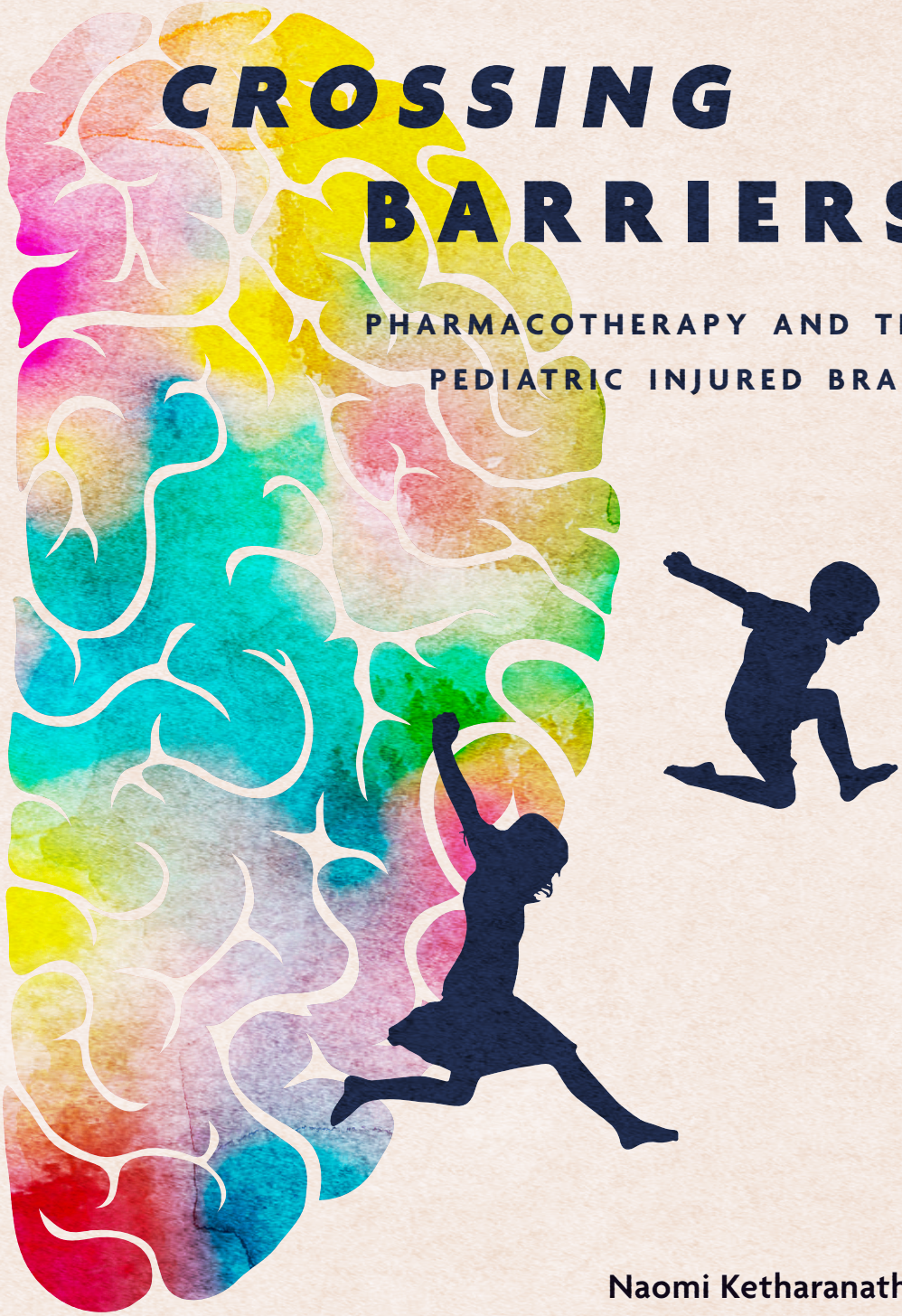
# CROSSING BARRIERS

## PHARMACOTHERAPY AND THE PEDIATRIC INJURED BRAIN



Naomi Ketharanathan

# *CROSSING* BARRIERS

## PHARMACOTHERAPY AND THE PEDIATRIC INJURED BRAIN

Naomi Ketharanathan

## COLOFON

**Title:** Crossing barriers - pharmacotherapy and the pediatric injured brain

**Printing:** Ridderprint, www.ridderprint.nl
**Layout and design:** Sara Terwisscha van Scheltinga, persoonlijkproefschrift.nl
**Cover design:** Sara Terwisscha van Scheltinga, persoonlijkproefschrift.nl
**Photography:** Pauline Stienstra, www.paulinestienstra.nl
**Cover silhouettes:** Eva & Jop

**ISBN:** 978-94-6458-770-8

**Crossing Barriers**

Pharmacotherapy and the pediatric injured brain

**Barrières doorkruisen**

Farmacotherapie en het beschadigd kinderbrein

**Thesis**

to obtain the degree of Doctor from the

Erasmus University Rotterdam

by command of the rector magnificus

Prof. dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.

