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

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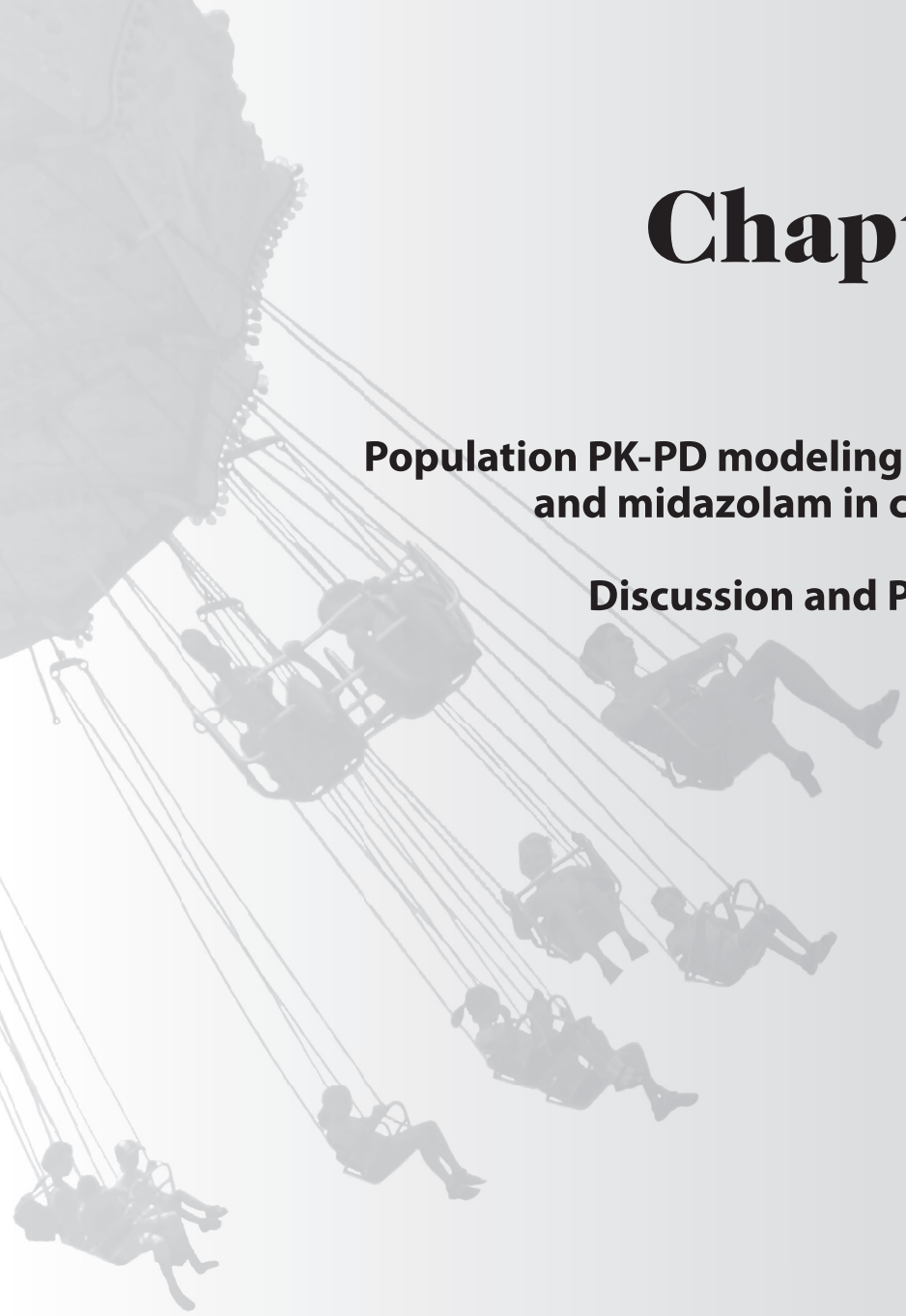
Discussion and perspectives



