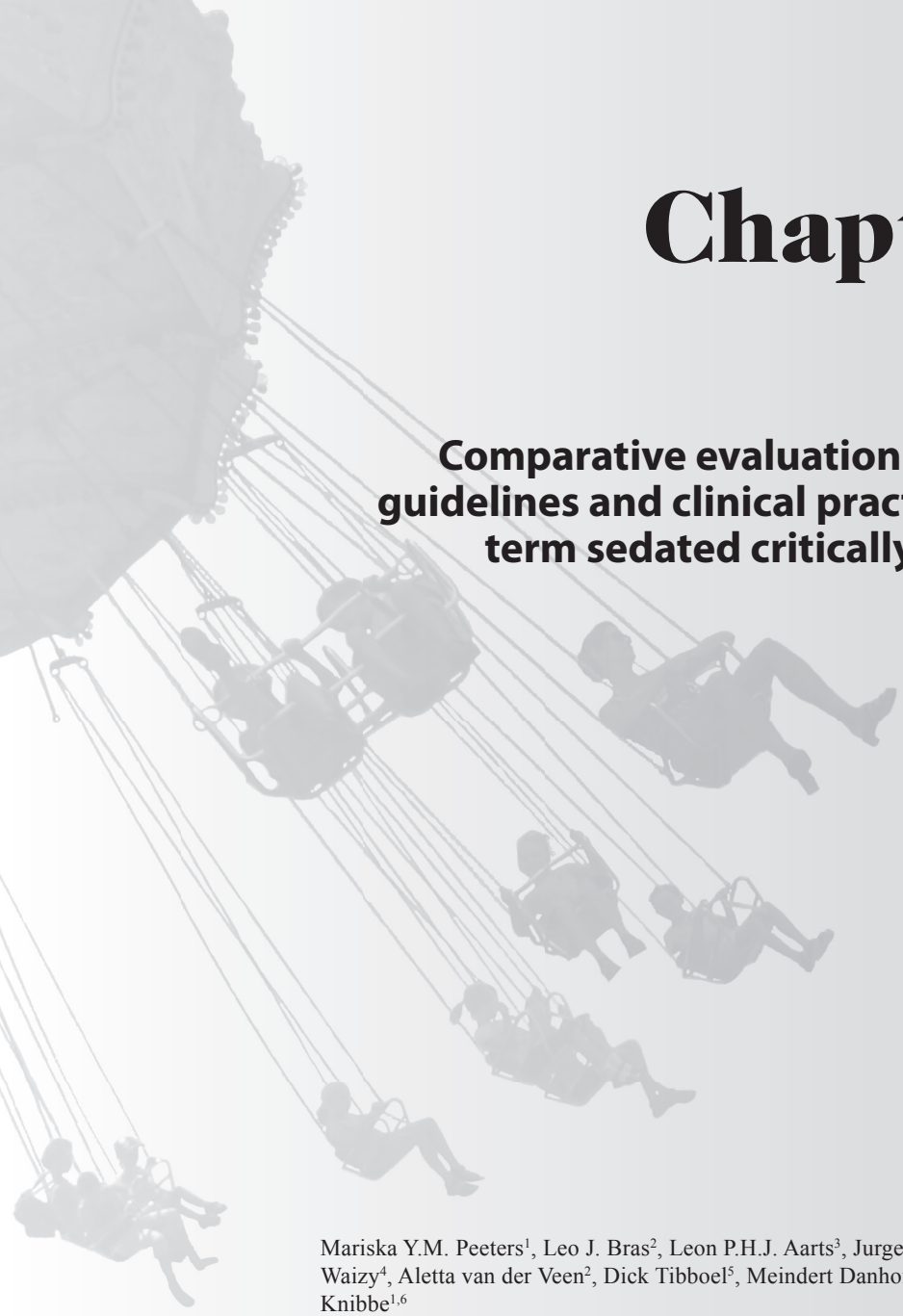
Sedation in critically ill patients

Chapter 5

Comparative evaluation of sedation guidelines and clinical practice in long-term sedated critically ill patients



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Abstract

Background: Sedation protocols in the intensive care have been shown to reduce the duration of mechanical ventilation and length of stay. In this study a sedation protocol for long-term sedated patients is implemented and evaluated by comparing target levels to observed levels of sedation.

Methods: Propofol administration was titrated by the nurses to a physician determined Ramsay score, using a protocol driven approach. Twenty-six critically ill patients were included, who were expected to require mechanical ventilation and sedation > 2 days. The BIS was recorded concurrently.

Results: 541 Ramsay observations were obtained with a median of 16 observations per patient. Target Ramsay scores were achieved in only 28% of the assessments (difference *d* between observed and target equals 0), while 35% were within clinical acceptable differences ($d = -1$ or $d = +1$) and 33% were recorded as oversedated ($d > 1$). The mean difference *d* was +0.93 (SD 1.3) and represented the consistent significantly ($P < 0.001$) deeper level of sedation titrated by the nurses than target by the physicians. When target scores were achieved, a dose reduction was attempted 15% of the time. At oversedation ($d > 1$) the infusion rate was mostly maintained (63%). Mean BIS values were significantly different between the groups agitation, light and deep sedation ($P < 0.001$). The Ramsay score and the BIS were moderately ($r = -0.570$, $P < 0.01$) correlated.

Conclusion: We found that in clinical practice, critically ill patients tend to be oversedated. Repeated feedback may be necessary in order to benefit from claimed advantages of a sedation protocol.

Introduction

Mechanically ventilated patients require an appropriate level of sedation and should not have excessive levels to reduce the risk of prolonged mechanical ventilation, related complications and length of stay in the intensive care unit (ICU). A nurse-driven sedation protocol[1] and daily interruption of sedation[2] can decrease these risks, which resulted in recommendation of the Society of Critical Care Medicine[3] to use sedation guidelines. However, there is considerable variability between published evidence and local guidelines with regard to the choice of sedative, sedation scoring systems and the practice of daily interruption.[4] In addition, although most ICUs have developed and stated a (local) sedation protocol, actual clinical practice may (wittingly or unwittingly) differ significantly and this may affect the intended improved health outcome.[5] Specifically, deeper levels of sedation used to be common in most ICUs before the introduction of sedation protocols. Surprisingly, little research is published on the adherence to sedation protocols in the ICU, especially for long term sedated critically ill patients who may benefit the most from the claimed advantages.

In this study we implemented a sedation protocol for critically ill patients who were expected

to be mechanically ventilated and sedated for more than 2 days. We evaluated the compliance to the target levels of sedation. Assessment of sedation was performed using the Ramsay score. The Bispectral index (BIS) was recorded concurrently, thereby exploring the BIS as an additional instrument to measure the level of sedation. This enables examination of the relation between the Ramsay and the BIS as a secondary objective, as BIS use is not yet clear in the ICU.[6]

Materials and Methods

The study was performed in a 30 bed mixed surgical/medical intensive care unit at the St Antonius Hospital in Nieuwegein, The Netherlands, a tertiary teaching hospital. Patients were eligible for participation in the study if they were between ages of 20-90 years and expected to be mechanically ventilated and sedated for more than 2 days with propofol as the primary sedative choice. Patients with known hypertriglyceridemia, allergic history to propofol or pregnancy were excluded as were patients with a known history of drug abuse. The study was approved by the Ethics Committee of the St Antonius Hospital, Nieuwegein, The Netherlands. Written informed consent was obtained from the next of kin.

Development of guideline

Two anesthesiologist-intensivists, two hospital pharmacists and seven ICU nurses developed the sedation guideline for propofol. Propofol was chosen as the drug of choice for long-term sedation, because of the high level of experience with propofol in our clinic, the short duration of action which enables rapid awakening and the local availability of Propofol 6% preventing high fat loads upon prolonged use. Before this study, the nursing staff was familiar with the Ramsay score, but levels of sedation were not systematically scored and recorded.[7] At the time of the investigation, the BIS had not been introduced to monitor sedation in the ICU, despite its routine use in anaesthesia. One ICU nurse tested the feasibility of daily wake up and assessment of the sedation level by the nurses in a pilot study during a period of 1.5 months. Eventually, the final guideline (Figure 1) was presented to and discussed with the physicians and nurses and distributed to the physicians by internal post. At inclusion of each patient, the guideline and disadvantages of inappropriately deep sedation were again discussed with the nurses in the morning and in the afternoon, reaching 2 of the 3 shifts of the primary care nurses daily. Nurses were asked to list reasons for dose adjustments and comment on the patients' sedation state on the Case Report Form. The nursing staff was instructed to titrate on the Ramsay as shown in the guideline and warned not to use BIS values because of lack of validation. They were told that the BIS decreases with level of consciousness during anaesthesia, but that the role and target values of the BIS in the intensive care patients (without muscle relaxants) are not clear.

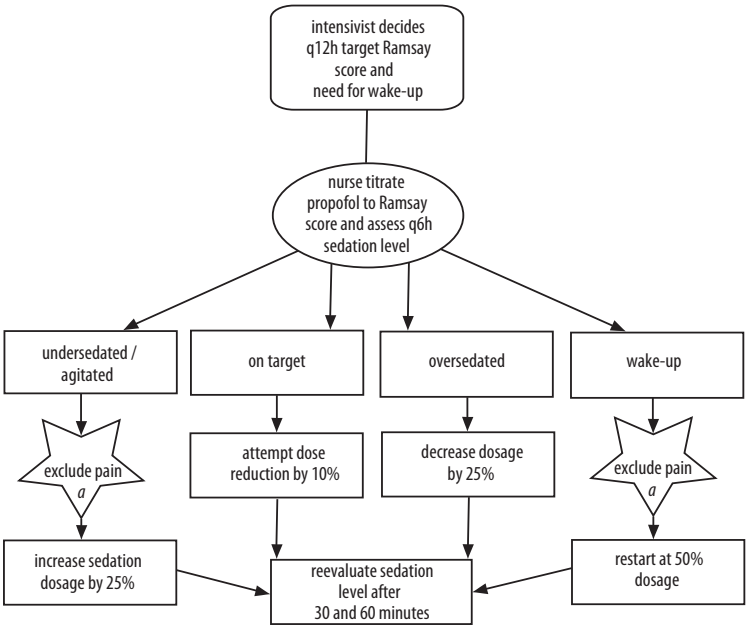

Figure 1 Schematic representation of the sedation protocol.
The Bispectral index was monitored continuously.
[a] At numeric rating score (NRS) > 4: increase analgesia dosage with 25% and reassess sedation level

Sedative and analgesic regimen

Propofol sedation (Propofol 6% [7,8] or Propofol 1% (AstraZeneca, Zoetermeer, The Netherlands) was guided by a sedation protocol (Figure 1), in which the attending physician determined twice daily the target Ramsay score, the need of interruption of propofol or the definitive discontinuation of the sedative. The Ramsay score[9] is a six point scale: 1) patient anxious, agitated, restless, 2) cooperative, orientated and tranquil, 3) drowsy or asleep, easily responding to commands, 4) patient asleep, brisk response to a light glabellar tap, 5) patient asleep, sluggish response to a light glabellar tap and 6) patient asleep, no response to a light glabellar tap. The primary care nurse adjusted the infusion rates according to the target Ramsay score and assessed in standard manner 4 times daily the level of sedation and 30 and 60 minutes after dose adjustment. If the target Ramsay score was achieved, a decrease in dose rate of approximately 10% was attempted. If patients were agitated, the Numeric Rating Scale (a 0-10 point scale) was used as pain instrument to determine whether analgesia was well controlled (NRS $\leq$ 4) before the propofol infusion rate was increased. Higher requirements than a maximum propofol infusion rate of 6 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} for a maximum of 6 h were considered therapeutic failures.

The BIS was recorded continuous concurrently as an objective marker for the depth of sedatives (BIS® XP, A 2000 revision 3.22, Aspect Medical Systems) using the quarto BIS® XP sensor electrodes. The values of the BIS ranges from 100 (awake) to 0 (isoelectric electroencephalogram).

Measurements

The Acute Physiology and Chronic Health Evaluation (APACHE II) score[10] was determined on the first 24 h at admission to the ICU. The severity of illness was measured by the Sequential Organ Failure Assessment (SOFA) score.[11] For safety purposes serum triglycerides were monitored.

Statistical analysis

Statistical analysis was performed using SPSS (version 12.01 for windows; SPSS, Chicago, IL, USA). Measurement of agreement between the target Ramsay score and the observed Ramsay score was performed using a Bland Altman plot.[12,13] The Wilcoxon signed ranks test for paired data was used to test the null hypothesis that the observed Ramsay score equalled the target Ramsay score.

To study the relation between the Ramsay and the BIS, four paired observations were randomly obtained per patient. The Spearman's rho was used to determine the correlation between paired Bispectral index and Ramsay scores. The Kruskal Wallis test was used to determine whether the mean BIS values differed between the Ramsay groups agitation (Ramsay 1), light sedation (Ramsay 2-4) and deep sedation (Ramsay 5-6).

Table 1 Patient characteristics (n=26). Data are numbers and median (minimum-maximum).

Gender, M/F	16 / 10
Age, years	70 (38-81)
Weight, kg	77.5 (50-120)
APACHE score at admission ICU	21 (12-49)
SOFA score at inclusion	12 (5-21)
Diagnostic group	26
Cardiac (surgical/medical)	4 / 3
(ruptured) (thoraco) abdominal aortic aneurysm	5
sepsis	6
pneumonia	4
miscellaneous [a]	4
Propofol infusion duration at inclusion, days	1.5 (0-12)
Studied propofol infusion duration, days	1.9 (0.7-9.7)
Propofol infusion rate, mg/h	147 (51-398)
Propofol infusion rate, $mg \cdot kg^{-1} \cdot h^{-1}$	2.0 (0.4-5.3)
Number of infusion rate adjustments per patient per day	
increases	1.1 (0-6.1)
decreases	1.1 (0-7.1)
Morphine infusion rate, mg/h	0.8 (0-3)

[a]: gastric tube reconstruction, femoropopliteal bypass surgery, hyperthermic intra-peritoneal chemotherapy, necrotizing pancreatitis.

Results

The characteristics of the patients participating in the study are shown in Table 1. The studied population included 12 surgical and 14 medical patients. Patients were studied for 0.7-9.5 days (median 1.9 days).

Evaluation of the stated sedation protocol

A total of 541 Ramsay observations were obtained with a median of 16 observations (4-67) per patient. In 15% of the observations a period of deep sedation (Ramsay 5 and 6) was desired according to the physicians, because of pressure - and volume controlled ventilation, prone position, defibrillation and/or severe critical illness (SOFA > 15). Light sedation (Ramsay 2-4) was desirable in 67%. In 17% (96 missing values), the target Ramsay score was not recorded. As a measure of agreement between the target Ramsay score and the observed Ramsay score, a Bland-Altman plot was constructed (Figure 2). In this plot, the mean difference between the observed and target Ramsay score (d) is + 0.93 (SD 1.3) and represents a consistently deeper level of sedation titrated by the nurses than target by the physicians. Thirty-five percent of the assessments were within clinical acceptable differences (d = -1 or d = 1). Thirty-three percent could be recorded as oversedated (d > 1). The observed deeper level of sedation was significantly different (P < 0.001). As the period of sedation and thus the number of assessments varied, pairs of means were also calculated from the mean of each patient. A comparable mean difference of + 0.96 (SD 1.4) Ramsay score was calculated and percentages of clinical acceptability and oversedation were comparable. In fourteen patients the difference between Ramsay observed and target was significantly different (P < 0.05) (all deeper). Nurses titrated in 62% to a deep sedation level of 5

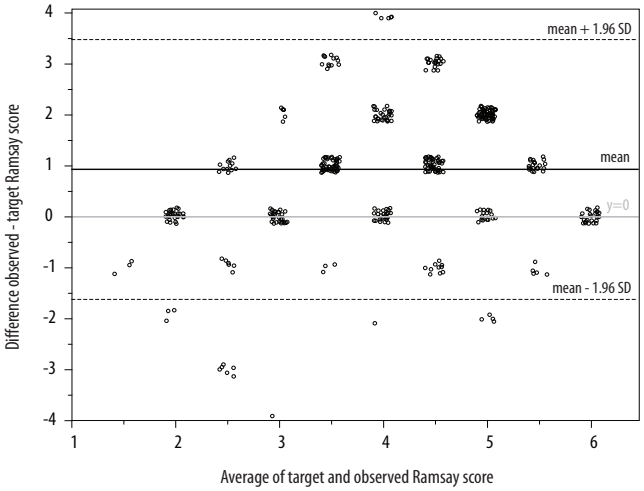

Figure 2 Bland-Altman plot of the differences between observed and target Ramsay score. The horizontal solid line represents the mean of the differences between the observed and the target Ramsay score. The horizontal dashed lines represent the limits of agreement at ±1.96SD.

and 6. Dose titrations occurred at all levels of sedation. At close titration (d = -1, n=27 and +1, n=118), the dose was increased and decreased within 3 hours by the nurses in both 19% of the assessments. At failure d < -1 (n=14) and d > 1 (n=128) the infusion was increased and decreased in 71% and 28%, respectively. At correct titration (n=112) a dose reduction was attempted in only 15% of all assessments. The assessments during interruption were excluded from this analysis (46 values). As reported in Table 1, infusion rates were adjusted on average 2.2 times per patient per day. Nurses reported the following reasons for lack of downwards titration in patients who were deeper sedated than target: motor agitation, nursing care, change in mechanical ventilation, hemodynamic effects of propofol, severity of illness, lack of time and difficulty in titration. Interruption was desired by the physician in 9 patients (35%), which were all postoperative patients who were at risk for neurological complications while undergoing pressure control ventilation. The median duration of interruption was 32 minutes (15-238, n=12). After restarting, in 33 percent the infusion rates could be decreased to 50% of the previous rate. In one patient, interruption after 44 hours infusion lead to agitation, manifested as extreme hypertension. In one patient there was no need to restart the sedative after the interruption, resulting in successful extubation.
Two patients showed high dose requirements of propofol and cholestasis, being therapeutic failures and sedation was continued with midazolam.

