Introduction
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 (≤ 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.\textsuperscript{28-30} To date, use of propofol in the ICU in neonates have been reported for short procedural sedation.\textsuperscript{31} Although consensus recommendations have been established for sedation, the management of sedation in the ICU is not ideal in practice.\textsuperscript{32-34} As a result optimization of sedation is still a matter of debate.\textsuperscript{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.\textsuperscript{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.\textsuperscript{42} In pediatric intensive care patients (aged 2 days to 17 years) no clear pharmacokinetic – pharmacodynamic relationship was found.\textsuperscript{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.\textsuperscript{18,40,43,44} For propofol, covariates as weight, age, gender, cardiac output and albumin have been shown to influence the pharmacokinetics,\textsuperscript{23,45-49} whereas an increased sensitivity to propofol has been shown in elderly patients.\textsuperscript{50} In children, larger doses are required and it has been suggested that this is due to differences in pharmacokinetics and/or sensitivity.\textsuperscript{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. The Ramsay score, 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, but it has been criticized by the fact that it is based on a motor response. In children, the COMFORT scale is recommended, 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 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) to 100 (fully awake). 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. 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 and influence of environmental factors. As a result, at present the BIS requires more validation before its role is established in the (P)ICU. 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. 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 $E_{\text{max}}$ 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.\textsuperscript{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.\textsuperscript{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 · kg$^{-1}$ · 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.

**References**


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