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

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Introduction

Chapter 1

Population PK-PD modeling as the basis for individualized dosing in children and critically ill
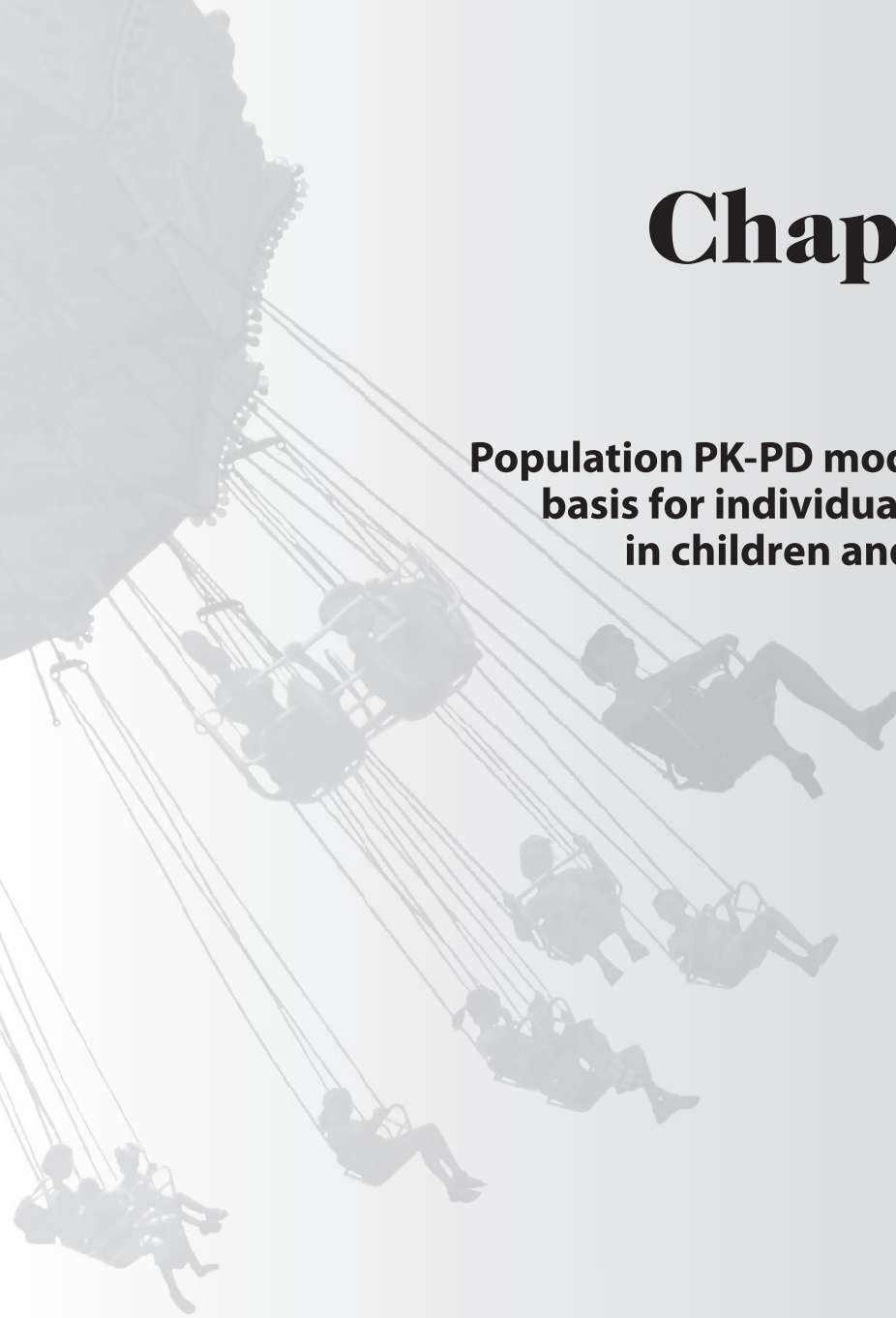
Introduction on sedation in pediatrics and long-term intensive care

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.[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 mul-tivariate 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 correla-tion 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 pharma-codynamic 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) struc-tural, 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 $< 4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, 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