Exploration of the role of the Bispectral Index:
A total of 104 paired observations were analyzed. Mean BIS values were significantly different between the groups agitation, light sedation and deep sedation (P < 0.001) (Table 2). BIS values less than 60, usually associated with deep sedation[14] were recorded in 78% of the oversedated patients ($d \geq 2$ Ramsay scores). There was a moderate, but statistically significant correlation between Ramsay and BIS (Spearman's rho = -0.570, P < 0.01). One critically ill patient showed during 3.7 days continuously a high BIS and electromyographic activity (EMG), while the level of sedation was clinically assessed at Ramsay 4-6. After administration of muscle relaxant (bolus dose of 50 mg rocuronium) for facilitation of endotracheal tube exchange, the BIS and EMG markedly decreased from 94 ± 3.6 to a minimum of 29 and 53 ± 3.2 dB to 26 dB, respectively.

Table 2 Mean Bispectral Index values for the grouped Ramsay sedation scores.

Ramsay		BIS mean	N	SD
1	(agitation)	93	4	2.20
2-4	(light sedation)	75	37	22.0
5-6	(deep sedation)	55	63	20.0
Total			104	

Discussion

In this study we show that actual clinical sedation practice often differs from sedation guidelines, evidenced by differences between the target and actually observed levels of sedation in long-term sedated critically ill patients. The intention of sedation guidelines to improve the patients' outcome by reduction of the duration of the mechanical ventilation, ICU and hospital length of stay[1,2] may therefore be not fully identified in current practice.

According to the advice of the Committee of the Society of Critical Care Medicine[3] and the Netherlands Society of Intensive Care, doses of the sedative were adjusted to the Ramsay scale using a protocol-driven approach, a situation similar to most ICUs. However, we found that patients were often sedated to a deeper level ($P < 0.001$) than was defined by the attending physician (Figure 2). Specifically, the differences between the observed and target Ramsay score (d) was +0.93 (SD 1.3) Ramsay score. Deep levels of sedation Ramsay 5 and 6 were scored by the nurses in 62% in total, whereas deep sedation was defined as ideal by the physician in only 15% of the cases.

The defined deep sedation by the physicians seems judged to the mode of mechanical ventilation, although definitions of ideal sedation in critically ill patients may be disputable. Previous publications have stated different Ramsay scores as ideal varying from Ramsay 3-4[15], 5-6[16], 2-3 to deep sedation for patients nursed with unconventional ventilator strategies (prone positioning, pressure controlled ventilation and low tidal volumes).[17] According to the nurses' opinion in our ICU, some patients required deeper sedation because of severe illness, motor agitation, facilitation of caring practices and variation of mode of ventilation during the day. The rate of infusion was often increased at undersedation, however, oversedation was not reliable followed by a decrease in infusion rate, which suggest that ICU nurses are particularly focused on reducing patient distress. Reported barriers to titrate correctly were lack of time, difficulty to titrate and concern on the hypotensive effects of propofol. However, the low median numbers of propofol adjustments per day indicate a tendency to keep the same infusion rate constant. Interestingly, Cabana *et al*.[18] offered reasons why physicians do not follow practice guidelines. For physicians, lack of familiarity and awareness affecting knowledge, lack of agreement affecting attitude and finally external barriers as lack of time affecting attitude were the most often reported reasons for limiting adherence. The present study suggests that for ICU nurses, lack of familiarity or awareness are not the exclusive reasons for low adherence and inappropriately deep sedation, as the nurses were instructed and special emphasis was put on the negative effects of oversedation. Similar results were shown in a previous study.[5] Unfortunately, comments on non-compliance were not extensively reported by the nurses in this study. Further studies are therefore needed to find the exact reasons of the nurses for not following guidelines in practice. In our view, potential quality improvement of guideline adherence may include frequent redefinition of the target levels in critically ill patients, since their condition may change rapidly during the day. Moreover, daily reevaluation of the achieved sedation level in the multidisciplinary meeting to allow for feedback from the primary care nurse.

Although patients were sedated to a deeper level than target, knowledge of the effects of

oversedation may have already resulted in our ICU in a less aggressive sedation level. In a previous study from our group in 1999/2000,[8] we noted a tendency to aggressively sedate critically ill patients during the whole ICU period, assessing 60-80% of the sedation levels at Ramsay 6 without sedation protocol, judged as adequate by the nurses, while in the current study 34% of the assessments were in Ramsay 6 at comparable severity of illness.
In contrast to the defined daily interruption in the studied protocol, interruption for neurological assessment was only standard practice in patients who were at risk for neurological complications following vascular surgery. Daily interruption was not primarily used to optimize the dosage or decrease the tendency to keep the same infusion rate, using lower infusion rates at restarting. However, if sedatives are well titrated a wake-up period will not be required theoretically and the benefit for sedatives with low risk of accumulation may be less pronounced.[2]
To evaluate the BIS as an objective endpoint of a patient's level of sedation, the BIS was monitored continuously in addition to the Ramsay score. Although the Ramsay score is the most widely used titration endpoint, it is well known that the Ramsay score is not ideal as sedation instrument. Due to the subjective nature of the score, it is for example difficult to discriminate between 3, 4 and 5,[19] while Ramsay 6 seems to be a mixture of different levels of unconsciousness.[20] In our study, BIS values were found to be significantly different between agitation, light sedation and deep sedation with values of 93, 75 and 55, respectively. Between the scales, a moderately significant correlation (r=-0.570) was found. In the oversedated patients ($d \geq 2$ Ramsay score) low BIS values less than 60, associated with deep sedation[14] were recorded in 78% of the critical ill patients. Apart from the shortcomings of the BIS, such as EMG interference,[21] the BIS in our view might be helpful to differentiate in level of sedation in deeply sedated patients and might stimulate nurses to decrease the infusion rate if low values of the BIS are recorded, which should be evaluated in further studies.
In conclusion, in order to benefit from claimed advantages of a sedation protocol in the ICU, its implementation should be accompanied with repeated feedback, since in clinical practice in 33% of the cases, patients were sedated to a deeper level by the nurses than was defined by the attending physician.

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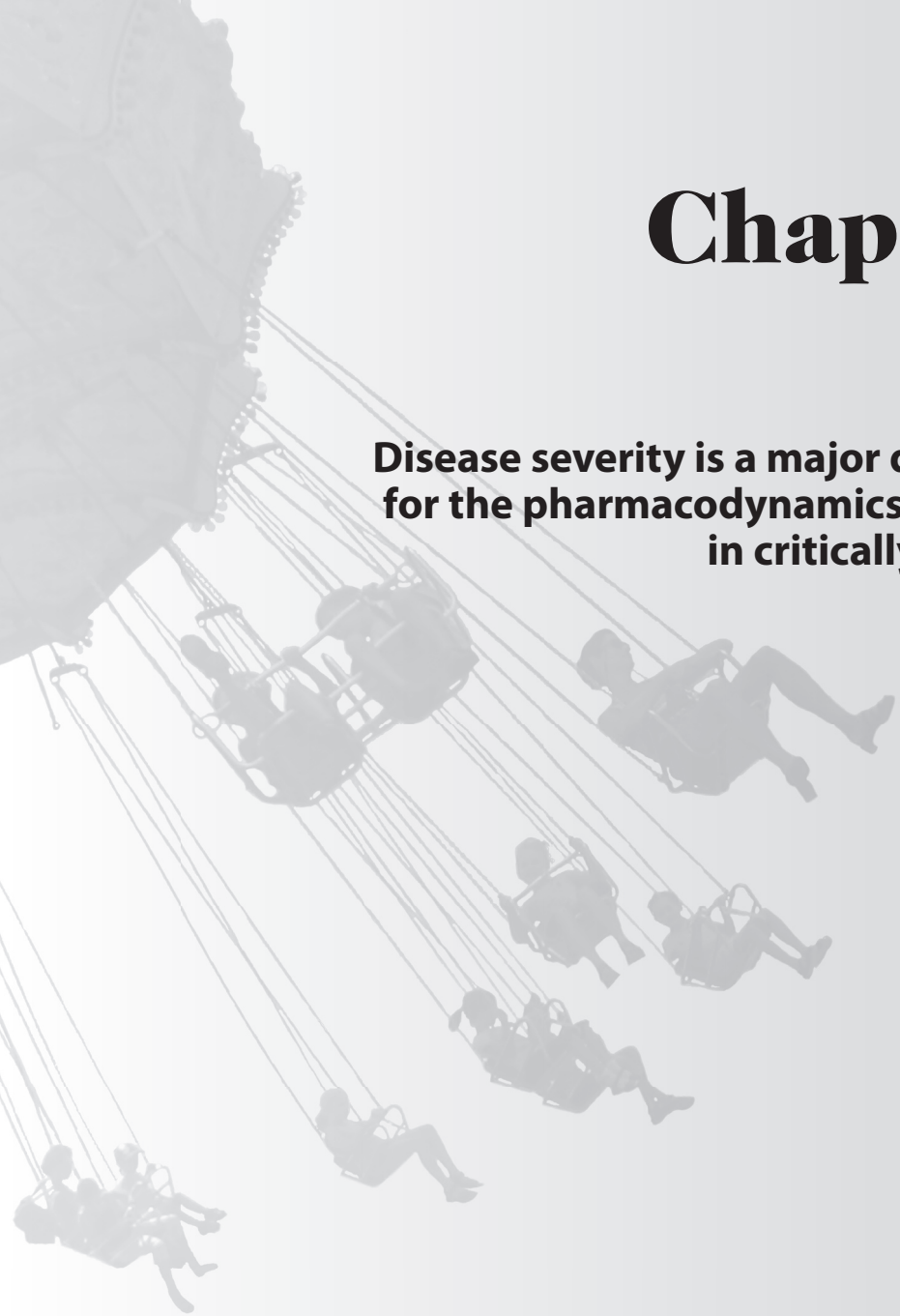

Chapter 6

Disease severity is a major determinant for the pharmacodynamics of propofol in critically ill patients

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Abstract

Objective: As oversedation is still common and significant variability between and within critically ill patients makes empiric dosing difficult, the population pharmacokinetics and pharmacodynamics of propofol upon long-term use are characterized, particularly focused on the varying disease state as determinant of the effect.
Methods: Twenty-six critically ill patients were evaluated during 0.7-9.5 days (median 1.9 days) using the Ramsay scale and the Bispectral index as pharmacodynamic endpoints. NONMEM V was applied for population pharmacokinetic and pharmacodynamic modeling.
Results: Propofol pharmacokinetics was described by a two-compartment model, in which cardiac patients had a 38% lower clearance. Severity of illness, expressed as a Sequential Organ Failure Assessment (SOFA) score, particularly influenced the pharmacodynamics and to a minor degree the pharmacokinetics. Deeper levels of sedation were found with an increasing SOFA score.
Conclusion: With severe illness, critically ill patients will need downward titration of propofol. In patients with cardiac failure, the propofol dosages should be reduced by 38%.

Introduction

Owing to its short duration of action, propofol is considered the preferred sedative in critically ill intensive care patients when rapid awakening is important, wheras lorazepam may be considered for sedation of more than 3 days.[1] Because of its ease of titration, its safety in patients with renal and hepatic disease, and the possibility of rapid awakening, propofol also appears to be very suitable for long-term sedation. However, the association of long-term use (> 48 h) and unlicensed high doses (> 4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) with propofol infusion syndrome[2] limits its use for long-term sedation. Additionally, independent of the choice of the sedative, oversedation remains a great problem, prolonging the duration of ventilation and the stay in the intensive care unit (ICU). This has led to the development of nursing-implemented sedation protocols and daily sedative interruption.[3,4] However, significant variability, not only between patients but also within individual patients, makes the empiric dosing of propofol difficult. To optimize propofol dosing for long-term use, pharmacokinetics and pharmacodynamics of propofol in critically ill patients are investigated during their stay in the ICU. A specific objective was to investigate the influence of the changing condition of the patients on pharmacokinetics and pharmacodynamics of propofol.

Materials and Methods

The study was approved by the local Ethics Committee of the St Antonius Hospital, Nieuwegein, The Netherlands. Written informed consent was obtained from the relatives. Inclusion criteria included patients between 20-90 years who were expected to be mechanically ventilated and sedated with propofol for more than 2 days. Exclusion criteria included hypertriglyceridemia, allergic history to propofol, pregnancy, or a known history of drug abuse.

Sedative and analgesic regimen

Propofol doses were adjusted to the Ramsay sedation scale using a protocol-driven approach. The attending physician determined twice daily the target Ramsay score, the need for interruption of propofol, or the definitive discontinuation of the sedative. The Ramsay scale distinguishes six levels of sedation[5]: (1) anxious, agitated, restless; (2) cooperative, orientated and tranquil; (3) drowsy or asleep, easily responding to commands; (4) asleep, brisk response to a light glabellar tap; (5) asleep, sluggish response to a light glabellar tap; and (6) asleep, no response to a light glabellar tap. The primary care nurse adjusted the infusion rates according to the target Ramsay score and assessed in standard manner four times daily the level of sedation. If patients were oversedated or undersedated, a dose adjustment of 25% was recommended. At agitation, the Numeric Rating Scale (a 0-10 point scale) was used as pain instrument to determine whether analgesia was well controlled (NRS $\leq$ 4) before the propofol infusion rate was increased. The efficacy was determined 30 and 60 min after dose adjustment. If the target Ramsay score was achieved, a decrease in dose rate of approximately 10% was attempted. At interruption, the recommended restarting infusion rate was 50% of the previous dose. The BIS was monitored continuously and the values were noted at 15 min intervals by the investigator (BIS® XP, A-2000 revision 3.22, Aspect Medical Systems) using the quatro BIS® XP sensor electrodes. The values of BIS range from 100 (awake) to 0 (isoelectric electroencephalogram). Each day, the nursing staff was instructed not to use BIS values because of lack of validation. Heart rate, blood pressure, central venous pressure, temperature, and saturation were monitored continuously. Clinical laboratory tests were routinely monitored. For safety purposes, serum triglycerides were monitored two times daily. The SOFA score was computed daily to evaluate the time course of the severity of illness and was based on the degree of organ dysfunction. For each organ system (respiration, coagulation, liver, cardiovascular, central nervous system, and renal), the worst value ranging from 0 to 4 in each 24-h period was considered, resulting in a total score of 0-24.[6]

Blood sampling and analysis

Arterial blood samples (2 ml) were collected in oxalate tubes four times daily at 3.00, 7.00, 15.00 and 21.00 h and 30, and 60 minutes after each dose adjustment. After discontinuation of the propofol infusion, samples were taken at 30 and 60 minutes intervals after stopping up to the closest daily collection time. The samples were stored at 4ºC. Propofol concentrations were measured by high-performance liquid chromatography with fluorescence detection.[7]

The limit of quantification was 0.035 mg/l. Inter- and intra-assay coefficients of variation were less than 9.6 and 2.6%, respectively, over the concentration range 0.5-5 mg/l.