The public defence shall be held on

Tuesday, 31st of January, 2023

at 15:30 hrs

by

**Naomi Ketharanathan**

Born in Melbourne, Australia

**Erasmus University Rotterdam**

Erasmus

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| | |
|---|---|
| **Promotors** | Prof. dr. D. Tibboel |
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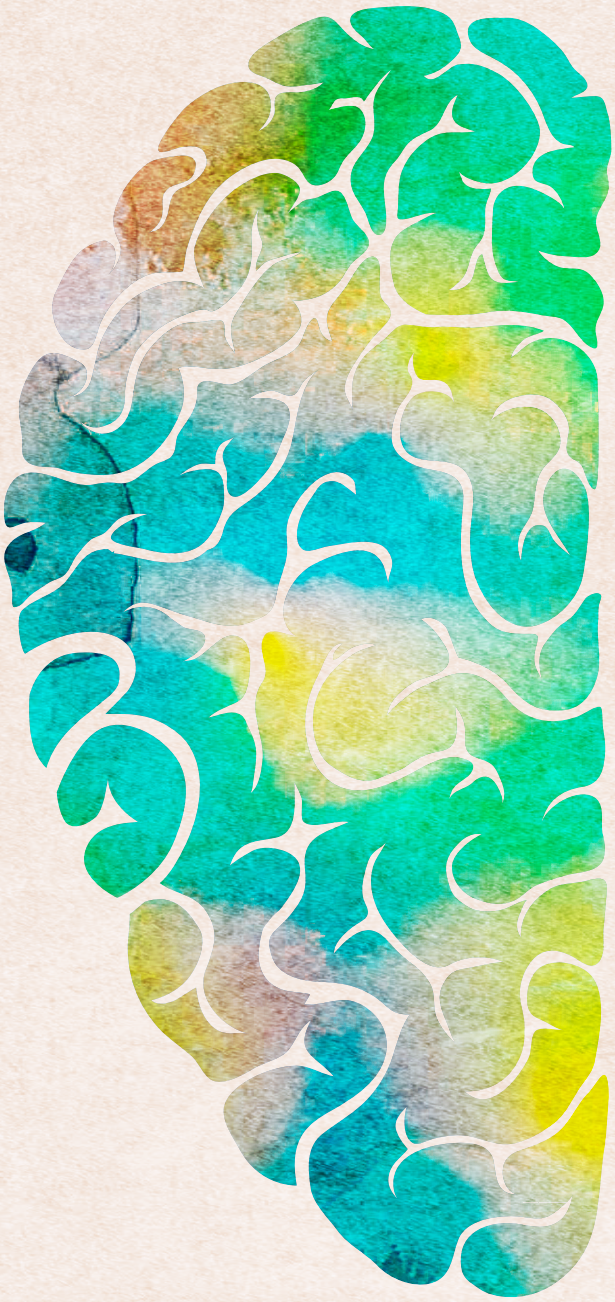
**The five rules of medicine**

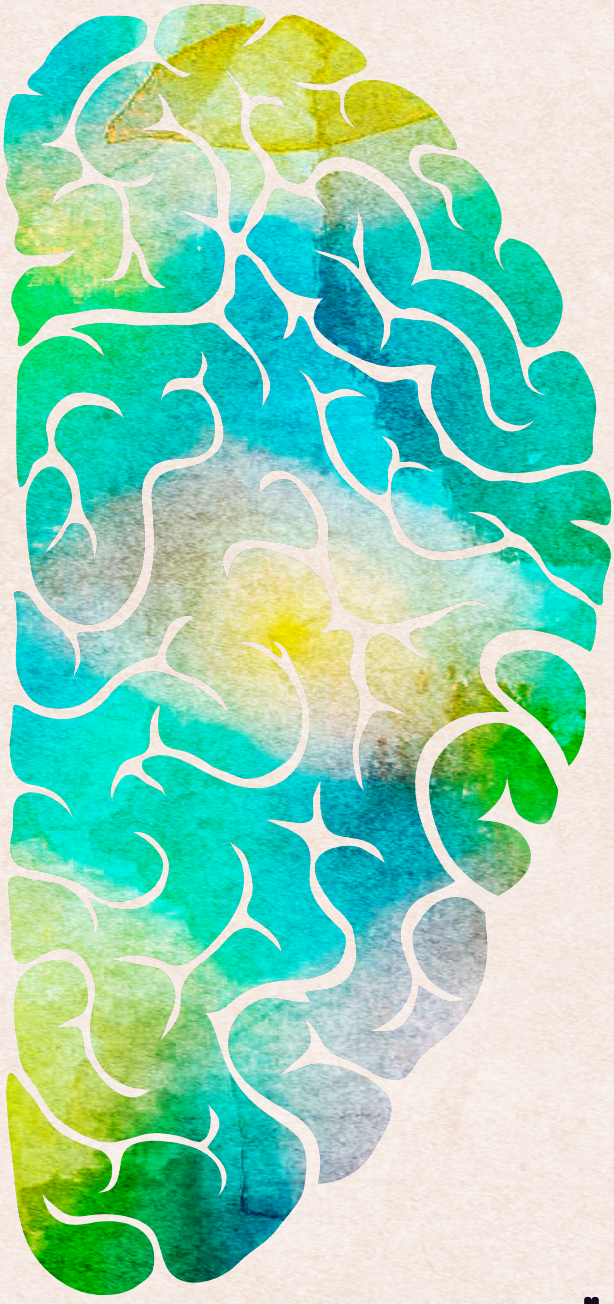
1. Ask an unscripted question
2. Don't whine
3. Count something
4. Write something
5. Change