1.   Fraser GL, Prato BS, Riker RR, Berthiaume D, Wilkins ML: Frequency, severity, and treatment of agitation in young versus elderly patients in the ICU. Pharmacotherapy 2000; 20: 75-82

2.   Atkins PM, Mion LC, Mendelson W, Palmer RM, Slomka J, Franko T: Characteristics and out-comes of patients who self-extubate from ventilatory support: a case-control study. Chest 1997; 112: 1317-23

3.   Woods JC, Mion LC, Connor JT, Viray F, Jahan L, Huber C, McHugh R, Gonzales JP, Stoller JK, Arroliga AC: Severe agitation among ventilated medical intensive care unit patients: frequency, characteristics and outcomes. Intensive Care Med 2004; 30: 1066-72

4.   Sydow M, Neumann P: Sedation for the critically ill. Intensive Care Med 1999; 25: 634-6

5.   Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G: The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest 1998; 114: 541-8

6.   Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW: Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006; 104: 21-6

7.   Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB: The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med 2003; 168: 1457-61

8.   Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999; 27: 2609-15

9.   Kress JP, Pohlman AS, O'Connor MF, Hall JB: Daily interruption of sedative infusions in criti-cally ill patients undergoing mechanical ventilation. N Engl J Med 2000; 342: 1471-7

10.   Schweickert WD, Gehlbach BK, Pohlman AS, Hall JB, Kress JP: Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. Crit Care Med 2004; 32: 1272-6

11.   Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, Luckett PM, Forbes P, Lilley M, Thompson J, Cheifetz IM, Hibberd P, Wetzel R, Cox PN, Arnold JH: Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. Jama 2002; 288: 2561-8

12.   Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA, Jr.,

Murray MJ, Peruzzi WT, Lumb PD: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002; 30: 119-41

13. Playfor S, Jenkins I, Boyles C, Choonara I, Davies G, Haywood T, Hinson G, Mayer A, Morton N, Ralph T, Wolf A: Consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med 2006; 32: 1125-36

14. Blumer JL: Clinical pharmacology of midazolam in infants and children. Clin Pharmacokinet 1998; 35: 37-47

15. Bauer TM, Ritz R, Haberthur C, Ha HR, Hunkeler W, Sleight AJ, Scollo-Lavizzari G, Haefeli WE: Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet 1995; 346: 145-7

16. Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R: Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. Arch Pediatr Adolesc Med 1999; 153: 331-8

17. Liu LL, Gropper MA: Postoperative analgesia and sedation in the adult intensive care unit: a guide to drug selection. Drugs 2003; 63: 755-67

18. Swart EL, Zuideveld KP, de Jongh J, Danhof M, Thijs LG, Strack van Schijndel RM: Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. Br J Clin Pharmacol 2004; 57: 135-45

19. Price SR: Rotation of propofol and midazolam for long-term sedation. Crit Care Med 2004; 32: 1435-6; author reply 1436

20. Young C, Knudsen N, Hilton A, Reves JG: Sedation in the intensive care unit. Crit Care Med 2000; 28: 854-66

21. Barrientos-Vega R, Sanchez-Soria MM, Morales-Garcia C, Cuena-Boy R, Castellano-Hernandez M: Pharmacoeconomic assessment of propofol 2% used for prolonged sedation. Crit Care Med 2001; 29: 317-22

22. Knibbe CA, Naber H, Aarts LP, Kuks PF, Danhof M: Long-term sedation with propofol 60 mg ml(-1) vs. propofol 10 mg(-1) ml in critically ill, mechanically ventilated patients. Acta Anaesthesiol Scand 2004; 48: 302-7

23. Knibbe CA, Zuideveld KP, DeJongh J, Kuks PF, Aarts LP, Danhof M: Population pharmacokinetic and pharmacodynamic modeling of propofol for long-term sedation in critically ill patients: a comparison between propofol 6% and propofol 1%. Clin Pharmacol Ther 2002; 72: 670-84

24. Cox EH, Knibbe CA, Koster VS, Langemeijer MW, Tukker EE, Lange R, Kuks PF, Langemeijer HJ, Lie AHL, Danhof M: Influence of different fat emulsion-based intravenous formulations on the pharmacokinetics and pharmacodynamics of propofol. Pharm Res 1998; 15: 442-8