Data analysis

The analysis was performed using NONMEM (Non-Linear Mixed effect Modeling) (GloboMax LLC, Hanover, MD, version V release 1.1)[8] by use of the first-order conditional estimation (Method 1) with η-ε interaction. S-plus (Insightful software, Seattle, WA, version 6.2) was used to visualize the data. Population pharmacokinetic and pharmacodynamic data were sequentially analyzed. Discrimination between different models was made by comparison of the objective function. A value of $P < 0.005$, representing a decrease of 7.8 points in the objective function, was considered statistically significant. In addition, goodness-of-fit plots, including observations *vs.* individual predictions, observations *vs.* population predictions, weighted residuals *vs.* time and population predictions *vs.* weighted residuals were used for diagnostic purposes of both pharmacokinetic and pharmacodynamic data. Furthermore, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the model.

Pharmacokinetic model

Propofol pharmacokinetics were adequately described by a two-compartment model (ADVAN3 TRANS4), parameterized in terms of volume of the central compartment (V_1), volume of the peripheral compartment (V_2), the intercompartmental clearance (Q), and clearance (CL). The individual value (*post hoc* value) of the parameters of the *i*th subject was modeled by

$$\theta_i = \theta_{mean} \cdot e^{\eta_i} \quad (1)$$

where θ_{mean} is the population mean and η_i is assumed to be a random variable with zero mean and variance ω^2. The residual error was best described with a proportional error model. This means for the *j*th observed concentration of the *i*th individual the relation

$$Y_{ij} = c_{pred,ij} \cdot (1 + \varepsilon_{ij}) \quad (2)$$

where c_{pred} is predicted propofol concentration and ε_{ij} a random variable with mean zero and variance σ^2.

Pharmacodynamic model using the Ramsay score as endpoint

The Ramsay sedation scores were described using a proportional odds model for the probability (π) of observing a particular Ramsay (RS_i) sedation level.[9] The cumulative logits L_i were modeled as:

$$L_{RS1} = \theta_1 + \theta_6 \cdot c_{1,ij} + \eta_1$$

$$L_{RS\leq 2} = \theta_1 + \theta_2 + \theta_6 \cdot c_{1,ij} + \eta_1$$

$$L_{RS\leq 3} = \theta_1 + \theta_2 + \theta_3 + \theta_6 \cdot c_{1,ij} + \eta_1$$

$$L_{RS\leq 4} = \theta_1 + \theta_2 + \theta_3 + \theta_4 + \theta_6 \cdot c_{1,ij} + \eta_1$$

$$L_{RS\leq 5} = \theta_1 + \theta_2 + \theta_3 + \theta_4 + \theta_5 + \theta_6 \cdot c_{1,ij} + \eta_1 \quad (3)$$

$\theta_{1\text{-}5}$ describes the sedation level without propofol and θ_6 describes the magnitude of the propofol effect. η is a normally distributed, zero mean random variable with standard deviation ω describing interindividual variability.
The corresponding probabilities (π) are given by:

$$F_i = \frac{\exp(L_i)}{(1+\exp(L_i))} \quad (4)$$

$$\pi(RS_i) = F_i - F_{i-1}$$

$$\pi(RS_6) = 1 - F_5 \quad (5)$$

For diagnostic purposes "naïve pooled observed" probabilities were defined as described by Knibbe *et al*.[10] and Somma *et al*.[11]. In brief, the available propofol individual predicted data and corresponding Ramsay sedation scores were rank-ordered, independent of the individual from whom the data were obtained (naïve pooled). For each concentration and its four closest lower and four closest higher concentrations, the cumulative probability for each of the Ramsay sedation score was calculated (fraction of 9). The naïve pooled observed probabilities were plotted *vs.* the concentrations and then compared with the predicted probabilities of the population model. The percentage of correct predictions (the actually observed sedation score equals predicted sedation score) and close predictions (the actually observed sedation score equals the predicted sedation score ± 1) were computed.

Pharmacodynamic model using the BIS as endpoint

The BIS data were described by a sigmoidal E_{max} model, which was directly linked to the propofol concentration in the central compartment.

$$BIS_{ij} = BIS_0 - \frac{(E_{\max,i} \cdot c_{1,ij}^{\gamma})}{(EC_{50,i} + c_{1,ij})^{\gamma}} \quad (6)$$

where BIS_0 is the baseline BIS value, which is equal to 100 (fully awake); $E_{max,i}$ is the

maximum possible effect of propofol on the BIS, which is assumed to be 100 in the *i*th subject; $C_{1,ij}$ is the individual predicted propofol concentration at the central volume; γ is the steepness of the concentration *vs.* response relation; and EC_{50} is the propofol concentration (mg/l) at half the maximum score. Pharmacodynamic parameters were assumed to be log-normally distributed. The interindividual variable (η_i) was assumed to be symmetrically distributed with mean zero and variance ω^2. One critically ill patient was excluded from the population estimate for EC_{50} as the electromyographic activity (continuously > 42 dB, median 51 dB) was considered to artifactually increase the BIS values.[12] The residual error was best characterized by a proportional error model.

$$Y_{ij} = BIS_{pred,ij} \cdot (1 + \varepsilon_{ij}) \quad (7)$$

where Y_{ij} represents the observed BIS effect in the *i*th subject at the *j*th time point.

Covariate analysis

The time-independent covariates body weight, age, body mass index, gender, and diagnostic group (*e.g*. cardiac failure) were plotted subsequently against the individual *post-hoc* parameter estimates and the weighted residuals to visualize potential relationships. Time-dependent covariates, such as duration of propofol administration and SOFA score, and the time-independent covariates were tested for statistical significance by formal inclusion of covariate effects in the model, followed by evaluation of the minimum value of the objective function and confidence intervals of the parameters. The pharmacokinetic parameters were also tested for correlation with heart rate, mean arterial blood pressure, continuous venovenous haemofiltration, temperature, triglycerides, positive end expiratory pressure, dopamine, norepinephrine, morphine dose and formulation. The pharmacodynamic parameters were additionally tested for correlation with urea concentration. Starting from the basic model without covariates, the covariate model was first built up using forward inclusion. The contribution of each covariate was confirmed by stepwise backward deletion. In the final model all covariates associated with a significant increase in objective function after elimination were maintained. The choice of the model was further evaluated as described in the data analysis.

Validation

The developed population pharmacokinetic and pharmacodynamic model using the Ramsay scale was externally validated by Knibbe *et al*.,[10] against data of the critically ill patients who had similar characteristics as the current population and who were studied in the same hospital. The pharmacodynamic model characterizing the BIS was internally validated by the bootstrap resampling method (100 times).

Results

Patients' characteristics are shown in Table 1.

Pharmacokinetics

The pharmacokinetic model was based on 494 samples from 26 critically ill patients (a median of 15 (3-54) propofol concentrations). A two-compartment pharmacokinetic model using cardiac failure and SOFA score as a covariate of clearance and peripheral volume, respectively, best described the observations. The clearance in critically ill patients recovering from complicated cardiac bypass surgery (rethoracotomy or need of inotropics) or heart failure (indicated as the cardiac failure group) was 62% that of critically ill patients without heart failure (-2LL decreased from -879.7 to -895.9). The peripheral volume (V_2) increased linearly with the improving condition of the patients expressed as SOFA score, as shown by a significant reduction in the -2LL from -879.7 to -888.9. No other covariates tested were found to improve the fit or to account for part of the observed interindividual variability. Table 2 shows the pharmacokinetic parameter values along with their confidence intervals and the interindividual variability of the basic model without covariates and the final model. The diagnostics and the concentration-time observations and individual predictions of the final model are shown in Figure 1 A-E. External validation of the final model against the data of Knibbe *et al.,*[10] demonstrated the robustness of the current model (Figure 1F). Evaluation of the basic model without covariates resulted in an overestimation of the concentrations over the total range, which demonstrates that the covariates are also of value in the external population.

On the basis of simulations from the final pharmacokinetic model, propofol concentrations

Table 1 Patient characteristics (*n*=26). Data are median (minimum-maximum).

Gender, M/F	16 / 10
Age, years	70 (38-81)
Weight, kg	77.5 (50-120)
APACHE score at admission ICU	21 (12-49)
SOFA score at inclusion	12 (5-21)
Diagnostic group	26
Cardiac (surgical/medical)	4 / 3
(ruptured) (thoraco) abdominal aortic aneurysm	5
sepsis	6
pneumonia	4
miscellaneous	4
Propofol infusion duration at inclusion, days	1.5 (0-12)
Studied propofol infusion duration, days	1.9 (0.7-9.7)
Propofol infusion rate (mg/min)	2.45 (0.8-6.6)
Propofol infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	2.0 (0.4-5.3)

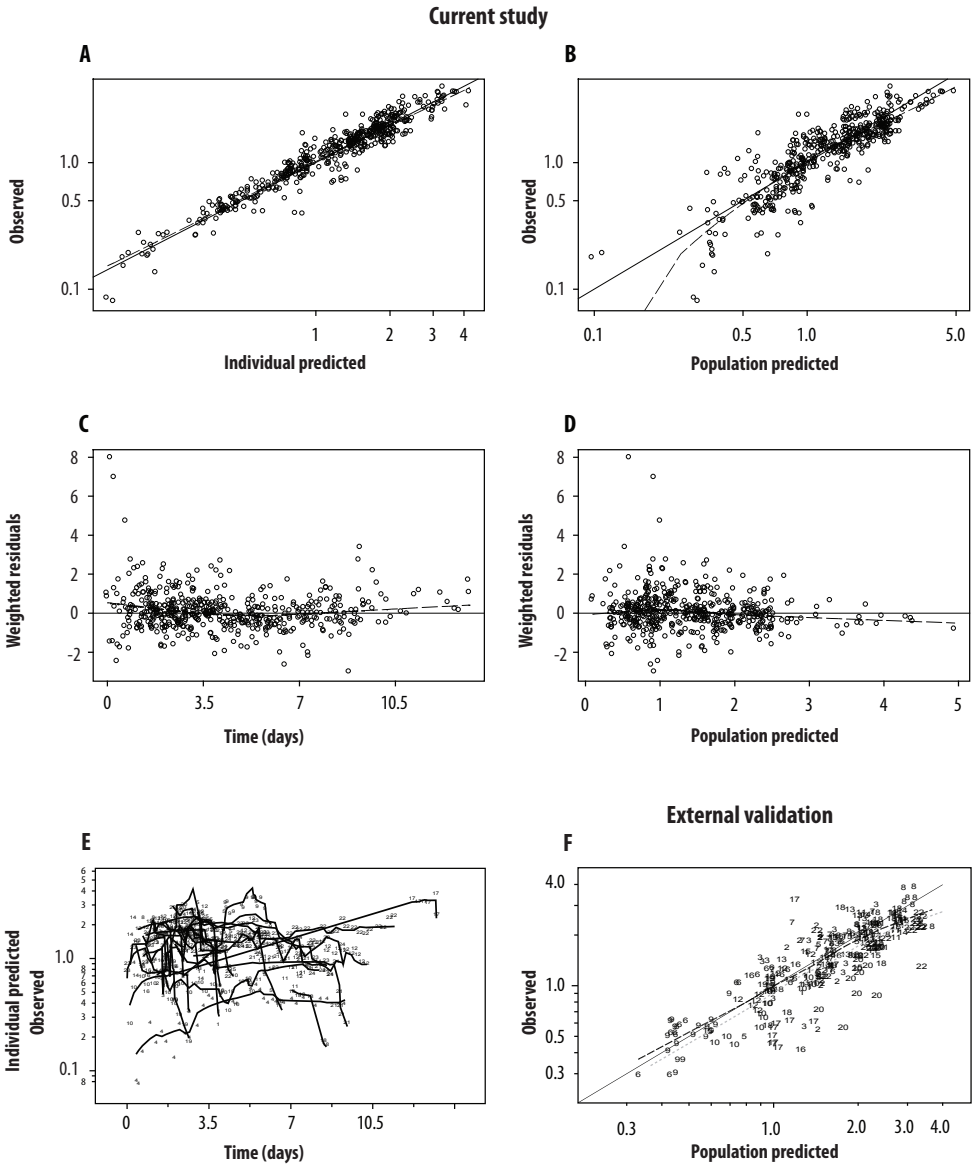

Figure 1

Diagnostic plots, including (A) observations *vs*. individual predicted propofol concentrations , (B) observations *vs*. population predictions, (C) weighted residuals *vs*. time , and (D) weighted residuals *vs*. population predictions by the final model, superimposed on the line x=y (line of identity) and the trend line (broken black line). (E) Individual predictions (lines) and observations (numbers) *vs*. time. (F) Diagnostic plot of the external validation data set, including measured propofol concentrations *vs*. predicted concentrations by the final model, superimposed on the line x=y (line of identity) and the loess smooth line (broken black line). The broken gray line shows the loess smooth line predicted by the basic model without covariates. The numbers represent the different critically ill patients.

Table 2 Population parameter estimates of the basic pharmacokinetic (PK) model and the final model with cardiac failure and SOFA score as covariates.

Parameter	Basic PK model Mean (CV%)	Final PK model Mean (CV%)
	Fixed effects	
CL, l/min CL cardiac failure, l/min	1.82 (6.5)	2.05 (5.5) 1.28 (8.5)
V_1, l	17.2 (37.1)	19.9 (28.8)
V_2, l	956 (19.3)	1140 (19.3) – 55.4 (38.8) • (SOFA-9)
Q, l/min	1.61 (19.9)	1.62 (19.4)
	Interindividual variability	
ω_{Cl}^2	0.09 (23.4)	0.04 (24.9)
ω_{V2}^2	0.81 (52.0)	0.69 (41.5)
ω_{Q}^2	0.66 (71.4)	0.64 (62.1)
	Residual error	
σ^2	0.03 (18.2)	0.03 (18.1)
	Performance measures	
-2LL	-879.7	-904.9

CL, clearance; CLcardiac failure, clearance for the cardiac failure group; V_1 central volume; V_2, peripheral volume; Q, intercompartmental clearance; ω^2, variance, the square root of the exponential variance of η minus 1 is the percentage of interindividual variability in the pharmacokinetic parameters; σ^2, proportional intraindividual variance; values in parentheses are CV, coefficient of variation of the parameter values; -2LL, objective function.

in ICU patients with cardiac failure are 1.6 times higher than that in patients without cardiac failure and only slightly different in ICU patients with an increasing SOFA score (ΔSOFA, 6) receiving the same propofol infusion scheme of 2.5 mg/min (Figure 2).

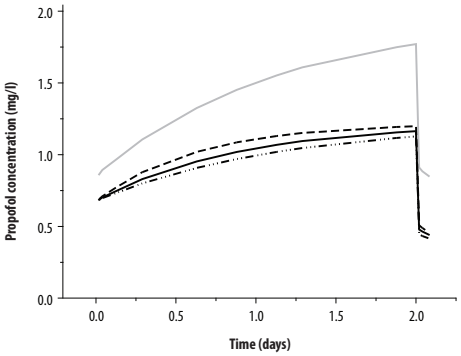

Figure 2 Simulated propofol concentration *vs*. time relationship in critically ill patients with different cardiac function (cardiac failure, solid gray line; noncardiac failure, solid black line), who receive a continuous infusion of 2.5 mg/min propofol and show varying severity of disease (SOFA 3, ---; SOFA 9, solid black line; SOFA 15, dashed line).