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

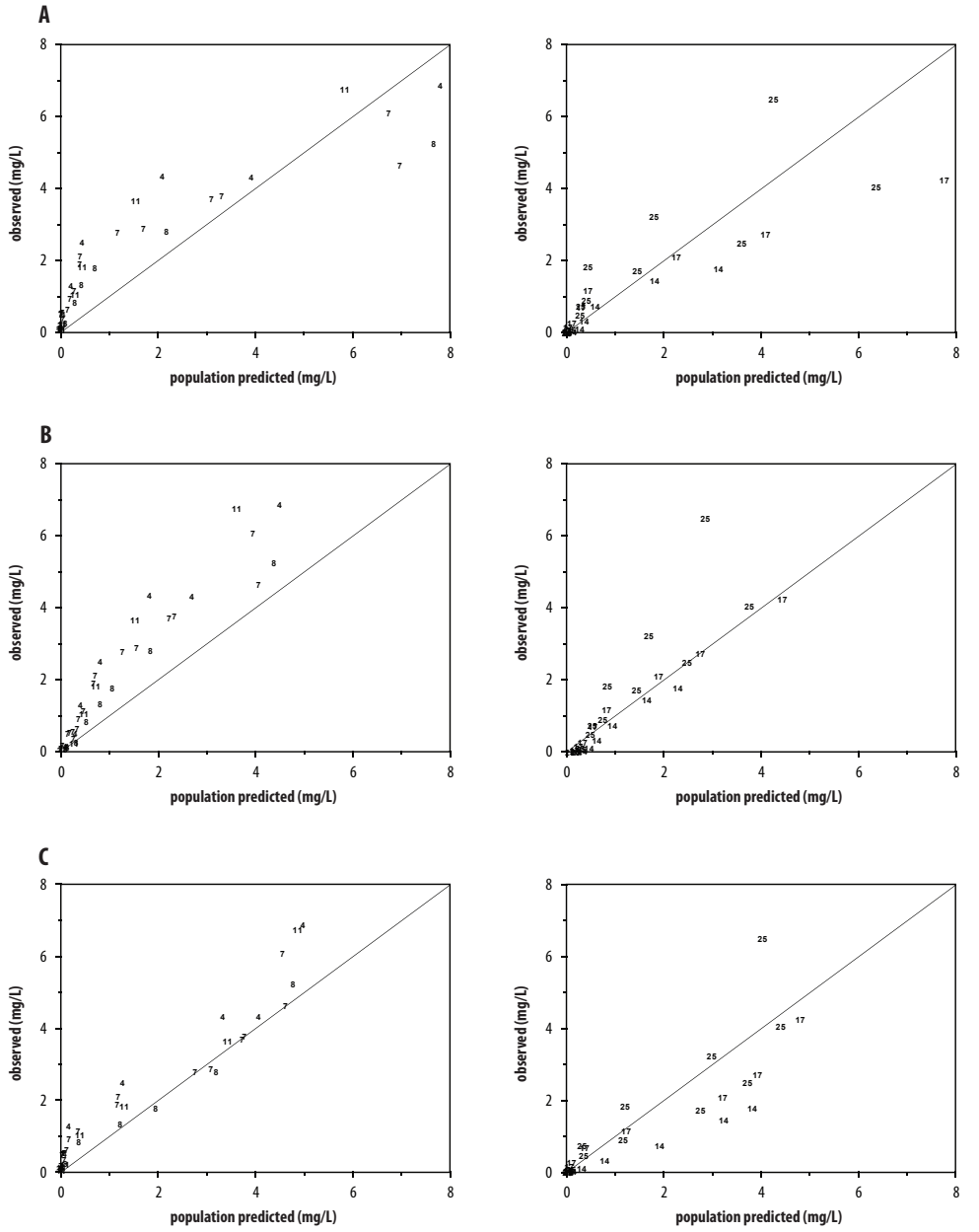


Figure 1 Predictive performance in neonates by presentation of observed *vs.* population predicted propofol concentrations based on allometry, cross species[44] (A), allometry from infant to child[45] (B), and the per kg model[9] (C) for neonates younger than 11 days (left) and older than 14 days (right)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