25. Knibbe CA, Voortman HJ, Aarts LP, Kuks PF, Lange R, Langemeijer HJ, Danhof M: Pharmacokinetics, induction of anaesthesia and safety characteristics of propofol 6% SAZN vs propofol 1% SAZN and Diprivan-10 after bolus injection. Br J Clin Pharmacol 1999; 47: 653-60

26. Knibbe CA, Koster VS, Aarts LP, Langemeijer HJ, Danhof M: Pilot study in humans on the pharmacokinetics and safety of propofol 6% SAZN. Pharm World Sci 1999; 21: 239-40

27. Knibbe CA, Aarts LP, Kuks PF, Voortman HJ, Lie AHL, Bras LJ, Danhof M: Pharmacokinetics and pharmacodynamics of propofol 6% SAZN versus propofol 1% SAZN and Diprivan-10 for short-term sedation following coronary artery bypass surgery. Eur J Clin Pharmacol 2000; 56: 89-95

28. Vasile B, Rasulo F, Candiani A, Latronico N: The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med 2003; 29: 1417-25

29. Wysowski DK, Pollock ML: Reports of death with use of propofol (Diprivan) for nonprocedural

(long-term) sedation and literature review. Anesthesiology 2006; 105: 1047-51

30. Parke TJ, Stevens JE, Rice AS, Greenaway CL, Bray RJ, Smith PJ, Waldmann CS, Verghese C: Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. Bmj 1992; 305: 613-6

31. Allegaert K, de Hoon J, Verbesselt R, Naulaers G, Murat I: Maturational pharmacokinetics of single intravenous bolus administration of propofol. Pediatr Anesth in press

32. Mehta S, Burry L, Fischer S, Martinez-Motta JC, Hallett D, Bowman D, Wong C, Meade MO, Stewart TE, Cook DJ: Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. Crit Care Med 2006; 34: 374-80

33. Martin J, Franck M, Fischer M, Spies C: Sedation and analgesia in German intensive care units: how is it done in reality? Results of a patient-based survey of analgesia and sedation. Intensive Care Med 2006; 32: 1137-42

34. Tallgren M, Pettila V, Hynninen M: Quality assessment of sedation in intensive care. Acta Anaesthesiol Scand 2006; 50: 942-6

35. Prins S, van Dijk M, Tibboel D: Sedation and analgesia in the PICU: many questions remain. Intensive Care Med 2006; 32: 1103-5

36. Swart EL, Zuideveld KP, de Jongh J, Danhof M, Thijs LG, Strack van Schijndel RM: Population pharmacodynamic modelling of lorazepam- and midazolam-induced sedation upon long-term continuous infusion in critically ill patients. Eur J Clin Pharmacol 2006; 62: 185-94

37. de Wildt SN, de Hoog M, Vinks AA, Joosten KF, van Dijk M, van den Anker JN: Pharmacodynamics of midazolam in pediatric intensive care patients. Ther Drug Monit 2005; 27: 98-102

38. Somma J, Donner A, Zomorodi K, Sladen R, Ramsay J, Geller E, Shafer SL: Population pharmacodynamics of midazolam administered by target controlled infusion in SICU patients after CABG surgery. Anesthesiology 1998; 89: 1430-43

39. Hughes J, Gill AM, Mulhearn H, Powell E, Choonara I: Steady-state plasma concentrations of midazolam in critically ill infants and children. Ann Pharmacother 1996; 30: 27-30

40. de Wildt SN, de Hoog M, Vinks AA, van der Giesen E, van den Anker JN: Population pharmacokinetics and metabolism of midazolam in pediatric intensive care patients. Crit Care Med 2003; 31: 1952-8

41. Wagner BK, O'Hara DA: Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. Clin Pharmacokinet 1997; 33: 426-53

42. Swart EL, van Schijndel RJ, van Loenen AC, Thijs LG: Continuous infusion of lorazepam versus medazolam in patients in the intensive care unit: sedation with lorazepam is easier to manage and is more cost-effective. Crit Care Med 1999; 27: 1461-5

43. Lacroix D, Sonnier M, Moncion A, Cheron G, Cresteil T: Expression of CYP3A in the human liver--evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth. Eur J Biochem 1997; 247: 625-34