Pharmacodynamic model using the Ramsay as endpoint

Five hundred and forty-one Ramsay observations were available for the model. A proportional odds model, relating the probability of sedation to the propofol concentration was used to describe the pharmacodynamic data. With increasing SOFA score, increased levels of sedation were observed. The final parameter estimates are shown in Table 3. The basic model predicted 31.7% correctly and 74.1% closely (*i.e.*, within ± 1 Ramsay score). In the final model, these values were 39.7 and 84.4%, respectively. The diagnostic plots of the naïve pooled observed probability and predicted cumulative probability at different SOFA scores are given in Figure 3. The results of the validation showed that the effect of the SOFA score could also be demonstrated in the population that was used for the external validation, with the percent of correctly predicted and closely predicted Ramsay scores increasing from 35.8 to 39.4% and from 70.5 to 77.2%. Figure 4 shows the probability for Ramsay score 1 to 6 as a function of the propofol concentration for the final model for critically ill patients with different severity of illness (SOFA 3, SOFA 9, and SOFA 15). The propofol infusion rates, which are based on the pharmacokinetic model, necessary to achieve the desired sedation level are also shown in this figure. For example, if deep sedation is desired, Ramsay 5 is most probable at infusion rates of 4.7 to 7.0 mg/min at SOFA 3, whereas with severe illness (SOFA 9 and 15), decreased infusion rates of 2.0 to 4.3 mg/min and less than 1.6 mg/min, respectively, are needed. At higher rates, the probability of Ramsay 5 deceases, and Ramsay 6 is the most probable sedation score.

Table 3 Population pharmacodynamic parameters of the basic and the final model with the SOFA score as covariate based on the Ramsay score.

parameter	Basic Ramsay Mean (CV%)	Final Ramsay model Mean (CV%)
	Fixed effects	
θ_1	-2.49 (-26.6)	-0.12 (-757)
θ_2	1.61 (33.9)	1.62 (34.8)
θ_3	1.18 (17.2)	1.21 (18.1)
θ_4	1.38 (16.9)	1.44 (17.1)
θ_5	1.60 (10.2)	1.75 (9.9)
θ_6 (propofol)	-1.71 (-19.3)	-1.34 (-26.8)
θ_7 (SOFA)	-	0.22 (38.2)
	Interindividual variability	
ω^2	2.34 (43.2)	1.82 (45.9)
	Performance measures	
-2LL	1440.2	1383.9

$\theta_1 - \theta_5$, cutpoints; θ_6, magnitude of the propofol effect; θ_7, influence of the SOFA score modeled as $\partial_6 \cdot (C_{1,ij} + \partial_7 \cdot SOFA)$; ω^2, variance, the square root of the variance of η is the percentage of interindividual variability in the pharmacodynamic parameters; values in parentheses are CV, coefficient of variation of the parameter values; -2LL, objective function.

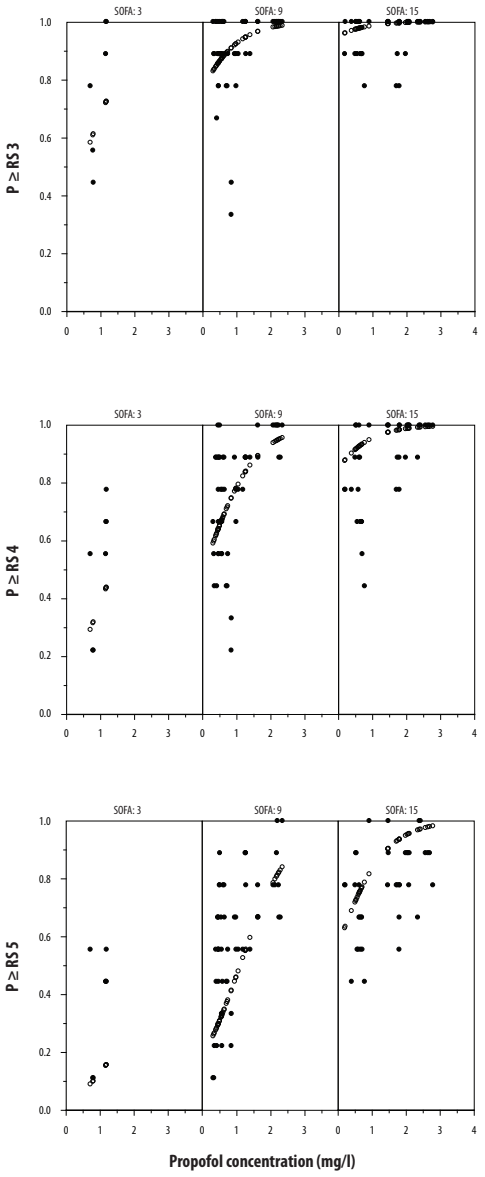

Figure 3 Diagnostic plots showing the naïve pooled observed probabilities (closed circles) and predicted probabilities on Ramsay score ≥3, ≥4, and ≥ 5 of the final population model (open circles) *vs*. propofol concentrations at SOFA scores 3, 9, and 15.

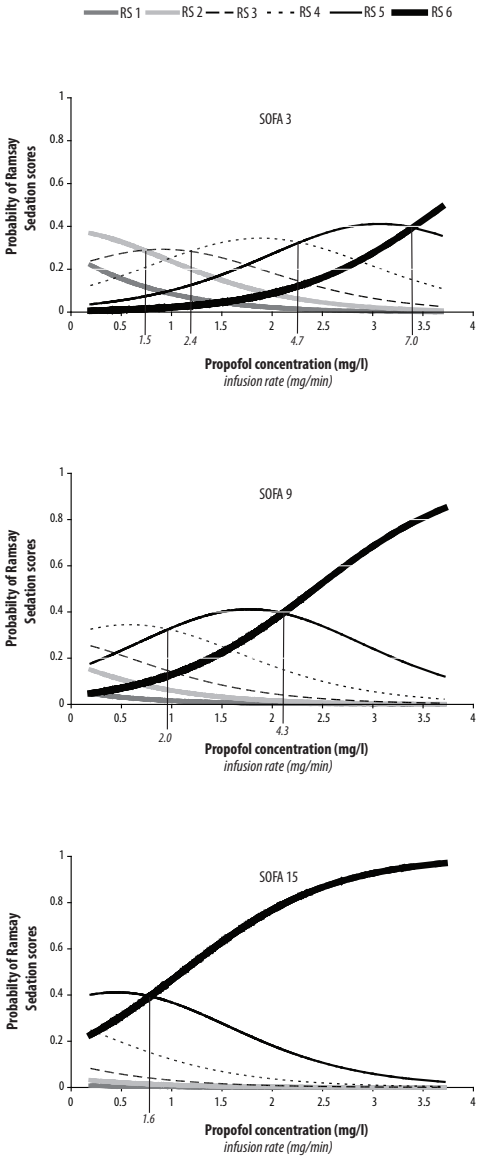

Figure 4 Simulated probabilities for a particular Ramsay sedation score, based on the final model with SOFA scores (A) 3 , (B) 9, and (C) 15 as a function of propofol concentration (mg/L) and infusion rates (*mg/min*).

Pharmacodynamic model using the BIS as endpoint

The data set included 7159 BIS values from 26 critically ill patients, yielding a median of 168 (36-737) observations per patient. Eighteen percent of all data and 85% of BIS values > 90 were associated with electromyographic activity > 42 dB.[13] Depth of sedation was best described with a sigmoid E_{max} model with the SOFA score as significant covariate for the EC_{50} (Table 4). The severity of illness influenced the level of sedation, shown by a highly significant reduction in the -2LL from 1440 to 1384. The population parameters of the basic and final pharmacodynamic model are reported in Table 4. The bootstrap validation (100 replications) confirmed the stability of the model. Figure 5 shows a median and a worse fit of the level of sedation, the influence of the propofol concentrations, and the high residual error. Figure 6 shows simulations of the influence of the severity of illness and cardiac failure on the BIS, following a continuous propofol infusion rate of 2.5 mg/min. Table 5 presents model-based propofol dose guidelines to achieve BIS values of 60 and 75, both of which have been correlated as values reflecting moderate sedation.[13,14]

Table 4 Population pharmacodynamic parameters for the basic and final model with the SOFA score as covariate for propofol induced changes of the Bispectral index and the stability of the parameters using the bootstrap validation (BS).

parameter	Basic BIS Mean (CV%)	Final BIS model Mean (CV%)	Bootstrap final BIS model Mean (CV%)
		Fixed effects	
EC_{50}, mg/l	2.59 (22.1)	5.14 (24.1) – (SOFA • 0.22 (26.6))	7.53 (43.6) – (SOFA • 0.33 (49.7))
γ	0.51 (26.7)	0.50 (20.0)	0.47 (33.4)
		Interindividual variability	
ω_{EC50}^2	0.40 (57.8)	0.63 (39.5)	1.46 (84.9)
		Residual error	
σ_1^2	0.07 (10.8)	0.06 (10.5)	0.06 (10.4)
		Performance measures	
-2LL	46223.3	45905.7	45143.6 (16.7)

E_0, baseline value equals 100 ; E_{max}, maximal effect was assumed to be 100; EC_{50}, propofol concentration at half the maximum score; SOFA, Sequential Organ Failure Assessment Score; γ, Hill coefficient; ω^2, variance, the square root of the exponential variance of η minus 1 is the percentage of interindividual variability in the pharmacodynamic parameters; σ_1^2, proportional intraindividual variance; values in parentheses are CV, coefficient of variation of the parameter values; -2LL, objective function.

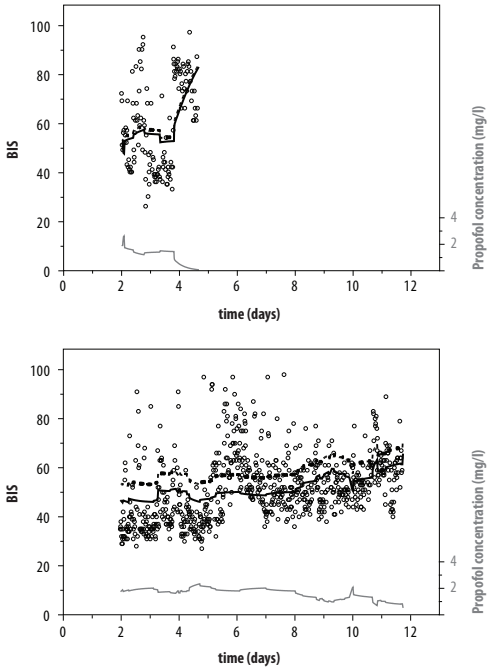

Figure 5 BIS *vs*. time (days) for a (A) median, and (B) worse performance. The open circles represent the BIS observations, the solid lines represent the individual predicted observations, and the dashed lines represent the population predicted observations. The gray line represents the individual predicted propofol concentrations.

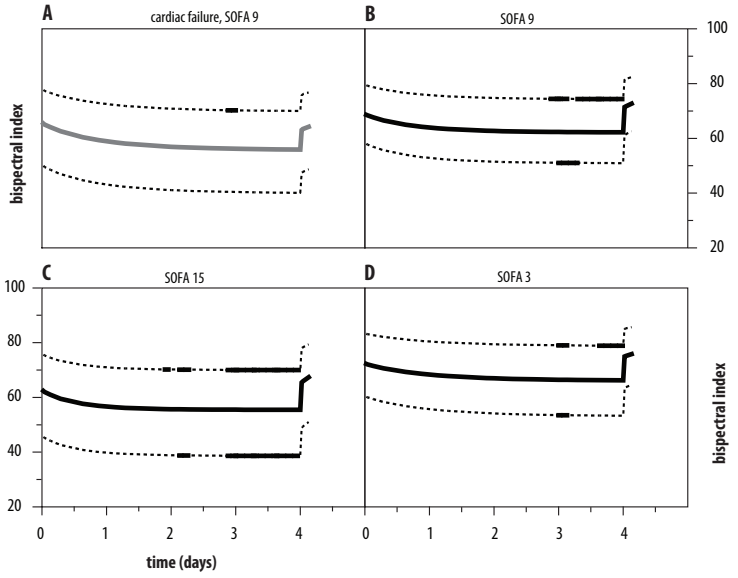

Figure 6 Simulated values for the BIS with medians (solid lines) and 90th percentiles (dashed lines), following a continuous propofol infusion rate of 2.5 mg/min in critically ill patients (A) with cardiac failure (SOFA 9) and without cardiac failure for different SOFA scores (B) 9 , (C) 15, and (D) 3.

Table 5 Dosing guidelines to achieve Bispectral index values of 60 and 75, based on simulations by the population pharmacokinetic-pharmacodynamic model of the current study, corresponding propofol blood concentrations and most likely to occur Ramsay scores.

	Cardiac failure	Noncardiac failure patients		
	SOFA 9	SOFA 3	SOFA 9	SOFA 15
BIS target 60				
Infusion rate (mg/min)	1.6	3.7	2.6	1.6
Blood concentration (mg/L)	1.28	1.78	1.28	0.78
Ramsay score	5	4	5	5
BIS target 75				
Infusion rate (mg/min)	0.4	1.0	0.7	0.4
Blood concentration (mg/L)	0.36	0.48	0.36	0.19
Ramsay Score	4	2	4	5

Discussion

In this study, we demonstrate that severity of illness expressed by the SOFA score particularly affects the pharmacodynamics and to a minor degree the pharmacokinetics of propofol in critically ill patients during long-term sedation. Additionally, cardiac failure (heart failure and complicated post-cardiopulmonary bypass surgery) influences the pharmacokinetics, resulting in approximately 1.6-fold higher propofol blood concentrations (Figure 2). In particular, severity of illness accounts for large differences in the model-based dosing guidelines (infusion rate requirements, as shown in Table 5 and Figure 4). When critically ill patients are given the same propofol infusion scheme (*e.g.,* 2.5 mg/min), the predicted level of sedation ranges from Ramsay 4 to 6 and the BIS value from 66 to 55 (Figure 6) when the severity of illness increases from SOFA 3 to 15.

The pharmacokinetic analysis revealed a 38% lower clearance in ICU patients with cardiac failure compared to critically ill patients without cardiac failure, and a smaller peripheral volume of distribution in ICU patients with a higher degree of illness. Evidence for need of lower dosages was found in patients with cardiac failure. In this group, three patients had undergone rethoracotomy due to hemorrhage after the coronary artery bypass graft surgery, which affects the hemodynamic status. One patient had a low cardiac output post-surgery and needed inotropics, and three patients with heart failure had a reduced ejection fraction of 20-30%, which may affect the hepatic perfusion and thus the clearance of propofol. Some evidence for a reduced clearance in cardiac patients was shown before in a study in children.[15] No significant correlation was found between cardiac failure and intercompartmental clearance or peripheral volume of distribution. Although of relatively small clinical influence, an increasing SOFA score (more severe degree of illness, based on six organ

functions) was associated with a smaller peripheral volume of distribution. An explanation for this decrease may be that tissue perfusion is altered in severe illnesses. In contrast, the covariates renal failure, mean arterial blood pressure, and doses of dopamine and norepinephrine, which are items of the SOFA, were not independent significant covariates.
The pharmacokinetic parameters estimated by the current study were comparable to estimates in other studies.[10,16,17] Our estimation of the peripheral volume of distribution (1140 L) was seven times larger than the previously reported peripheral volume of 168 L.[10] This larger estimate may be a result of the longer duration of propofol administration, during which more extensive tissue distribution may have occurred.
The effects of propofol have been analyzed by a sigmoidal E_{max} model using the BIS and by a proportional odds model using the Ramsay score as pharmacodynamic endpoint. The BIS has been classified as ordinal or interval data, and up to now there is no consensus.[18] We choose to analyze the BIS as if it were a linear scale (parametric approach). The non-parametric approach would require a large number of categories to model and most likely a substantial number of observations in all parts of the BIS scale. The BIS data were described adequately; however, the BIS showed a large scattering (Figure 5), which was reflected in the large residual error of 24% (Table 4). This large residual error may be caused partly by excessive EMG activity and negatively affects predictions of correct dosing. This should be taken into account when the BIS monitor is considered for use in clinical practice.
The pharmacodynamics of propofol was significantly influenced by the severity of illness for both the Ramsay and the BIS as pharmacodynamic endpoints. The probability for a deeper Ramsay score increases with progressive illness, which means that lower infusion rates suffice to maintain a discrete Ramsay score if the condition of critically ill patients worsens (Figure 4). The influence of the severity of illness is also demonstrated in the external validation, in which the percentage of correct predictions increased after incorporation of this covariate. Using the BIS as a pharmacodynamic endpoint, the propofol infusion dose needs to be reduced up to 60% when the condition of an ICU patient worsens from SOFA 3 to 15 (Table 5). In this study, there was no evidence for tolerance (a decrease in the effect of a drug over time or the need to increase the dose to achieve the same effect) in patients given long-term propofol infusion. Tolerance of propofol has been reported by Buckley,[19] but the fact that the need for an increased dose was related to the improving condition of the patients was not ruled out. Our findings are important for clinical practice, because until now it has been a common practice to aim at deeper sedation in more severely ill patients and consequently to use a high infusion rate in the early course of the critical illness, followed by a downwards titration over time.[20] Conversely, our results may indicate that ICU patients will need upwards titration over time with recovering. Specific dosing guidelines are given in Table 5 and Figure 4.
In conclusion, this study illustrates that severity of the illness particularly influences the pharmacodynamics and, to a minor degree, the pharmacokinetics of propofol in critically ill patients during long-term sedation. This means that with severe illness, infusion rates must be reduced. Furthermore,in patients with cardiac failure, the propofol dosages should be reduced by 38%.