*Atul Gawande*

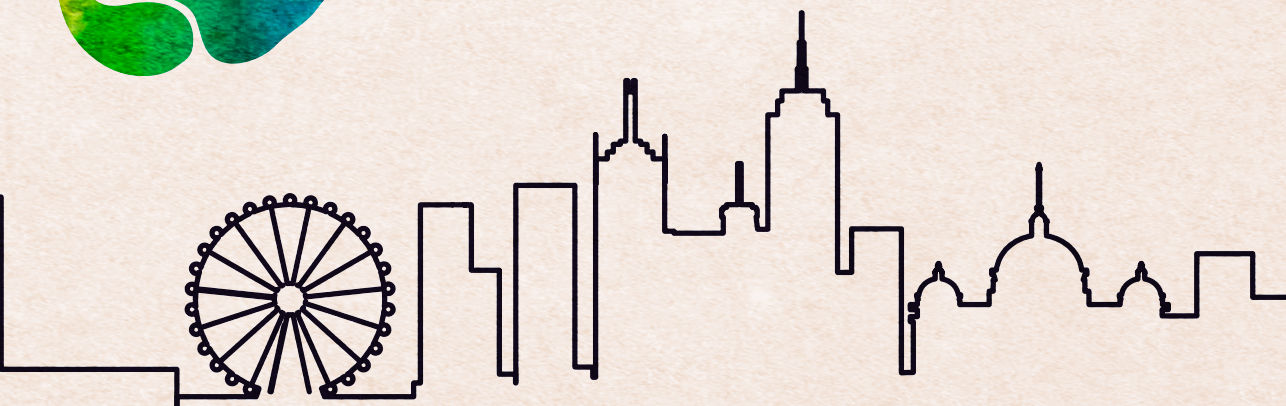
# CONTENTS

# PART I





# Introduction



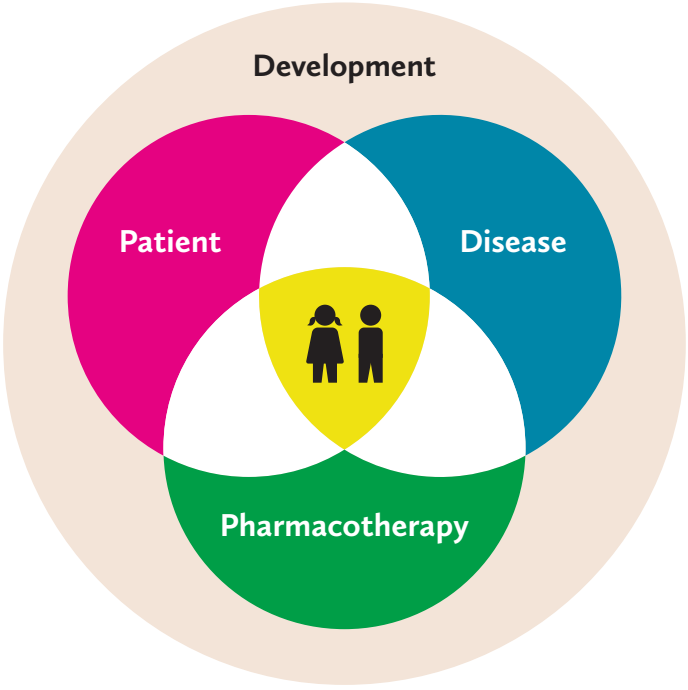
# 1

# General introduction

# GENERAL INTRODUCTION

*"The whole is greater than the sum of the parts"* has been attributed to Aristotle who stated this more than 2000 years ago (Aristotle, 360 BC). It remains relevant to this day. To a certain extent, this statement helps us understand how the final effect can be explained by the dynamic and interrelated parts that comprise the whole. In terms of pharmacotherapy, these parts can be summarized as depicted in **Figure 1**. Each 'part' constitutes multiple subcategories that are patient and disease specific and influence the way we dose medication which in turn influences the patient and disease condition and so forth. Yet many factors are still undetermined and elusive in pediatric pharmacotherapy, resulting in effects that cannot merely be explained by adding up the different parts. This thesis investigates the dynamic interplay of pharmacotherapy and the injured brain in the pediatric patient.

**Figure 1.** A conceptual visualization of the 3 main categories (disease, patient and pharmacotherapy) that influence the net result of pharmacotherapy against the backdrop of significant developmental changes.



## Disease

The disease process highlighted in this thesis is traumatic brain injury (TBI). TBI is defined as a temporary or permanent change in brain functioning due to external force, which can be accompanied by signs of other brain pathology (1). It is classified by severity in mild, moderate and severe TBI (sTBI) (1, 2). This classification of TBI severity is often done based on the Glasgow Coma scale (GCS) whereby sTBI is defined by a GCS of 8 or lower (3). TBI is a leading cause of pediatric morbidity and mortality worldwide resulting in a tremendous impact on the individual, their families and society as a whole (2, 4). The incidence of pediatric moderate and severe TBI is estimated to be 14/100,000 person years in The Netherlands, whereby mechanism of injury and injury severity vary with age. Falls are most common below 10 years of age and road traffic accidents are most prevalent above 10 years of age consisting mostly of bicycle-related accidents (4).

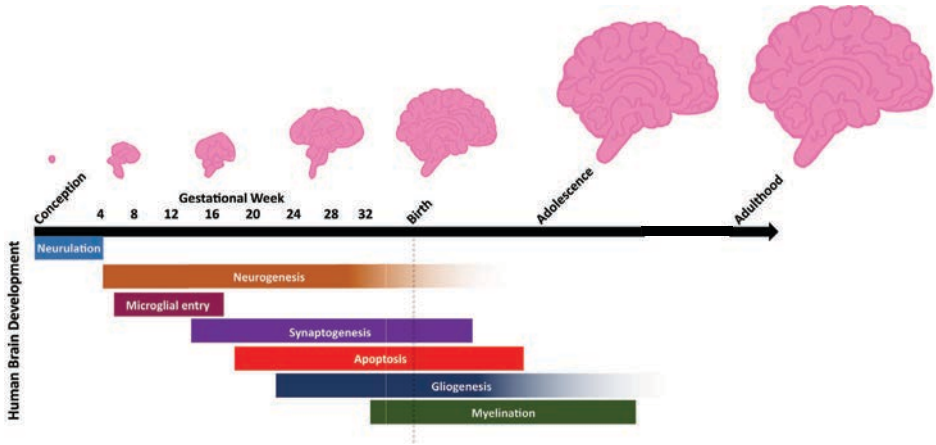
The pathophysiology of sTBI can be divided into two phases: the moment of impact resulting in (irreversible) cranial and cerebral injury which is referred to as 'primary injury'. The ensuing time after this primary injury is characterized by a cascade of pathophysiological events, such as brain swelling, which results in increased intracranial pressure. Elevated intracranial pressure leads to compromised cerebral perfusion and failure to meet cerebral metabolic demand. This can lead to potential ischemic brain tissue injury, so-called 'secondary injury' (1, 2, 5). There is increased appreciation for the heterogenic nature of the injury and thereby the overall disease state.