44. Stevens JC, Hines RN, Gu C, Koukouritaki SB, Manro JR, Tandler PJ, Zaya MJ: Developmental expression of the major human hepatic CYP3A enzymes. J Pharmacol Exp Ther 2003; 307: 573-82

45. Schuttler J, Ihmsen H: Population pharmacokinetics of propofol: a multicenter study. Anesthesiology 2000; 92: 727-38

46. Kurita T, Morita K, Kazama T, Sato S: Influence of cardiac output on plasma propofol concentrations during constant infusion in swine. Anesthesiology 2002; 96: 1498-503

47. Hiraoka H, Yamamoto K, Okano N, Morita T, Goto F, Horiuchi R: Changes in drug plasma concentrations of an extensively bound and highly extracted drug, propofol, in response to altered plasma binding. Clin Pharmacol Ther 2004; 75: 324-30

48.   Takizawa D, Hiraoka H, Nakamura K, Yamamoto K, Horiuchi R: Influence of the prone position on propofol pharmacokinetics. Anaesthesia 2004; 59: 1250-1

49.   Upton RN, Ludbrook GL, Grant C, Martinez AM: Cardiac output is a determinant of the initial concentrations of propofol after short-infusion administration. Anesth Analg 1999; 89: 545-52

50.   Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90: 1502-16

51.   Murat I, Billard V, Vernois J, Zaouter M, Marsol P, Souron R, Farinotti R: Pharmacokinetics of propofol after a single dose in children aged 1-3 years with minor burns. Comparison of three data analysis approaches. Anesthesiology 1996; 84: 526-32

52.   Knibbe CA, Melenhorst-de Jong G, Mestrom M, Rademaker CM, Reijnvaan AF, Zuideveld KP, Kuks PF, van Vught H, Danhof M: Pharmacokinetics and effects of propofol 6% for short-term sedation in paediatric patients following cardiac surgery. Br J Clin Pharmacol 2002; 54: 415-22

53.   De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, Outin H: Using and understanding sedation scoring systems: a systematic review. Intensive Care Med 2000; 26: 275-85

54.   Ramsay MA, Savege TM, Simpson BR, Goodwin R: Controlled sedation with alphaxalone-alphadolone. Br Med J 1974; 2: 656-9

55.   Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, Sessler CN, Dittus RS, Bernard GR: Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). Jama 2003; 289: 2983-91

56.   Ambuel B, Hamlett KW, Marx CM, Blumer JL: Assessing distress in pediatric intensive care environments: the COMFORT scale. J Pediatr Psychol 1992; 17: 95-109

57.   Carnevale FA, Razack S: An item analysis of the COMFORT scale in a pediatric intensive care unit. Pediatr Crit Care Med 2002; 3: 177-180

58.   Ista E, van Dijk M, Tibboel D, de Hoog M: Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. Pediatr Crit Care Med 2005; 6: 58-63

59.   Johansen JW: Update on bispectral index monitoring. Best Pract Res Clin Anaesthesiol 2006; 20: 81-99

60.   Courtman SP, Wardurgh A, Petros AJ: Comparison of the bispectral index monitor with the Comfort score in assessing level of sedation of critically ill children. Intensive Care Med 2003; 29: 2239-46

61.   Berkenbosch JW, Fichter CR, Tobias JD: The correlation of the bispectral index monitor with clinical sedation scores during mechanical ventilation in the pediatric intensive care unit. Anesth Analg 2002; 94: 506-11

62.   LeBlanc JM, Dasta JF, Kane-Gill SL: Role of the bispectral index in sedation monitoring in the ICU. Ann Pharmacother 2006; 40: 490-500

63.   Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B: Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant. Anesthesiology 2003; 99: 9-17

64.   Kim DW, Kil HY, White PF: The effect of noise on the bispectral index during propofol sedation. Anesth Analg 2001; 93: 1170-3

65.   Beal SL, Sheiner LB: NONMEM User's Guide. NONMEM Project Group, University of California at San Francisco, CA 1999

66.   t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN: A survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 2001; 108: 1089-93

67.   Roberts R, Rodriguez W, Murphy D, Crescenzi T: Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. Jama 2003; 290: 905-11
68.   Anderson BJ, McKee AD, Holford NH: Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. Clin Pharmacokinet 1997; 33: 313-27