Acknowledgements

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Chapter 7

Pilot study on the influence of liver blood flow and cardiac output on the clearance of propofol in critically ill patients

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Abstract

Objective: To investigate the effect of the cardiac output and liver blood flow on propofol concentrations in critically ill patients in the intensive care unit.
Methods: 5 medical/surgical critically ill patients were enrolled in this preliminary study. Liver blood flow was measured using sorbitol. The cardiac output was measured by bolus thermodilution. NONMEM V was applied for propofol pharmacokinetic analysis.
Results: Clearance of propofol was positively influenced by the liver blood flow ($P < 0.005$), whereas no significant correlation between cardiac output and propofol clearance was found. A correlation between liver blood flow and cardiac output or cardiac index, could not be assumed in this patient group.
Conclusion: Liver blood flow is a more predictive indicator than cardiac output for propofol clearance in critically ill patients. Further study is needed to determine the role of the liver blood flow and cardiac output on the pharmacokinetics of highly extracted drugs in order to reduce high observed interindividual variabilities in response in critically ill patients.

Introduction

Propofol is a drug with a high hepatic extraction,[1] which means that its clearance highly depends on liver blood flow. The hepato-splanchnic blood flow amounts to 25-30% of the cardiac output (CO)[2] and is influenced by different physiological conditions such as the ingestion of food and exercise.[3,4] Previous reports have shown the inverse relationship between the CO and propofol concentrations in animals and in relatively healthy surgical patients during anaesthesia.[5-8] In critically ill patients, liver blood flow (LBF) and cardiac output may vary widely, which may have a major impact on the pharmacokinetic profile of drugs with flow-dependent clearance. Hypotensive patients with severe sepsis may have low, normal or increased cardiac output.[9] In patients with shock, blood flow to heart, brain and muscle is maintained at the expense of renal and splanchnic blood flow. Hemodynamic support, resuscitation and inotropic therapy[10] can change the LBF/cardiac output ratio. Similar liver blood flow but higher COs have been shown in chronic hemodialysis patients compared to healthy volunteers.[11] In addition, mechanical ventilation can influence cardiac output and liver blood flow.[12,13]
The aim of this pilot study was to explore the influence of variability in liver blood flow and cardiac output on the pharmacokinetics of propofol in critically ill patients with different underlying disease. This is important, because it is known that there is a large unexplained interindividual variability in response of drugs in critically ill patients, which complicates dosing. The results of this pilot study also provide information on the relation between cardiac output and liver blood flow in critically ill patients.

Materials and Methods

The study was approved by the local Ethics Committee of the St Antonius Hospital, Nieuwegein, The Netherlands. Written informed consent was obtained from the patients' relatives. Patients were eligible for participation in the study if a pulmonary artery catheter was inserted, were between 20-90 years, were expected to be mechanically ventilated and sedated with propofol for more than 2 days. Patients with known hypertriglyceridemia, history of drug abuse, allergic history to propofol or pregnancy were excluded as were patients with a known history of fructose intolerance or lactic acidosis. The patients of this sub study also participated in a larger study.[14]

Blood and urine sampling and analysis

Arterial blood samples (2 ml) for determination of propofol and sorbitol concentrations were collected in glass oxalate tubes. Propofol whole blood samples were stored at 4ºC and analysis was carried out within 2 weeks by high-performance liquid chromatography with fluorescence detection.[15] The limit of quantification was 0.035 mg/l. Inter- and intra-assay coefficients of variation were less than 9.6 % and 2.6% respectively over the concentration range 0.5-5 mg/l. Sorbitol samples were taken before sorbitol administration and at 40 and 45 minutes after the start of the sorbitol infusion. The samples were immediately kept on ice water until centrifuged within 30 minutes at 4ºC. Urine was collected during the start of the sorbitol bolus until 1 h after stopping of the infusion. Sorbitol plasma samples and aliquots of urine were stored at -20ºC. Sorbitol concentrations in plasma were measured with gas chromatography-mass spectrometry using the method of Jakobs C *et al.*[16] The coefficient of variance of 1.04 µmol/l was 22%, *n*=14. Sorbitol concentrations in urine were measured with capillary gas chromatography as described by Jansen G *et al.,*[17] with a coefficient of variance of 18% at 14 mmol/mol creatinine , *n*=44.

LBF calculation

Liver blood flow was determined using the concentration of sorbitol at steady state.[18,19] A 2 gram loading dose of sorbitol 30% (Tilburg, The Netherlands) was given, followed by a 50 mg/min infusion during 45 minutes.
Liver blood flow (LBF) was calculated according to Schoemaker *et al.,*[20] using the following equations:

$$CL_H = (1 - Ht) \cdot LBF \cdot E \quad (1)$$

in which Ht is the hematocrit as sorbitol does not concentrate in the erytrocytes and CL_H is hepatic sorbitol clearance. The extraction ratio E was assumed to be 0.96.[3] Hepatic sorbitol clearance was assumed to be equal to the extrarenal clearance.

$$CL_H = (1 - renalfraction) \cdot CL_{total} \quad (2)$$

Renal fraction was calculated as the total sorbitol excretion in urine divided by total dose administered. Total sorbitol excretion was calculated with the urine collected during the first 2 h (assuming excretion beyond 2 h was negligible). Total sorbitol plasma clearance was calculated as sorbitol infusion rate divided by the steady state plasma concentration.

From the equations follows:

$$LBF = \frac{(1 - renalfraction) \cdot CL_{total}}{(1 - Ht) \cdot E} \quad (3)$$

Pharmacokinetic analysis

Pharmacokinetic parameter analysis of propofol was performed in NONMEM (Non-Linear Mixed effect Modeling) (GloboMax LLC, Hanover, MD, version V release 1.1) [21] by use of the first-order conditional estimation (Method 1) with η-ε interaction. Discrimination between different models was made by comparison of the objective function. A value of $P<0.005$, representing a decrease of 7.8 points in the objective function, was considered statistically significant. In addition, goodness of fit plots including observations *vs.* individual predictions, observations *vs.* population predictions and weighted residuals *vs.* time and population predictions *vs.* weighted residuals were used for diagnostic purposes. Furthermore, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the model. The pharmacokinetic parameters were tested for correlation with cardiac output, cardiac index (CI) and liver blood flow.

Cardiac output

Cardiac output was measured just before the sorbitol loading dose by using the gold standard bolus thermodilution pulmonary artery catheter in triplicate.

Table 1 Patient characteristics.

Patient	Sex	Age (years)	Body weight (kg)	Diagnosis	SOFA	Mechanical ventilation	Liver function	
1	M	73	96	thoraco abdominal aortic aneurysm surgery	10	PC 8 PEEP	AF GGT Bili tot AST ALT LD	42 48 20 73 29 603
2	M	55	92	abdominal sepsis	17	PC 18 PEEP	AF GGT Bili tot AST ALT LD	51 49 12 146 39 586
3	F	70	67	abdominal sepsis hyperthermic intra-peritoneal chemo-therapy	7	PS 12 PEEP	AF GGT Bili tot AST ALT LD	235 308 15 21 15 588
4	M	69	90	ruptured thoraco aortic aneurysm surgery	12	PS 8 PEEP	AF GGT Bili tot AST ALT LD	85 71 172 108 46 1333
5	M	58	80	cardiomyopathy with poor EF (20%) and respiratory insuffi-ciency	13	PS 10 PEEP	AF GGT Bili tot AST ALT LD	163 102 52 17 26 511

PEEP = positive end-expiratory pressure; PS = pressure support ventilation; PC = pressure control ventilation, EF= ejection fraction, SOFA = Sequential Organ Failure Assessment score on the day of study.[24]

Results

Five patients were included in this pilot study. The characteristics of the patients are presented in Table 1. Table 2 shows the calculated liver blood flow and the measured cardiac output of the patients.

Table 2 Cardiac output and liver blood flow (LBF) of the studied patients.

Patient	LBF (l/min)	Cardiac index (CI) (l/min/m^2)	Ratio LBF/CI	Sorbitol plasma concentration (mg/l)	hepatic sorbitol plasma clearance (l/min)	Renal fraction
1	2.47	3.16	0.78	29.3	1.660	0.027
2	1.56	3.09	0.50	49.8	1.003	0.0005
3	1.32	3.92	0.34	49.0	0.975	0.044
4	1.08	2.05	0.53	74.3	0.633	0.056
5	0.922	2.08	0.44	76.1	0.655	0.003

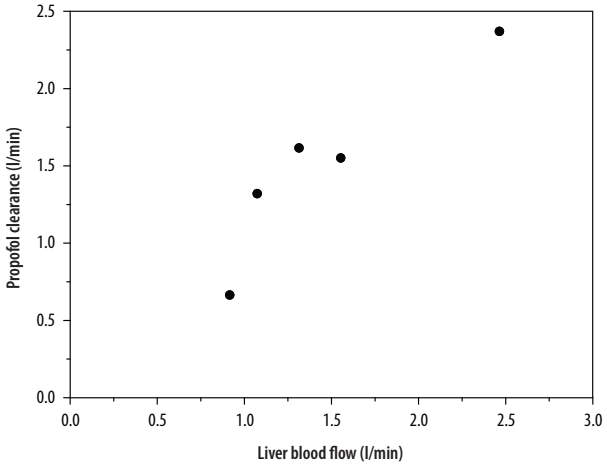

Figure 1 The relationship of propofol clearance and liver blood flow.

Propofol pharmacokinetics were adequately described by a two-compartment model, parameterized in terms of volume of the central compartment (V_1), volume of the peripheral compartment (V_2), the intercompartmental clearance (Q) and the elimination clearance (CL). The residual error was best described with a proportional error model. The clearance of propofol was significantly influenced by the liver blood flow ($P < 0.005$; objective function decreased from -134.9 to -142.9). Figure 1 shows the relationship between liver blood flow and the propofol clearance. The diagnostics of the final model are shown in Figure 2. For propofol, clearance (SE) was 1.35(0.5) + (1.19(0.44) · (LBF – 1.32)) L/min with an interindividual variability (CV) of 17%. The central volume was 26.5 (SE 5.57) L, the peripheral volume 1350 (SE 530) L and the intercompartmental clearance 1.87 (SE 0.34) L/min (CV of 42%). The residual error was 13%. Figure 3 shows a simulation of the predicted propofol concentrations at two different LBFs. The simulation illustrates two-fold higher propofol concentrations when the LBF decreases from 2.45 to 1.32 L/min.

No significant correlation between cardiac output or cardiac index and propofol clearance was found. A correlation between liver blood flow and cardiac output or cardiac index, could not be assumed on the basis of the available data (Table 2).

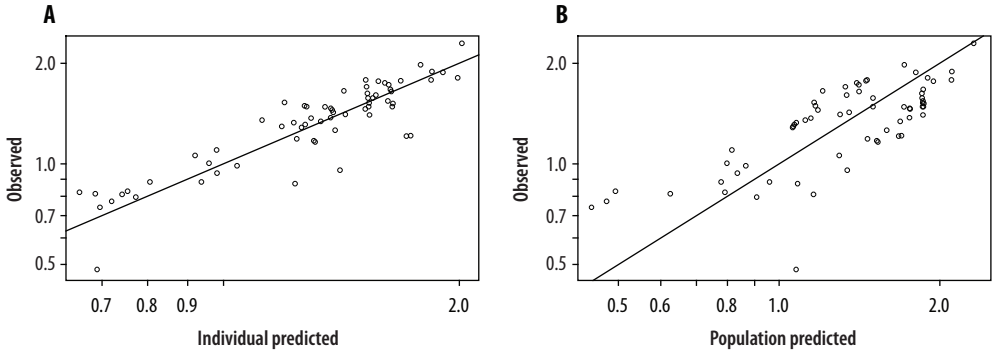

Figure 2 Diagnostic plots of (*A*) measured propofol concentrations *vs.* individual predicted and (*B*) measured propofol concentrations *vs.* population predicted concentrations by the final model, superimposed on the line x=y (line of identity).

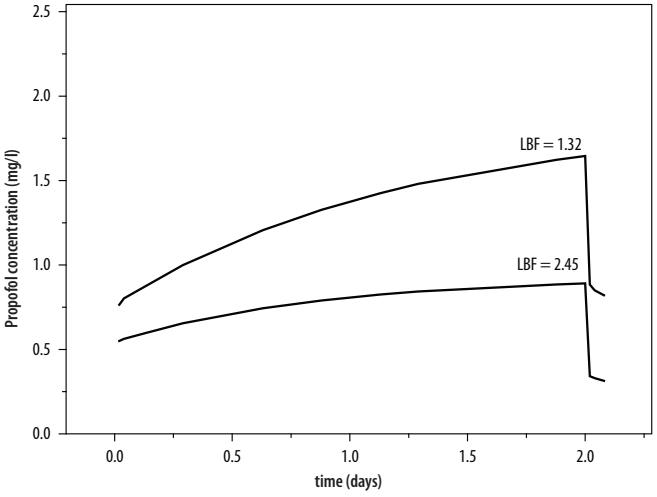

Figure 3 Simulated propofol concentrations following continuous infusion of 2.5 mg/min in critically ill patients with liver blood flow (LBF) of 1.32 and 2.45 L/min.

Discussion

Our results of this pilot study (n=5) suggests that liver blood flow was a more predictive indicator than cardiac output for propofol pharmacokinetics and presumably also for other highly extracted drugs. A significant relationship between liver blood flow and propofol clearance was found, whereas the relation to cardiac output was not clear. Higher liver blood flows increased the rate of propofol clearance and resulted in lower propofol concentrations (Figure 3). The impact of CO on propofol pharmacokinetics in these critically ill patients was not statistically significant. Although a higher CO roughly implied higher liver blood flows, its relation could not be specified or predicted from the LBF (Table 2). One reason for the lack of correlation between these parameters could be the quality of measurement of CO, as previous studies have highlighted high levels of ignorance in the understanding of the use of the pulmonary artery catheter.[22,23] However, the physicians in our clinic have high expertise in the use of this catheter, allowing for reliable CO measurements in our patients. It seems therefore that the relation between CO and LBF in critically ill patients is complex and deserves further study.

A wide range of hepatic sorbitol clearances, which reflects the liver blood flow was noted in our patients, ranging from 0.63-1.66 L/min. For healthy volunteers the hepatic plasma clearance was found to be 0.77 L/min[18] and 1.00 L/min[11,18] and showed low interindividual variability (± 0.18, n=6 and ± 0.22 L/min, n=11, respectively). The broad range in liver blood flow in our five patients is accompanied by different diagnoses and levels of organ failure, characterizing the special group of critically ill patients. This large variability has important consequences for dosing of propofol and probably other flow dependent drugs.

In previous studies, sorbitol has proven to be a suitable marker to assess the liver blood flow, having the advantage that the extraction ratio is higher and better preserved in liver diseases compared to the commonly used marker indocyanine green (ICG) and therefore may be more accurate.[3,20] However, the method is not ideal for standard care, because of its duration of administration and its method of analysis.

In conclusion, insight in liver blood flow is an important determinant to optimize the propofol dosing and prevent oversedation. Further study is needed to determine the exact role of the liver blood flow and cardiac output and its influence on the pharmacokinetics of propofol and other flow dependent drugs in critically ill patients.