This thesis investigated the subgroup of sTBI patients who require admission to the pediatric intensive care unit (PICU) for invasive neuromonitoring.

## Patient

A well-known adage in pediatrics is: *"children are not small adults"* and refers to the incredible developmental changes that occur in childhood. In terms of the brain, and central nervous system (CNS) in general, these developmental changes are the most pronounced in the first 8 years of life (**Figure 2**) whereby processes such as cortical development, synaptogenesis and myelination lead to a rapid upregulation in (baseline) cerebral metabolism and subsequent cerebral blood flow (CBF) (6). Therefore, extrapolation of adult data and pharmacotherapy practice to children is not only inappropriate but also potentially dangerous as it can compromise both the safety and efficacy of drug dosing (6-8). In a broader sense, other patient specific factors such as organ maturation, genetic polymorphisms in drug enzyme activity and dietary factors can all influence administered drugs (7-11).

**Figure 2.** Schematic representation of human brain development from conception to adulthood. Adapted from Schnoll JG et al (2021, fig 2, p.177) with permission from the Publishers (12).




Other challenges that hamper rapid development of evidence-based pediatric CNS pharmacotherapy are practical aspects such as obtaining adequate samples, both in size and number as well as from the target site of action (i.e. the brain). This is highly restricted in children due to medical-ethical issues and lower circulating volumes (6, 10). These challenges further compound disparities in pediatric pharmacotherapy understanding and practice in comparison to adults.

Potential approaches to solve these challenges are advanced mathematical models and statistical techniques such as population-based pharmacokinetic (PK) analysis. This approach pools samples (so-called data points) from numerous patients, thereby allowing sparse sampling per patient, which is often already the case in the pediatric population. If specific covariates are identified, i.e. disease or patient specific factors such as renal function or inflammation, the PK model fit per patient can be improved and clarifies PK variation between patients (10). Another approach is the physiological based PK (PBPK) model whereby data from the pre-clinical setting (i.e. animals) is used to design a multi-compartmental PK model, that can be adapted to (pediatric) physiological parameters. The PBPK model can be used to predict drug disposition in all defined body compartments for that particular individual and (patho-)physiological situation by adjusting specific patient and drug parameters. Subsequent comparison of measured and predicted drug concentrations validates the PBPK model and enables its use as a PBPK model template for that drug without the need for further patient samples (13-15).

This thesis investigates different PK model approaches to improve our pharmacotherapeutic understanding of analgosedation in the pediatric patient with sTBI with a focus on morphine and pentobarbital.