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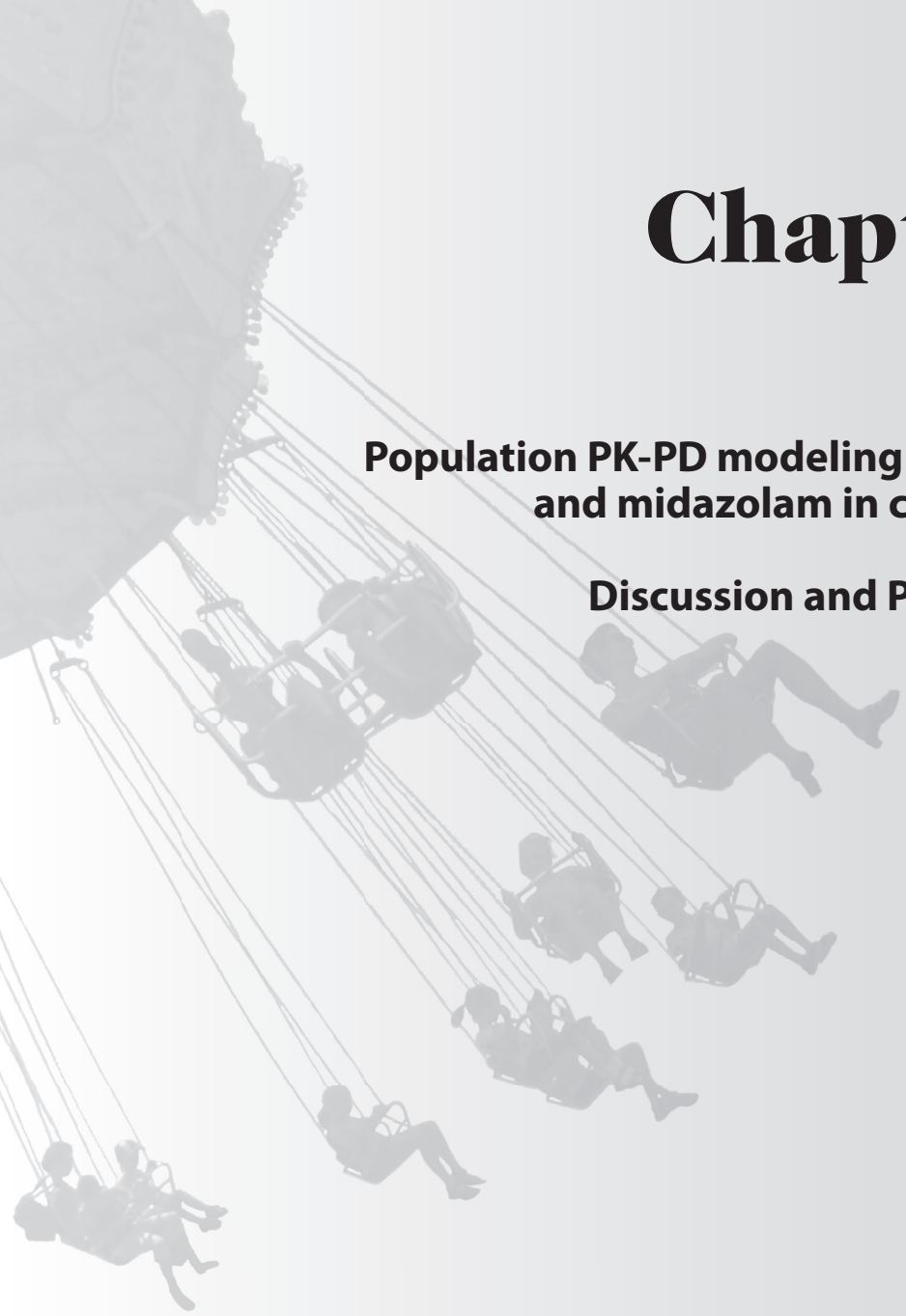
Discussion and perspectives



Chapter 8

Population PK-PD modeling of propofol and midazolam in children and critically ill: Discussion and Perspectives

The overall goal of the investigations described in this thesis was to develop novel strategies to individualize dosing of propofol and midazolam in infants and in critically ill patients, on the basis of population pharmacokinetic-pharmacodynamic (PK-PD) modeling. In the investigations the emphasis was on the modeling of the influence(s) of the covariates age, severity of illness and organ failure on the pharmacokinetics and the pharmacodynamics.

Providing adequate, predictable and safe sedation in (pediatric) intensive care patients is still a problem. In addition to the fact that agitation significantly and adversely affects patient outcome, there is increasing evidence that over sedation may be an even larger problem associated with worse sequelae.[1] However, due to the high variability in dose requirements and reports on adverse events following propofol doses higher than advised according to the product characteristics, dosing is complicated.[2,3] This underscores the importance of developing rational dosing schemes for individual patients. In this context population pharmacokinetic-pharmacodynamic modeling constitutes a sophisticated research tool.

Sedation in pediatrics

During childhood, many physiological changes take place, especially during the first two years of life with dynamic changes in organ structure and function, which have an impact on the pharmacokinetics and pharmacodynamics of drugs.[4] In the investigations described in this thesis the sedatives propofol and midazolam were studied in a population of relatively healthy nonventilated infants aged 3-24 months following elective craniofacial surgery.
Propofol is widely used for anaesthesia in pediatrics, because of its short duration of action and the rapid onset of the effect. However, sedation with propofol in children has been controversial, because of reports on the so-called "propofol infusion syndrome", defined as bradycardia, lipemia, metabolic acidosis and rhabdomyolysis after use at high doses (≥ 4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) and for long durations (> 48 h).[2,3] Children are often exposed to risks of adverse reactions by lack of information from dedicated studies on the pharmacokinetics and pharmacodynamics in this particular age group. This forces clinicians to extrapolate data from adults to children and to prescribe outside the terms of product license. As only 25-50% of drugs delivered to children are licensed for this population,[5,6] studies in children in various age-groups are nowadays encouraged and supported by the European Regulation Authority from early 2007.
In **Chapter 2** the safety of propofol in children in the paediatric intensive care unit (PICU) was evaluated on the basis of serum triglycerides, creatine phosphokinase, blood gases and physiological parameters. No adverse events were observed, when using dosages < 4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} during short-term sedation (median of 11 h). In **Chapter 3** dosing guidelines were developed for propofol using population pharmacokinetic and pharmacodynamic modeling. The population of nonventilated, relatively healthy infants aged 3-17 months was characterized by a markedly high propofol clearance of 0.70 L/min standardized to a

median body weight of 8.9 kg, which was two times higher than reported in the literature for ventilated children and for adults[7-9] and a high central volume of 18.8 L. Bodyweight was found to influence the clearance by $CL = 0.70 \cdot (BW/8.9)^{0.61}$ L/min. These two pharmacokinetic findings explain why pharmacokinetic models for patients aged 2-88 years during anesthesia[7] and for children after cardiac surgery[8,9] over predict the propofol concentrations and can therefore not be used in the population of nonventilated relatively healthy sedated infants. Interestingly our model was found to correctly predict propofol concentrations in the group of children studied by Murat *et al*.,[10] who gave a bolus dose of 4 mg/kg to spontaneously breathing children with burns with a median age of 15 (12-31) months and a median weight of 11.2 (8.7-18.9) kg (data not shown). As relatively healthy ventilated children undergoing anesthesia[7,11] did show a lower estimate of the clearance, this underlines that apart from the state of health, spontaneous breathing may also be a determinant for the selection of initial dose regimens. This also implies that caution is needed to extrapolate outside the studied covariate range, even within the same age-group. Compared to adults[8,12] the observed higher clearance of propofol may physiologically be explained by the higher liver weight (and the corresponding hepatic blood flow) as a fraction of bodyweight, which gradually decreases during maturation from about 3.6% at birth to about 2.4% in normal adults.[13] The higher infusion rates that are required as a result of the differences in the pharmacokinetic parameters may even explain why the propofol infusion syndrome is more often observed in children than in adults. Dosages up to 10.7 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} for sedation of critically ill children have been described to result in fatalities.[14] The (pharmacodynamic) sensitivity of infants to propofol appears to be comparable to adults. We reported EC_{50} values of 3.71 mg/L in infants, which are comparable to previous published values of 3.91 mg/L[15] and 3.16 mg/L in adults (Chapter 6). A large pharmacodynamic interindividual variability and residual error were observed on the COMFORT-behavior score (COMFORT-B) (47% and 32%, respectively) and Bispectral index (BIS) monitor (145% and 13 BIS units, respectively), without a pertinent covariate which could account for this variability. The considerable variability and the safety concerns emphasize the importance to further study possible covariates influencing the PD of propofol. In the meantime, dose titration of propofol is important whereby doses should not exceed 4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}.[2,3]

In **Chapter 4**, we developed dose regimens for midazolam in nonventilated infants under the age of 2 years in the PICU. Midazolam is still the most commonly used sedative in children. However, paradoxical reactions are not uncommon. Midazolam has an intermediate extraction ratio and its elimination is almost exclusively mediated by CYP3A4/5 and to a lesser extent by CYP3A7. For this reason, midazolam is often used as a model drug for the evaluation of CYP3A4/5-dependent hepatic clearance.[16,17] Comparable to the results on propofol in Chapter 3, midazolam clearance was remarkably high. The estimated total clearance of midazolam of 157 ml/min (16.7 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}) in nonventilated children in our study was 3 times higher than clearance described in ventilated critically ill children (6.01[18] and 5.0 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} [19]) and was also slightly higher compared to the values in nonventilated children aged 6 months to 2 years (11.3 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}).[20] Reported clearance values in ventilated critically ill adults are 188 ml/min (2.7 ml $\cdot$ kg^{-1} $\cdot$ min^{-1})[21] and in non-

ventilated healthy adults 523 ml/min (7.6 ml · kg^{-1} · min^{-1}).[22] Clearance in our study tended to be related to age, but the relatively small number of infants older than 15 months may explain why this trend did not reach statistical significance. Generally, it can be expected that midazolam clearance values are related to the degree of enzyme maturation and liver weight. Midazolam is only marginally metabolized by CYP3A7, which is predominantly expressed in the fetal liver and of which the activity decreases immediately after birth to approximately 10% of newborn levels between 6 and 12 months of age. During the first year of age, CYP3A4 activity increases gradually.[23,24] The expression of CYP3A5 was found to be independent of age.[24] The unpredictable sedation levels observed in clinical practice requiring titration of midazolam dosages, was reflected by the observed wide interindividual variability in pharmacodynamics and the high residual error. The interindividual variability was found to be 89% on the COMFORT-B and 66% on the BIS for the infants whose response on midazolam could be characterized on the BIS, which was only in 43% of the patients. The residual error was found to be 31% on the COMFORT-B and 13 units on the BIS. None of the studied patient characteristics could explain these variabilities. This implies that children between 3 and 24 months should receive the same initial dose after which titration remains important. Concerning the observed trend in clearance with age, the dosing regimens may be less appropriate for infants aged 15-24 months, requiring further study in a wider age range.

When comparing the results of the PK-PD model of propofol (Chapter 3) and midazolam (Chapter 4), propofol may be preferred over midazolam because of the lower interindividual variability in pharmacodynamics compared to midazolam (47% *vs*. 89%), which is recognized in clinical practice. Although this implicates preference for the use of propofol over midazolam, its use for sedation in children is formally still prohibited because of safety concerns. However, by limiting the propofol infusion rates up to 4 mg · kg^{-1} · h^{-1} during less than 48 h propofol and by monitoring of safety parameters as bradycardia and lipemic blood, propofol may be a favourable alternative for midazolam, especially in children who experience paradoxical responses to midazolam, who have renal failure or during co-administration of interacting drugs.

Sedation in critically ill patients

In the Chapters 6 and 7, propofol was studied in the population of critically ill adult patients during long-term sedation (0.7-9.5 days). These patients are typically characterized by high variability in dosing requirements, while fatalities have been reported after long term administration (> 36 h) of high doses (> 5.5 mg · kg^{-1} · h^{-1}).[2] Evidence is now emerging that the sedative strategy is important in determining the patient outcome. Sedation protocols and daily interruption of sedation demonstrated reductions in the duration of ICU and hospital length of stay, duration of ventilation and demonstrated improved psychological functioning.[1,25-27] Therefore, in the investigations propofol doses were titrated by the nurses

to the physician determined optimal Ramsay score using a protocol-driven approach.
In **Chapter 5**, we showed that actual clinical sedation practice significantly differed from sedation guidelines, as evidenced by a consistent significantly ($P < 0.001$) deeper level of sedation titrated by the nurses than targeted by the physician in long-term sedated critically ill patients. The intention of sedation guidelines to improve the patients' outcome[25,26] may therefore be not fully achieved in current practice. The low median numbers of propofol dose adjustments per day (2.2) indicate a tendency to keep the infusion rate constant. More frequent daily reevaluation of the achieved sedation level in the multidisciplinary meeting to allow for feedback from the primary care nurse is indicated, which may result in either "deeper" target levels or "lighter" actual levels.
Another aspect of this study was to explore the utility of the BIS. Between the Ramsay and the BIS, a moderately significant correlation (r= -0.570) was found. In over sedated patients (difference between the observed and target Ramsay score ≥ 2 points), low BIS values of less than 60, often associated with deep sedation[28,29] were recorded in 78% of the critically ill patients. It seems therefore that for deeply sedated patients (Ramsay 5 and 6), the BIS may be added to the standard sedation monitoring instruments in order to prevent over sedation. This should be evaluated in further studies. For moderate and light sedation, the clinical assessment scales, although subjective, remain preferred, because the BIS showed shortcomings,[30,31] such as EMG interference (Chapter 6),[32] low sensitivity to midazolam in children (Chapter 4), high residual error which negatively affects predictions (Chapter 3, 4 and 6) and reported influence of environment[33] and neurological status.[34,35] The direct effect of opioids on the BIS is still controversial. However, opioids can influence BIS monitoring by enhancing the effect of sedatives.[36,37] The lower sedative requirements and hence higher recorded BIS values may lead to oversedation when titrating to the same BIS values.[38] In Chapter 3, the total dose of fentanyl administration during surgery was no covariate for the pharmacodynamic parameters. In Chapter 6, morphine dose was no significant covariate for the PK of propofol. In general, pain is difficult to assess in the non-communicative critically ill patients, because the gold standard (self report) is not possible, and this will therefore need further attention and research. The design of PK-PD interaction models for analgesia and sedation in critically ill patients may allow for more precise dosing guidelines and different target BIS values. Furthermore, since the concept of providing analgesia first supplemented by sedation, provided a more satisfactory sedation level than the sedation based approach, especially in patients requiring significant respiratory support,[39] incorporation of this concept in the sedation protocol (Chapter 5) may be advisable.
In **Chapter 6**, dosing guidelines for propofol in long-term sedated critically ill patients were provided using pharmacokinetic and pharmacodynamic modeling. Propofol clearance in the critically ill adult patients with cardiac failure was 62% of the value in patients without cardiac failure (1.28 L/min *vs*. 2.05 L/min). Although of relatively small value in clinical practice, an increasing Sequential Organ Failure Assessment (SOFA) score (degree of illness, based on 6 organ functions) was associated with a smaller peripheral volume of distribution expressed as $V_2 = 1140 - 55.4 \cdot (\text{SOFA-9})$. However, severity of the illness was found to be a major determinant of the level of sedation, using the Ramsay score (proportional

odds model) and the Bispectral index (E_{max} model) as pharmacodynamic endpoints. Large differences in the model-based dosing guidelines were found, indicating lower propofol dosing requirements with increasing severity of illness. There was no evidence for tolerance (a decrease in the effect of a drug over time or the need to increase the dose to achieve the same effect), which has been reported before, although the authors of that report did not rule out the possible relation to patients' improving condition.[40,41] The role of disease severity as a determinant of the pharmacodynamics is an important finding for the clinical setting, since the condition of critically ill patients can change quickly and it is now common to aim at deep sedation levels in severely ill patients with volume or pressure controlled ventilation or prone position. Especially since we have noted in Chapter 5 that nurses do not adhere to sedation protocols and favour the lock-in principle of maintaining (too high) infusion rates, lower initial dosages should be recommended during severe illness. Additional improvements in clinical outcomes associated with incorporation of initial dosing PK-PD dosing guidelines should be identified, showing that there is still much work to do.
For critically ill patients, another important covariate that accounts for differences in dose requirement between patients was identified in a preliminary study in **Chapter 7**. Liver blood flow, as determined by sorbitol administration, was found to be a significant covariate for the clearance of propofol expressed by $CL = 1.35 + 1.19 \cdot (LBF-1.32)$ L/min. It was also shown that in this patient group, variability in hepatic blood flow was unrelated to variability in cardiac output. The role of the cardiac output and liver blood flow on the clearance requires further investigation. Given that propofol is a high-extraction drug, which makes its clearance primarily dependent upon liver blood flow, identified covariates for the clearance may be representative for other high clearance drugs.

Perspectives: sedation in neonates

The ultimate goal of the development of PK-PD models is not only to develop dosing guidelines for the studied population, but also to predict the time course of the concentration and the effect in populations in which no information is yet available, thereby providing initial guidelines for a safe and effective dose regimen, which could also serve as a starting point for dedicated investigations. In this context it is of interest to explore the predictive value of developed models in the youngest group of children, namely neonates. The group of neonates is hardly studied, because of ethical and practical constraints with regard to blood sampling. As a result many drugs are not labelled for use in neonates. It is therefore of considerable interest to use modeling and simulation in neonates, as a starting point for the design of limited confirmatory clinical studies. Recently, safety concern was raised for use of anesthetics including propofol in neonates, after the report that the administration may increase apoptotic neurodegeneration in the developing rat brain.[42] Further study showed that the administered dose may be an important factor in the induction of neurodegeneration[43] and that these high doses would be not achieved in clinical practice. To provide a starting point,

the prospective use of three published population PK models for propofol in children is explored by comparison of population predicted propofol concentrations with corresponding measured concentrations. The details of the three population PK models are summarized in Table 1.

Table 1 Explored pharmacokinetic models for predictive value in neonates .

Model	References	Characteristics	Parameter estimates
(*A*) Allometric, cross species	Knibbe *et al.*[44]	Rats, 6 children aged 1-5 years following cardiac surgery and adults	CL, L/min = $0.071 \times BW^{0.78}$ V_1, L = $0.30 \times BW^{0.987}$ Q, L/min = $0.062 \times BW^{0.73}$ V_2, L = $1.2 \times BW^{1.1}$
(*B*) Allometric, from infant to child	ShangGuan *et al.*[45]	35 children aged 4 months to 9 years undergoing general or urinary surgery	CL, L/min = $0.185 \times (BW/13.7)^{0.75}$ V_1, L = $7.41 \times (BW/13.7)$ Q_2, L/min = $0.614 \times (BW/13.7)^{0.75}$ V_2, L = $54.6 \times (BW/13.7)$ Q_3, L/min = $0.692 \times (BW/13.7)^{0.75}$ V_3, L = $7.2 \times (BW/13.7)$
(*C*) Per kg	Rigby-Jones *et al.*[9]	21 critically ill ventilated children aged 1 week to 12 years	CL, L/min = $0.0302 \times BW$ V_1, L = $0.584 \times BW$ Q_2, L/min = $0.016 \times BW$ V_2, L = $1.36 \times BW$ Q_3, L/min = $0.0133 \times BW$ V_3, L = $103 + 5.67 \times BW$

For evaluation of the predicted concentrations, actual data from nine preterm and term neonates admitted to the Neonatal Intensive Care Unit in the University Hospital Gasthuisberg, Leuven, Belgium, who received a bolus dose of 3 mg/kg propofol just before removal of the chest tube,[46] were used. In patients of this investigation the median postmenstrual age was 36 (27-43) weeks, the median postnatal age 11 (4-25) days and the median weight was 2.42 (0.91-3.8) kg. A median of 8 (7-9) arterial blood samples were obtained up to 8 (3-24) h after the bolus dose.

Figure 1 shows the observed propofol concentrations *vs*. predicted concentrations of the three pharmacokinetic models. According to this figure, neonates at a postnatal age younger than 11 days (4, 7, 7, 8 and 11 days, respectively) appeared to be a distinctly different group, in which systematically higher propofol concentrations were observed compared to neonates with postnatal age older than 14 days (14, 17, 25 and 25 days). Moreover the cross species allometric model (A), which in the past has been used successfully for cross species extrapolation of propofol pharmacokinetics[44] systemically underpredicted propofol concentrations in neonates younger than 11 days, whereas from 14 days postnatal, the model performed reasonably well. Similar observations were obtained with the allometric model from infant

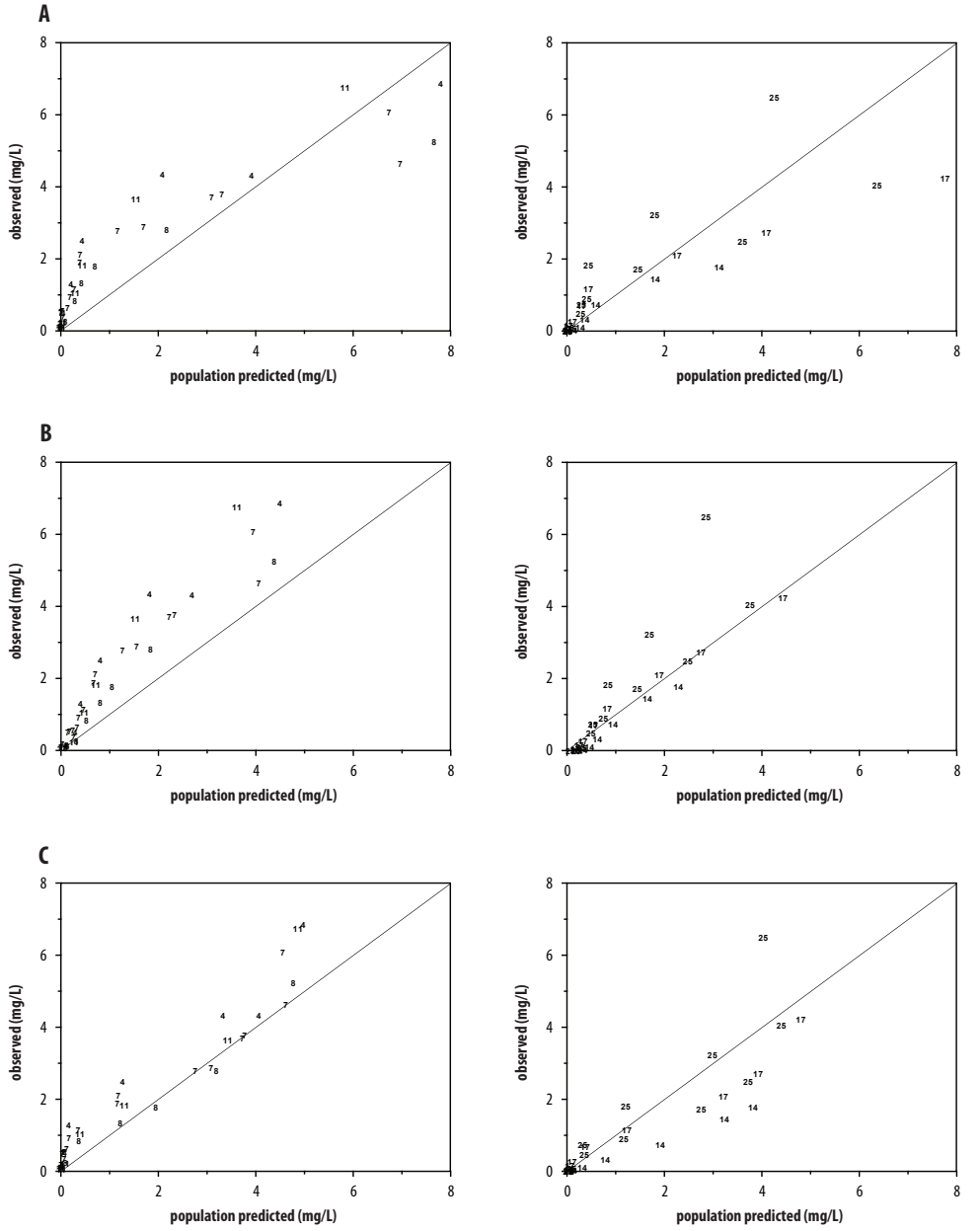


Figure 1 Predictive performance in neonates by presentation of observed *vs.* population predicted propofol concentrations based on allometry, cross species[44] (A), allometry from infant to child[45] (B), and the per kg model[9] (C) for neonates younger than 11 days (left) and older than 14 days (right) of life postnatal. The numbers indicate postnatal age (days).

to child (B)[45] and the per kg model of Rigby-Jones *et al*., (C)[9] indicating a distinctly different pharmacokinetic behaviour for the two age groups. Compared to the allometric models (A and B), the per kg model (C) showed more over prediction of the propofol concentrations for the older neonates and was more precise for the younger neonates. Therefore, allometric scaling may be suitable from 14 days postnatal age, but can not be used for the youngest neonates. An explanation of the inaccurate prediction may be that it takes a week or longer after birth for spontaneous closure of the ductus venosus. In the fetus, this shunt allows oxygenated blood from the placenta to bypass the liver to the systemic circulation for distribution to the rest of the body. Another explanation may be an immaturity of the UGT1A9 activity, which mediates 60% of propofol elimination by direct glucuronidation in the adult. It cannot be excluded that during the first 14 days of life liver blood flow plays only a minor role in the elimination of propofol neonates and that the intrinsic clearance may be more important. Data on UGT1A9 activity in children as a function of age are yet not available.[47]
From this exploration, it can be concluded that although caution is needed in extrapolating to distinctly different populations, allometric scaling seems to predict propofol concentrations reasonably well in neonates from 14 days of age. Additional data from neonates are needed to refine existing models by determining the exact relation between patient characteristics as age or bodyweight and specific pharmacokinetic and ultimately pharmacodynamic parameters to provide individualized dosing regimens.

In conclusion, in this thesis dosing guidelines were provided for propofol and midazolam in the special group of infants and critically ill patients, on the basis of population pharmacokinetic-pharmacodynamic (PK-PD) modeling. Part of the interpatient variability has been explained with covariate analysis by bodyweight, cardiac function, severity of illness and liver blood flow and unexplained interindividual variability has been characterized, which will be essential for optimizing quality of sedation in clinical daily practice and improving patients' outcome. Using population PK-PD modeling, clinical questions can be answered even in pediatric populations by circumventing restrictions in sampling amount. In the future, the vulnerable group of neonates should be further studied for safe and more appropriately prescribing dosages.

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Samenvatting in het Nederlands

Sedatie vormt een essentieel onderdeel van de zorg van patiënten op de (kinder) intensive care (IC). Sedatie kan angst en agitatie verminderen en eventuele kunstmatige beademing vergemakkelijken. Het standpunt met betrekking tot de ideale diepte van sedatie is in de afgelopen jaren gewijzigd van diepe sedatie in combinatie met spierrelaxantia naar lichte sedatie. De ontwikkeling van nieuwe beademingstechnieken en nieuwe inzichten in de negatieve effecten van oversedatie hebben daarbij een belangrijke rol gespeeld. Inadequate sedatie kan levensbedreigende agitatie veroorzaken met als gevolg bijvoorbeeld auto-extubatie. Aan de andere kant, kan overmatige diepte van sedatie leiden tot een hogere morbiditeit en het voor de patiënt onmogelijk maken om te communiceren. Inmiddels is eenduidig vastgesteld dat oversedatie het verblijf op de IC onnodig kan verlengen. Dagelijks onderbreken van de infusie van sedativa blijkt de duur van mechanische beademing en het verblijf op de ICU te verkorten. Ook het gebruik van geprotocolleerd werken heeft invloed op de duur van mechanische beademing en de lengte van verblijf.
Hoewel er inmiddels richtlijnen zijn ontwikkeld voor sedatie, blijkt dat in de praktijk de sedatie vaak niet optimaal is en dat patiënten in het algemeen nog teveel sedativum krijgen. Een van de redenen is de hoge mate van variabiliteit in benodigde doseringen van sedativa. Het toepassen van de juiste doseringsschema's vereist kennis van de intra- and interindividuele variatie in farmacokinetiek en -dynamiek om doseringen te individualiseren. Een belangrijk hulpmiddel in dit verband zijn zgn. covariaten waarmee de variabiliteit kan worden verklaard.
In dit proefschrift wordt populatie farmacokinetische (PK) en farmacodynamiche (PD) modeling gebruikt om richtlijnen te ontwikkelen voor de geïndividualiseerde dosering van de sedativa propofol en midazolam in de populatie van kinderen en van kritische zieke patiënten. De nadruk ligt op de rol van leeftijd, orgaanfalen en mate van ziekte als oorzaken van intra- en interindividuele variabiliteit.

Sedatie in kinderen

In de huidige praktijk is midazolam het sedativum van eerste keuze bij kinderen. Echter, in vergelijking met midazolam heeft propofol een aantal voordelen als 1) een korte halfwaardetijd, waardoor de dosering gemakkelijk te titreren is, 2) farmacokinetiek die onafhankelijk is van de lever- en nierfunctie en 3) het feit dat bij stoppen van de toediening de patient snel ontwaakt. Ondanks het feit dat propofol veel en met succes wordt toegepast op de volwassen intensive care, is begin jaren '90 het gebruik van propofol bij sedatie van kinderen op de intensive care ter discussie komen te staan na het verschijnen van een aantal publicaties over gevallen van ernstige bijwerkingen waarvan enkele met fatale afloop. Toch wordt propofol bij jonge kinderen op de ICU regelmatig toegepast als andere middelen niet toereikend zijn. Kinderen worden vaak blootgesteld aan risico's bij gebrek aan gegevens over de juiste dosis, werking en bijwerking in kinderen, waardoor doseringen meestal op een betrekkelijk empirische manier worden geëxtrapoleerd vanuit volwassenen. Hierbij wordt dan geen

rekening gehouden met het feit dat de functie van de organen afwijkend kan zijn. Non-lineair Mixed Effect Modeling (NONMEM) is met name geschikt voor PK-PD onderzoek bij kinderen, onder meer omdat er relatief weinig waarnemingen per individu nodig zijn om intra- en interindividuele variabiliteit in farmacokinetiek en farmacodynamiek te beschrijven en te verklaren.
In het Erasmus MC-Sophia worden jaarlijks 50 à 60 kinderen onder de leeftijd van 2 jaar geopereerd vanwege afwijkingen aan de schedel. Door vochtophoping rondom de ogen, het gescheiden worden van de ouders en de stress van het verblijf op de intensive care worden de peuters postoperatief vaak onrustig, waardoor sedatie noodzakelijk is.
Om te komen tot rationele doseeradviezen voor veilig gebruik van midazolam en propofol voor de sedatie van niet-beademde kinderen na uitgebreide craniofaciale chirurgie op de intensive care in, is de veiligheid bestudeerd (Hoofdstuk 2) en zijn er populatie PK en PD modellen voor propofol en midazolam opgesteld (Hoofdstukken 3 en 4). In deze studies werden de effecten van beide sedativa gekwantificeerd op basis van COMFORT-behavior schaal (COMFORT-B) en de Bispectal index (BIS). De COMFORT-B bestaat uit 6 items; alertheid, kalmte, huilen of ademhalingsreactie, spierspanning, lichaamsbeweging en gezichtsspanning, en varieert van 6 (geen onrust) tot 30 (ernstige onrust). De BIS is een parameter die is afgeleid van het Electro Encephalo Gram (EEG), maar die (nog) niet is gevalideerd voor kinderen < 1 jaar. De numerieke waarde van de BIS varieert van 0 (geen cerebrale activiteit) tot 100 (volledig wakker). De resultaten in Hoofdstuk 2 laten zien dat er bij een dosering van propofol tot 4 $mg \cdot kg^{-1} \cdot uur^{-1}$ gedurende een mediane duur van 11 u, de serum triglyceride concentraties en de creatininekinase activiteit niet zijn gestegen. Ook zijn er geen metabole acidose, temperatuurstijging of andere ongewenste bijwerking geconstateerd. Op basis van de populatie farmacokinetische analyse van het beloop van de propofol concentraties kon worden vastgesteld dat de farmacokinetiek van propofol in deze patienten het beste kan worden beschreven met behulp van een 2-compartimenten model waarbij lichaamsgewicht een covariaat is voor de klaring (Hoofdstuk 3). De populatie gemiddelden van de waarden van de farmacokinetische parameters zijn $Cl = 0.70 \cdot (BW/8.9)^{0.61}$ l/min, $V_1 = 18.8$ l, $Q = 0.35$ l/min and $V_{ss} = 146$ l met een interindividuele variabiliteit van respectievelijk 20% voor Cl en 145% voor V_{ss}. De gevonden klaring was 2x zo groot vergeleken met de waarden in de literatuur voor beademde kinderen en volwassenen. Dit verschil kan mogelijk verklaard worden door de verder gezonde conditie van de patiëntjes en het ontbreken van effect van beademing op de leverdoorbloeding. De propofol concentratie bij 50% van het maximale effect (EC_{50}) was 1.76 mg/l met een interindividuele variabiliteit van 47% op de COMFORT-B schaal en 3.71 mg/l met interindividuele variabiliteit van 145 % op de BIS schaal. Er kon geen invloed van patientkarakteristieken (covariaten) op de waarden van de PD parameters worden vastgesteld. Omdat de EC_{50} vergelijkbaar was met de EC_{50} van volwassenen, lijkt het dat kinderen vooral hogere doses propofol nodig hebben op basis van verschillen in farmacokinetiek en niet door verschillen in farmacodynamiek. Op grond van het populatie model adviseren we een propofol dosering van 30 mg/u voor een patiënt van 10 kg voor een COMFORT-B van 12-14 en een BIS van 70-75. Grote farmacodynamische variabiliteit benadrukt de noodzaak tot verdere titratie.