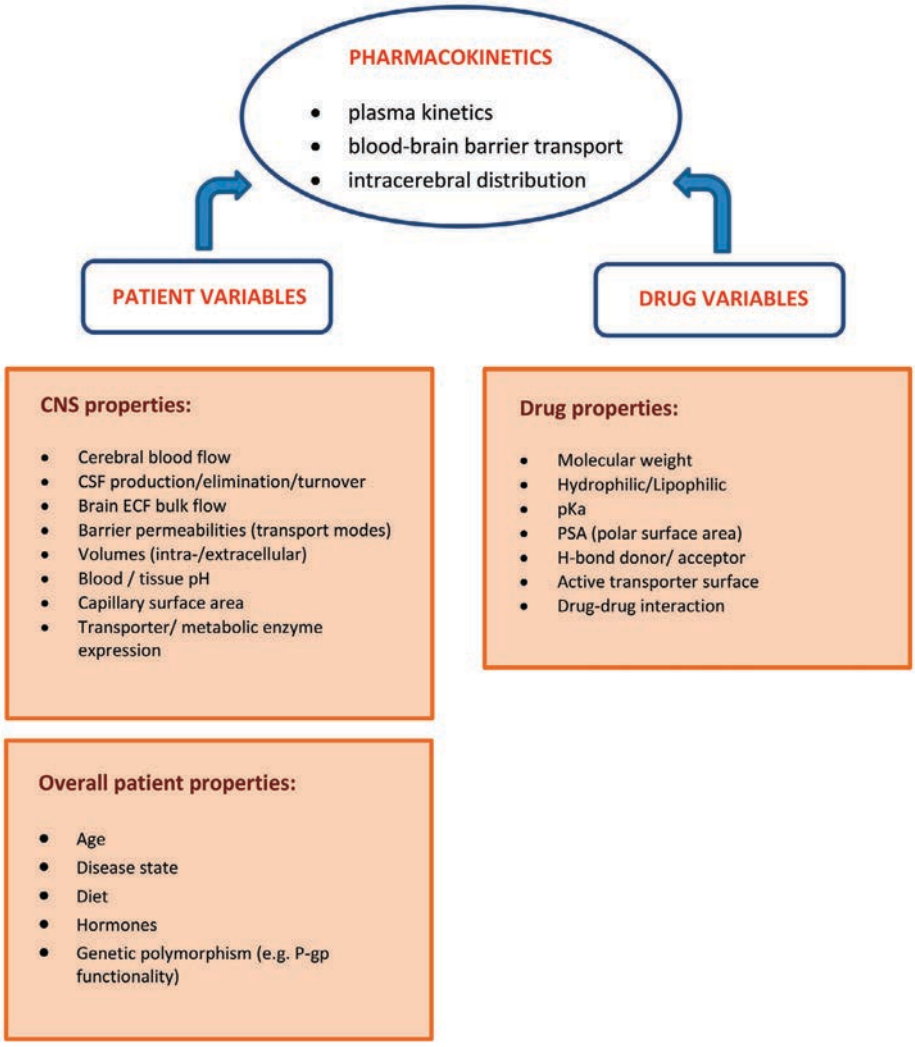
## Pharmacotherapy

Pharmacotherapy can be divided into two distinct parts: pharmacokinetics (PK) and pharmacodynamics (PD). Simply put, PK describes *'what the body does to the drug'* in terms of absorption, distribution, metabolism and elimination and describes the temporal drug concentration profile, while PD describes *'what the drug does to the body'* (7). Regarding pharmacotherapy in sTBI management, the overall goal is the prevention or reduction of secondary injury. Pharmacotherapy in the form of analgesia and sedation has a fundamental role in the management of sTBI as it lowers cerebral metabolic demand. In doing so, cerebral perfusion is more likely to match cerebral metabolic need and tip the balance in favor of the patient. Currently only limited evidence (level III) supports the use of various agents in children (5). It has been reported that up to 80% - 90% of medication prescribed in the neonatal and pediatric intensive care unit is off-label or prescribed in an unlicensed manner (10, 16). Although this is worrisome, at the same time it is not surprising. Especially for CNS medication. CNS pharmacotherapy is distinct and challenging due to the various CNS compartments and compartmental barriers with unique transport characteristics. Knowledge of this physiology and how it influences CNS drug distribution is crucial before proceeding to understand optimal dosing of medication. In general, the lack of CNS specific PK data is reflected by the high failure rate in CNS drug development whereby only approximately 8% of CNS drug candidates becoming clinically available (17, 18). Detailed information on CNS drug concentrations, and their relationship to drug response, is needed for more effective and safe drug dosing strategies. A technique called brain microdialysis (MD) enables sampling of extracellular (interstitial) brain fluid to obtain unbound drug concentrations at or close to the brain (19). The unbound CNS drug concentrations obtained using this technique provides information on the net result of CNS drug distribution secondary to the interplay of CNS compartments and their barrier transport mechanisms as well as patient and brain specific drug factors. This PK data in combination with PK modeling, provides unique opportunities to study which drugs are appropriate for CNS treatment and optimize patient specific drug therapy.

CNS PK variation between patients despite the same dosing strategy can be the result of differential intra-patient blood brain barrier (BBB) integrity over time or at various brain locations. The same holds true for heterogeneity in the degree of CNS injury and patient specific factors (e.g. age-related differences in CNS maturation, overall disease state and variation in cerebral perfusion). All these factors and their dynamic interplay ultimately contribute to PK differences (7, 11, 14, 19, 20). This is summarized in **Figure 3** which elaborates on the disease, patient and pharmacotherapy categories depicted in **Figure 1**.

This thesis focusses on developing pharmacokinetic models that incorporate both patient, disease and drug specific properties to improve individualized pharmacotherapy in pediatric sTBI.

**Figure 3.** Overview patient and drug specific properties that influence CNS pharmacokinetics




Abovementioned variations in patient, disease and drug specific variables explain the different PK of the same dose of (CNS) drug in different subjects, and can therefore lead to different pharmacodynamic effects. CNS = central nervous system, CSF = cerebrospinal fluid, ECF = extracellular fluid, P-gp = P-glycoprotein, PK = pharmacokinetic, pKa = the negative base -10 logarithm of the acid dissociation constant (Ka) of a solution (indicates the strength of an acid), PSA = polar surface area. Adapted from Yamamoto et al (2017, Fig 1, p. 892) (9) with permission from the Publishers.

## Outcome

The goal of (CNS) pharmacotherapy is to provide effective and safe treatment to reduce secondary injury. As PD refers to the effect of the drug on the body, PD markers should reflect (potential) signs of impending secondary brain injury so pharmacotherapy can be adjusted in a timely fashion and prevent PD markers from reaching undesirable values, such as intracranial pressure. However, the question remains which targets to choose, how to deal with varying targets over time depending on developmental status, how to define targets, i.e. cut off values versus time-weighted exposure and the need for normative data. Development of such PKPD models enables linking drug concentration time profiles to PD markers and further improve individualized drug dosing and patient specific therapies. This is necessary, as sTBI is still a leading cause of death or lasting disability worldwide and therefore improvement of current therapies is imperative (2).

To gain insight into the outcome trajectory, it is of the utmost importance to understand the process of end-of-life decisions in the acute phase of sTBI management as well as the rehabilitation course of survivors. Both these elements determine overall mortality and morbidity demographics. Since 2012, the Erasmus MC Sophia Children's Hospital has a multidisciplinary, standardized follow-up program which includes the cohort of sTBI patients admitted to our PICU as part of patient care. Children and their parents or caregivers are invited to visit this outpatient program at 3 to 6, 12 and 24 months post-injury and at the ages of 5, 8, 12 and 17 years, depending on the age at injury. Both the patient and their family are evaluated by a pediatric intensivist and pediatric neurologist. In addition, a pediatric psychologist performs extended neuropsychological assessments using validated instruments that cover different domains at various time points post-injury. Although this follow-up program is firstly and foremost part of patient care, data collected during these visits are used for research with the ultimate aim of improving pediatric sTBI outcome.

This thesis explores the specific outcome of sTBI patients taking into account pharmacotherapy related interventions and overall outcome in terms of morbidity and mortality.

## Aims and outline of this thesis

The aims of this thesis are:

- To provide a framework on the practice, pitfalls and possibilities of analgosedation in pediatric sTBI
- To study the pharmacokinetics of pentobarbital and morphine in pediatric sTBI with population and physiologically-based pharmacokinetic modelling techniques
- To describe neuroprognostication practice in pediatric sTBI and its influence on outcome



## Crossing barriers: pharmacotherapy and the injured brain

This thesis consists of 4 parts which reflect the scope of pharmacotherapy in pediatric sTBI. **Part 1** gives a general introduction (**chapter 1**) into the categories and challenges that comprise the net effect of pharmacotherapy: the patient, the disease and the specific medication. **Chapter 2** provides a review of common analgosedation practice in pediatric sTBI and highlights both potential pitfalls and unique possibilities. The spectrum of steps involved in CNS drug development, with special emphasis on the application of cerebral MD, is detailed in **chapter 3**.

**Part 2** investigates methods to improve our understanding of plasma and CNS PK of frequently applied pharmacotherapy in pediatric sTBI. To this end, different types of PK modelling are studied. **Chapter 4** presents a pilot study of a humanized PBPK CNS model for morphine in pediatric sTBI. The validity of a plasma PK model for pentobarbital in pediatric sTBI and status epilepticus is investigated in **chapter 5**.

The ultimate goal in sTBI management and research is to improve outcome. **Part 3** explores different aspects of outcome**.** Firstly, how we categorize patient subgroups is crucial to how we link these categories to outcome measures such as morbidity and mortality. In **chapter 6** two different approaches to defining hyperoxia are compared as this is associated with adverse outcome and since oxygen is considered the most frequently prescribed 'drug' in the intensive care unit. **Chapter 7** describes the process of end-of-life decisions as well as prospective, long-term follow-up data that can provide valuable context in the neuroprognostication process**.** Neuroprognostication in pediatric sTBI might be facilitated by biomarkers, which is reflected by an editorial in **chapter 8**.

**Part 4** discusses the results of the aforementioned studies in the broader context of pediatric CNS PK by detailing current barriers in this field of research and the potential steps to cross these barriers in **chapter 9**. A summary in Dutch and English of all study results is provided in **chapter 10**.

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# 2

# **Analgosedation in paediatric severe traumatic brain injury (TBI):** practice, pitfalls and possibilities

**Naomi Ketharanathan, Yumi Yamamoto, Ursula Rohlwink, Enno Wildschut, Maayke Hunfeld, Elisabeth de Lange, Dick Tibboel**

***Childs Nerve Syst*** *2017; 33: 1703-1710.*

## ABSTRACT

Analgosedation is a fundamental part of traumatic brain injury (TBI) treatment guidelines, encompassing both first and second tier supportive strategies. Worldwide analgosedation practices continue to be heterogeneous due to the low level of evidence in treatment guidelines (level III) and the choice of analgosedative drugs is made by the treating clinician. Current practice is thus empirical and may result in unfavourable (often hemodynamic) side effects. This article presents an overview of current analgosedation practices in the paediatric intensive care unit (PICU) and addresses pitfalls both in the short- and long-term. We discuss innovative (pre-)clinical research that can provide the framework for initiatives to improve our pharmacological understanding of analgesic and sedative drugs used in paediatric severe TBI and ultimately facilitate steps towards evidence-based and precision pharmacotherapy in this vulnerable patient group.

## INTRODUCTION

The main goal of (paediatric) TBI treatment is the provision of supportive care to guarantee adequate cerebral perfusion to meet cerebral metabolic demands and limit secondary brain injury.(1, 2) Appropriate management is critical as paediatric TBI still causes major morbidity and mortality worldwide.(3, 4) One of the cornerstones in severe paediatric TBI treatment is providing analgesia and sedation, however, current research efforts have not provided any level 1 evidence to support a specific regimen. This has resulted in the international 2012 TBI guideline recommendation that: *'the choice of and dosing of sedative, analgesics .... should be left to the treating physician..'*.(5) This leads to heterogeneous analgosedation prescribing practices based on local expertise and guided by (hemodynamic) side effects which can lead to both over- and under-sedation. Furthermore, it seems that exposure to certain analgosedation drugs might lead to neurotoxic injury and could be associated with unfavourable outcome in the long-term (e.g. radiographic decrease in brain mass, learning disabilities), especially in the developing paediatric patient.(6-8) Although it is difficult to differentiate between the sequelae of primary vs. secondary brain injury, such observations necessitate better pharmacological understanding to achieve both effective and safe analgesia and sedation. To that end, it is important to gain insight into the pharmacokinetics (PK; i.e. 'what the body does to the drug') and the resulting pharmacodynamics (PD; i.e. 'what the drug does to the body') of frequently used analgosedative drugs. It should be noted that plasma PK may differ substantially from brain target site PK due to the functionalities of the blood-brain-barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) (9) and information on drug target site distribution is essential to understand PK-PD relationships in different TBI disease states. Collaboration between preclinical and clinical research is essential in this respect. Techniques such as high-frequency multimodal neuromonitoring, including cerebral microdialysis, combined with advanced PK-PD modelling are promising tools.(10, 11) The physiologically-based (PB) pharmacokinetic (PBPK) modelling approach is particularly useful as it allows translation from animals to humans. Measurements that cannot be performed (or only highly limited) in humans can be performed in animals, and the resulting data can be physiologically scaled to predict PK in humans. This is imperative to fully understand how drugs behave in the body and vice versa. This improved pharmacological understanding will facilitate development of more patient-specific treatment strategies in a heterogeneous condition like paediatric TBI, which requires a tailored approach to achieve effective and safe therapy. This narrative review aims to provide an overview of current practice; its potential pitfalls, and discusses possibilities of developing more evidence-based analgosedation practices in paediatric TBI.

## METHODS

A literature search was performed using search strategies with MeSH terms and synonyms of "brain injury", "analgesia", "sedation" and "children" with the search databases Embase, Ovid, Cochrane Central, Web of Science and Google Scholar. A total of 1160 potential references were found that were reviewed by the primary author for relevance based on the aim to provide a pharmacological overview of paediatric severe TBI analgosedation practice and principles. Additional references were added by cross-reference check. It must be emphasized that the 2012 international guidelines for paediatric TBI management remain the mainstay of treatment recommendations. (5) This article provides additional pharmacological background information and highlights novel approaches in pharmacological research.



## PRACTICE

The application of analgesia and sedation in the stabilisation and (supportive) treatment of paediatric severe TBI occurs in various settings from the scene of the accident, emergency department, perioperatively and after admission and stay in the paediatric intensive care unit (PICU). The primary aim for administering analgosedation is to lower cerebral metabolic demand which can be increased by anxiety, stress and pain induced by the primary trauma and further exacerbated by noxious stimuli such as (invasive) procedures and invasive ventilation.(2, 12-14) This article will focus on analgosedation practices in the PICU. The ideal properties of analgosedation drugs in paediatric severe TBI would be to induce an immediate analgesic and/or sedative effect without negatively affecting hemodynamic stability or intracranial pressure (ICP), and have rapid offset of action to enable neurological examination. The compound should also be safe in the long-term with respect to neurotoxicity. Many frequently used compounds offer some of the aforementioned characteristics, but none have so far demonstrated all favourable elements. Perhaps this is not possible given the physiological and developmental differences between patients from ages 0 to 18 years and the heterogeneous nature of brain injury itself.