De farmacokinetiek van midazolam kon het beste worden beschreven met behulp van een 2-compartimenten model voor midazolam en een 1-compartimenten model voor de metabolieten (Hoofdstuk 4). De onderzochte covariaten verbeterden de voorspelbaarheid van het model niet significant. De populatie gemiddelden van de belangrijkste farmacokinetische parameters van midazolam zijn: een totale klaring van 0.157 l/min, V_1 = 3.8 l, V_2 = 30.2 l, Q = 0.30 l/min, V_3 = 6.69 l, Cl_2 = 0.21 l/min, V_4 = 1.69 l, Cl_3 = 0.047 l/min met een interindividuele variabiliteit van respectievelijk 54% voor Cl_1, 82 % voor V_2, 26% voor Cl_2, 135% voor V_4 en 42% voor CL_3. De EC_{50} van midazolam was 0.58 µmol/l met een interindividuele variabiliteit van 89% op de COMFORT-B schaal. In 57% van de patiëntjes kon geen effect van midazolam worden geïdentificeerd op de BIS. De EC_{50} van de patiëntjes waarbij een midazolam effect kon worden aangetoond was 0.63 µmol /l met interindividuele variabiliteit van 66 %. Op basis van het populatie model adviseren we startdosering van 1 mg, gevolgd door een continu infuus van 0.5 mg/u voor een COMFORT-B van 12-14 voor een kind van 1 jaar. Door de grote farmacodynamische variabiliteit zal titratie noodzakelijk zijn.
Op basis van de resultaten in de Hoofdstukken 3 en 4 kan worden geconcludeerd dat op grond van de waargenomen verschillen in interindividuele variabiliteit propofol een beter voorspelbaar effect heeft dan midazolam. Vervolgonderzoek met behulp van populatie PK en PD modeling in kinderen is nodig om variabiliteit in effect verder te verklaren en waar mogelijk de doseringen verder te individualiseren om veilig gebruik in kinderen te garanderen.

Sedatie in kritisch zieke patiënten

Bij ernstig zieke patiënten is er sprake van een hoge variabiliteit in de benodigde doseringen van sedativa, zowel tussen patiënten onderling als binnen een en dezelfde patiënt als gevolg van o.a. verschillen in hemodynamiek en orgaanfunctie. Volgens de richtlijnen van de Society of Critical Care Medicine is propofol 2e keuze sedativum vanwege de mogelijkheid tot het optreden van hypertriglyceridemie bij langdurig gebruik van Propofol 1%. In dit verband is van belang dat ook bij volwassenen gevallen zijn gemeld van het propofol infusie syndroom bij gebruik van hoge doseringen propofol.
In de studies die gericht waren op het ontwikkelen van doseeradviezen voor veilig en effectief gebruik van propofol bij langdurige toediening is er gebruik is gemaakt van een sedatieprotocol. Het gebruik van een sedatieprotocol wordt aangeraden in de richtlijnen om de duur van mechanische ventilatie en de lengte van verblijf te verkorten.
In hoofdstuk 5 wordt de effectiviteit van het gebruik van een sedatieprotocol geëvalueerd. De diepte van de sedatie werd daarbij bepaald op basis van de Ramsay sedatie score (een 6-puntsschaal). De resultaten van dit onderzoek laten zien dat verpleegkundigen geneigd zijn dieper sederen dan is aangegeven door de intensivist-anesthesist ($P < 0.001$). Slechts 28% van de bestudeerde patiënten was correct getitreerd en 33% van de patiënten werd overgesedeerd. Opvallend was dat verpleegkundigen vooral geneigd zijn de eenmaal gekozen

doseringen te handhaven, ook bij oversedatie. Het voordeel van een sedatieprotocol zal hierdoor mogelijk niet worden bereikt. Als secundair doel is in deze studie ook ook gekeken naar de waarde van het sedatieinstrument de BIS in vergelijking met de Ramsay score. De Ramsay en de BIS waren matig gecorreleerd. De gemiddelde BIS waardes waren 93, 75, 55 voor de groepen agitatie, lichte sedatie (Ramsay 2-4) en diepe sedatie (Ramsay 5-6).
In hoofdstuk 6 wordt het onderzoek beschreven naar de interindividuele variabiliteit in farmacokinetiek en farmacodynamiek van propofol in kritisch zieke patienten. De propofol PK data konden adequaat beschreven worden met een 2-compartimenten model, waarbij gecompliceerde harten een 38% lagere klaring hebben (1.28 *vs*. 2.05 L/min) . De mate van ziekte, beschreven door de Sequential Organ Function Assessment (SOFA) score, waarbij punten worden toegekend bij orgaansystemen die falen, was geassocieerd met het verdelingsvolume van propofol (V_2= 1140-55.4 [SOFA-9]), hetgeen echter klinisch van relatief weinig waarde is. De PD data, gekarakteriseerd op de Ramsay schaal werden beschreven met behulp van een proportional odds model en de BIS schaal met behulp van een E_{max} model. De mate van ziekte bleek een belangrijke covariaat te zijn voor de diepte van sedatie op zowel de Ramsay als BIS schaal, waarbij ziekere patiënten minder propofol nodig hebben. Uit de modellen blijkt dat veranderingen in mate van ziekte continue titratie vereist, waarbij bijbehorende dosisadviezen worden gegeven. In hoofdstuk 7 is in een pilot onderzoek de invloed van de cardiac output en de leverdoorbloeding bestudeerd op de farmacokinetiek van propofol. De leverdoorbloeding, gemeten met behulp van de sorbitol concentratie bleek een significante covariaat voor de klaring van propofol (CL = 1.35 + 1.19 · (LBF-1.32) L/min). De cardiac output (gemeten met de Swan-Ganz) was niet van invloed op de PK. Deze bevindingen suggereren dat de leverdoorbloeding een betere voorspeller zou zijn van de PK van propofol dan de cardiac output, en mogelijk ook voor andere geneesmiddelen met een hoge extractie ratio. In het hoofdstuk perspectives is de voorspellende waarde van gepubliceerde ontwikkelde modellen onderzocht in de groep van neonaten. Een leeftijdsgroep waar weinig informatie over bekend is en die uitermate kwetsbaar is. De modellen voorspelden systematisch te lage spiegels in neonaten onder de leeftijd van 11 dagen, waardoor oversedatie een risico vormt en vervolgonderzoek nodig is bij deze groep.

Conclusie

In dit proefschrift werden doseringen geïndividualiseerd van propofol en midazolam voor kinderen en kritisch zieke patienten op basis van PK-PD modeling door variabiliteit te verklaren met de covariaten lichaamsgewicht, mate van ziekte, hartfalen en leverdoorbloeding om kwaliteit van sedatie te optimaliseren in de dagelijkse praktijk.

Nawoord

Nawoord

Dit proefschrift is tot stand gekomen door de fijne samenwerking met heel veel personen in het St. Antonius Ziekenhuis te Nieuwegein, het Leiden/Amsterdam Center for Drug Research te Leiden en het Erasmus MC-Sophia te Rotterdam.

De patiënten, ouders en directe familieleden ben ik zeer erkentelijk voor de deelname aan het onderzoek en het in ons gestelde vertrouwen.

Van de afdeling Klinische Farmacie van het St. Antonius Ziekenhuis in Nieuwegein wil ik in het bijzonder mijn collega ziekenhuisapotheker Catherijne Knibbe noemen, voor haar enorm stimulerende, enthousiaste (zelfs vetbollen tellen leek een prachtig onderzoek) en praktische bijdragen. Het was bijzonder de Propofol 6% onderzoekslijn, die indertijd door Jan-Gerard Maring en Victorine Koster is geïnitieerd, te mogen voortzetten.
Mathieu Tjoeng ben ik zeer erkentelijk voor de mogelijkheden die hij heeft geboden om het promotieonderzoek uit te voeren.
Mijn collega ziekenhuisapothekers Vera Deneer, Arie van Dijk, Kathleen Simons en Ed Wiltink, hebben zich flexibel opgesteld tijdens mijn opleiding tot ziekenhuisapotheker en mij de ruimte gegeven om te promoveren.
De collega's in opleiding en deels kamergenoten hebben gezorgd voor de nodige gezelligheid en stimulans: Robert ten Broeke, Jeroen Diepstraten, Ewoudt van de Garde (met wie ik op bijzondere wijze de laatste fase samen heb doorlopen), Tjetske Gerbranda, Ankie Harmsze en Gitte Melenhorst-de Jong.
Verder heeft de hele afdeling Klinische Farmacie zijn steentje bijgedragen. Dit betreft in het bijzonder het FarmaToxLab waar ik met veel plezier de concentraties van propofol in grote aantallen bloedmonsters heb kunnen bepalen; de afdeling productie, die wekelijks de propofol 6% spuiten bereidde voor het onderzoek en de afdeling logistiek die het transport verzorgde naar Rotterdam.
Ook de oud-collega ziekenhuisapothekers wil ik graag noemen: Loraine Lie-A-Huen, Paul Kuks, mijn tijdelijke opleider en Rogier Lange die mij als projectapotheker enthousiast maakte voor de Propofol 6% onderzoekslijn.
Kobra Waizy heeft in het kader van haar bijvak belangrijke bijdragen geleverd aan het volwassen ICU onderzoek en heeft gezorgd voor een nieuwe impuls aan deze studie.

De afdeling Intensive Care van het St. Antonius Ziekenhuis ben ik zeer erkentelijk voor de goede samenwerking, de ondersteuning van het onderzoek en de zeer fijne sfeer. In het bijzonder wil ik hierbij alle anesthesiologen en assistenten in opleiding (m.n. Ferenc Boom en Jurgen de Graaff) vermelden voor hun bijgedragen aan de patiëntenselectie, de uitvoering van het protocol en de klinische uitleg.
De ICU verpleegkundigen hebben een grote rol gespeeld bij het afnemen van de talloze bloedmonsters, het scoren van de diepte van de sedatie en het creëren van een goede sfeer. De leden van de Sedatiewerkgroep: Leon Aarts, Leo Bras, Annette de Bruijn, Roelie Deuten,

Enny Noordzij en Aletta van der Veen hebben belangrijke bijdragen geleverd aan de ontwikkeling en de implementatie van het onderzoeksprotocol.

Leon Aarts ben ik in het bijzonder erkentelijk voor het opstarten indertijd van de ICU studie in Nieuwegein en voor het leggen van de contacten in Rotterdam. Ik vind het bijzonder plezierig dat er inmiddels een vervolgstudie loopt in samenwerking met de afdeling Neurologie en het Laboratorium van de Apotheek van het UMCG te Groningen.

Het Klinisch Chemisch Laboratorium van het St. Antonius Ziekenhuis heeft de logistiek van de propofol buizen verzorgd en de serum concentraties van de triglycerides bepaald.
Ellen Tromp heeft hulp geboden op gebied van de statistische analyse van de onderzoeksgegevens met het programma SPSS.

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Paula Berkemeyer heeft gezorgd voor de lay-out van het boekje. Haar creativiteit en puntjes op de i heb ik zeer gewaardeerd.

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Lieve Wendy en Kim,
de laatste in de rij van de zussen. Wen, ik realiseer mij nu pas wat promoveren inhoudt. Ik heb jou eigenlijk nooit horen klagen. Je adviezen heb ik zeer op prijs gesteld! Kim, de jaren van onderzoek heb ik met jou mogen delen. Heerlijk om even bij je langs te kunnen lopen (zal ik straks wel missen) en alle onderzoeksperikelen op de tennisbaan te delen. Ik heb je in de laatste fase wel gemist, hoor!
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Last but not least: Lieve Herman en lieve Jasmijn, jullie zijn mijn zonnetjes!

Curriculum Vitae

Rifka Peeters werd geboren op 24 oktober 1972 te Heerlen. Na het behalen van het VWO-B diploma aan het Boschveldcollege te Venray startte zij in 1991 met de studie Farmacie aan de Universiteit van Utrecht. Tijdens de doctoraalstudie deed zij haar onderzoeksstage, een microdialyse studie, bij Solvay-Duphar te Weesp. Na het behalen van het apothekersdiploma in 1998 werkte zij een jaar als projectapotheker bij de apotheek van het Gemini ziekenhuis te Den Helder. Vanaf 1999 trad zij in dienst als projectapotheker bij de afdeling Klinische Farmacie van het St. Antonius ziekenhuis te Nieuwegein ten behoeve van het stabiliteitsonderzoek van Propofol 6%. Van mei 2001 tot december 2006 combineerde zij de opleiding tot ziekenhuisapotheker (opleider Drs. M.M. Tjoeng) en onderzoek in nauwe samenwerking met het Leiden/Amsterdam Center for Drug Research (Prof. Dr. M. Danhof) en het Erasmus MC-Sophia (Prof. Dr. D. Tibboel). Na de registratie tot ziekenhuisapotheker in oktober 2005 volgde zij in het St. Antonius Ziekenhuis de opleiding tot klinisch farmacoloog (opleiders Dr. V.H.M. Deneer en Dr. C.A.J. Knibbe), waarbij in juni 2006 de aantekening werd verkregen. Sinds december 2006 werkt zij als ziekenhuisapotheker bij de afdeling Klinische Farmacie van het St. Antonius Ziekenhuis te Nieuwegein.

Stellingen behorend bij het proefschrift

Don't be afraid! Population PK-PD modeling as the basis for individualized dosing in children and critically ill

1. Populatie PK-PD modellering is een krachtige methode om te komen tot geïndividualiseerde doseeradviezen bij kinderen.
   Dit proefschrift
2. Kinderen hebben hogere propofol doses nodig als gevolg van verschillen in farmacokinetiek en niet in farmacodynamiek.
   Dit proefschrift
3. Propofol heeft in kinderen een beter voorspelbaar effect dan midazolam.
   Dit proefschrift
4. De mate van kritisch ziek-zijn is een belangrijke determinant voor de diepte van sedatie, waarbij ziekere patiënten minder propofol nodig hebben.
   Dit proefschrift
5. Bij pasgeborenen is allometrische schaling van de klaring op basis van lichaamsgewicht en de factor ¾ niet toepasbaar.
   Dit proefschrift
6. Werken volgens protocol levert verrassende werkwijzen op.
7. Betrokkenheid bij de verzameling van de data is een essentieel onderdeel van populatie PK-PD modellering.
8. Alle dingen zijn giftig en er is niets dat geen gif bevat; alleen de dosis zorgt ervoor dat iets niet giftig is.
   Paracelsus 1493-1541
9. De ziekenhuisapotheker heeft een belangrijke rol bij het aanpassen van de geneesmiddeldosering aan individuele patiënt karakteristieken.
10. Wij zingen vaak slaapliedjes voor onze kinderen opdat wijzelf zouden kunnen slapen.
    Kahlil Gibran 1883-1931
11. De beste tijd om op vakantie te gaan is wanneer je er geen tijd voor hebt.

Rifka Peeters Leiden, 28 november 2007