Most PICUs adopt a TBI protocol based on international guidelines, consensus and local variations in practice. The provision of sedation and analgesia is subdivided in so-called first and second tier therapies in a step-up approach to control ICP and maintain adequate cerebral perfusion pressure (CPP). (5, 15) Adherence to local protocols with respect to analgosedation varies based on personal preference and patient specific factors. A survey in the United States explored physician-agreement with published recommendations and guidelines for paediatric TBI showed a 91% agreement with first-tier sedation recommendations and a 89% agreement with the use of barbiturates as second tier therapy. However, no specification was provided as to which agents were

used when providing analgosedation. (16) One study, which audited its analgosedation practice, reported a 64% adherence to their written protocol with patient specific adjustments in 30% of these cases.(17) This illustrates the variation in analgosedation practice for paediatric TBI, which is not surprising given the lack of evidence-based regimen.

Analgesic compounds described in the literature for paediatric severe TBI are opioids (Fentanyl, Remifentanil, Morphine), Acetaminophen and Metamizole.(12, 17-20) Sedative compounds include benzodiazepines (Midazolam, Lorazepam, Diazepam), Ketamine, Propofol, Dexmedetomidine and Etomidate.(12, 14, 17, 18, 21) Barbiturates (Thiopental and Pentobarbital) are part of second tier therapeutic strategies for lowering refractory intracranial hypertension under electroencephalogram (EEG)-monitoring to ascertain burst-suppression. (2, 12, 14, 18, 22-24) Table 1 and 2 provide an overview of the pharmacological properties of the various analgosedative drugs (only Food and Drug Administration (FDA) approved drugs included).

Most commonly a combination of an analgesic and sedative drug is prescribed as a continuous infusion with a step-up approach in dosing based on clinical effect (often a combination of neurological exam, ICP-threshold, and pain and sedation scoring systems). The sedative effect of most analgesic compounds during dose escalation is often an added benefit in ICP control.(14) Additional bolus medication is common to combat prolonged ICP elevation and determine if pain could be a possible cause thereof.(14) Reports indicate that Fentanyl and Midazolam (separately or in conjunction) are mostly used as bolus analgosedation. Various studies have been performed to clarify which bolus medications are most effective to lower high ICP and present conflicting and sometimes paradoxical results.(25) The benefit of Ketamine for episodic use during potential noxious stimuli (e.g. endotracheal tube suctioning) is that it does not decrease blood pressure and could be a valuable adjuvant for interventions. (26) However, historically this compound has been avoided as it was associated with an increase in ICP.(27-29) Recent paediatric studies using (racemic) Ketamine as bolus medication for episodes of sustained ICP elevation demonstrate its effect in lowering intracranial hypertension.(18) Adult studies show similar findings and support its use when combined with Midazolam.(30) Remifentanil has been shown to be an effective analgesic drug (mostly demonstrated in the adult critical care setting) due to its rapid onset and offset of action enabling frequent, serial neurological examinations. (19, 20, 31) Barbiturates (Thiopentone and Pentobarbital) are implemented as second tier therapy to control refractory intracranial hypertension and have been shown to be effective in reducing ICP in the paediatric population in 30-52% of patients. (23, 32) Dexmedetomidine is gaining increasing interest as a sedative agent in the PICU due to its limited side effects although the majority of publications are based on postoperative cardiac patients. It has been approved by the FDA for sedation < 24 hours in adults with invasive ventilation and there are reports of its use in the PICU

for severe TBI patients (who went on to have good neurological outcomes) and it has been reported to have a opioid-sparing effect in PICU patients requiring sedation. (21, 33) Finally, a brief word on neuromuscular blockade (NMB) is warranted as this is combined with analgosedation in first tier strategies to reduce energy expenditure (e.g. shivering) and improve mechanical ventilation synchronization. Again no class I evidence for NMB is available but it is imperative that at the same time continuous electroencephalography is implemented when continuous NMB infusion is used to determine the presence of posttraumatic seizures.(5, 14, 34)



At this point it needs to be noted that 'efficacy' of analgosedation is often titrated solely on the effect of ICP- and CPP-control and clinical signs of agitation. However, there is increased awareness that there are additional factors which need to be considered to develop a holistic picture of risk factors for secondary injury that could serve as pharmacodynamic (PD) markers in analgosedation studies. Multimodal neuromonitoring seems especially important when defining clinical parameters of therapeutic efficacy. PD markers of effective drug therapy could include cerebral oxygenation ($PbtO_2$), cerebral metabolic state (cerebral microdialysis yielding information on lactate and pyruvate) and brain activity as monitored by continuous electroencephalogram (EEG). (10) Furthermore, it might be beneficial to differentiate between patients with or without intact cerebral autoregulation as certain drugs could actually induce an ICP increase (and CPP decrease) when cerebral autoregulation is preserved.(35, 36).In this respect the time from initial injury can also be an important factor, resulting in a different response of the brain to analgosedative drugs over time.

## PITFALLS

The potential negative effects of commonly used analgosedative drugs can be subdivided into short- and long-term pitfalls. Short-term pitfalls mostly refer to undesirable hemodynamic side-effects, i.e. a decrease in mean arterial blood pressure (MAP) resulting in a decrease in cerebral perfusion pressure (CPP), which can further exacerbate secondary brain injury. Potential pitfalls based on specific drug or patient characteristics are summarized in the following paragraph. A more extensive overview of side effects is provided in **Tables 1 and 2**.

Continuous infusion of Propofol is associated with Propofol infusion syndrome (PRIS), which is characterized by the onset of metabolic acidosis, rhabdomyolysis, acute renal failure, cardiac dysrythmias and hyperlipidemia. (37, 38) Although there is evidence that continuous Propofol infusion < 4 mg/kg/hour for periods > 48 hours can be safe (39, 40), the cost-of-error is deemed so great that the FDA recommends withholding from continuous Propofol infusion in paediatric TBI. (41) As for bolus medication, Propofol is sometimes briefly used as an adjuvant for procedural sedation. However, it

is noteworthy that delayed posttrauma administration of Propofol could be associated with induction of apoptosis due to increased expression of the P75 neurotrophin receptor, sensitizing the brain for neurotoxic effects in juvenile neurons.(42) Etomidate could be useful as bolus therapy for intracranial hypertension episodes due to its favourable hemodynamic profile (43), however its use is often restricted to intubation settings due to the association with adrenal insufficiency.(2) Thiopental can potentially cause life-threatening electrolyte imbalances, especially regarding potassium. (44) Dexmedetomidine has been reported to induce hypertension at high-dose infusion (> 4 µg/kg/hour) for several hours.(45) Other reports have noted the occurrence of bradycardia, which is more pronounced when this agent is combined with other medications that yield a negative chronotropic effect.(21) Metamizole is frequently used as a non-opioid first-line analgesic for adults in many countries but there are still many controversies about potential risks (like agranulocytosis), leading to a ban by the FDA. A recent systematic review and meta-analysis showed that Metamizole is safe (no reports of agranulocytosis) for short-term use in hospital.(46) Although its role in paediatric analgesia is unclear, it is reportedly used in certain countries.(17) Various studies have demonstrated that opioids could potentially increase ICP in TBI patients with preserved cerebral autoregulation in conjunction with systemic effects of mean blood pressure decrease. This effect was most pronounced for Fentanyl. (36, 47) Furthermore, a recent study on the effectiveness of pharmacological therapies for intracranial hypertension demonstrated that Fentanyl was significantly associated with frequent treatment failure when compared to Pentobarbital and hypertonic saline.(48) Fentanyl and Midazolam as bolus therapies for intermittent intracranial hypertension have been associated with ICP increase and CPP reduction. (35)

Spreading depolarizations present a potential threat to functional neurons, resulting in necrosis or degeneration and possibly poor outcome after brain injury. Analgosedation acts by influencing neuronal homeostasis and has been investigated for preventing or propagating spreading depolarizations. One study found that *N*-methyl-D-aspartate (NMDA) receptor agonists (such as Ketamine) led to less spreading depolarizations, but Midazolam increased the amount of spreading depolarization clusters. These findings need to be investigated further but provide an interesting angle into pitfalls and possibilities of these drugs.(49) Finally, it must be emphasized that the severe TBI patient is often subject to polypharmacy (i.e. multiple drugs being prescribed concurrently). It is important to be aware of drug-drug-interactions, which can lead to subsequent undesirable effects. For example, the proton-pump inhibitor Esomeprazole is frequently prescribed in critically ill patients. It has been reported that prescribing Esomeprazole increases the volume of distribution and half-life of Thiopentone, which needs to be taken into account when aiming for certain target concentrations. (50)

Long-term pitfalls have been described in the context of (major) withdrawal symptoms and delirium, which obscure adequate neurological evaluation. This suggests not only

the need for dose escalation in the acute phase of patient stabilisation but also the development of guidelines to optimally taper analgosedation afterwards.(51) Validated tools to assess withdrawal symptoms (which can already occur after 5 consecutive days of opioid and/or benzodiazepine administration) and delirium in the PICU are the Withdrawal Assessment Tool version 1 (WAT-1) and Sophia Observation withdrawal Symptoms – Paediatric Delirium scale (SOS-PD). (52, 53)

Pharmacogenetics can be considered part of patient-specific pitfalls. Important examples are so-called ABCB1 polymorphisms, which encode for P-glycoprotein transporter that is responsible for morphine efflux over the blood-brain barrier. This can result in different cerebral morphine concentrations and associated (prolonged) effect. The latter has mostly been investigated in the context of prolonged respiratory depression after opioid administration during elective procedures.(54, 55)



Finally, there are concerns about the potential neurotoxic apoptotic effects of certain drugs, especially in the developing brain. Animal studies have demonstrated mechanisms by which analgosedative agents of different classes (which are also used in the PICU for TBI) trigger upregulation of apoptotic cerebral cascades (i.e. blocking of glutamate NMDA receptors, activation of gamma-aminobutyric acid (GABA) receptors or blocking of voltage gated sodium channels. This results in inactivation of cell survival signalling proteins and activation of inflammatory cytokines.(7) Furthermore, anaesthetic opioid exposure in animals showed a possible neurotoxic effect as demonstrated by elevated levels of S100B, a biomarker of brain injury.(56) It is of interest that these effects in animals and cultured neuronal cells were dose dependant and dependant on the maturity of neuronal tissue. (57) Studies in preterm infants exposed to Fentanyl suggest that a higher cumulative dose correlated with an increased incidence of cerebellar injury and lower cerebellar size when compared at term equivalent age. (6) However, the results from paediatric general anaesthesia studies evaluating long-term neurodevelopmental outcome are more difficult to interpret as these are heterogeneous populations often with a pre-existing condition (e.g. congenital defect) giving rise to an a priori increased risk of deficits in neurological development. (8) (58) Of course extrapolation of preclinical and paediatric anaesthetic clinical study findings to analgosedation practices in paediatric TBI should be done with caution, despite the use of similar compounds. However, these observations are important as they emphasise the necessity to search for both effective and safe analgosedation dosing strategies in paediatric TBI.

## POSSIBILITIES

To date current approaches have not been able to conclusively yield the desired answers, i.e. which drugs are safe and effective to prescribe in (paediatric) TBI? The high failure rate in CNS drug development and research can in part be attributed to the fact that 'golden standard' approaches, such as randomized controlled trials (RCTs) and comparative effectiveness designs, fail to take into account the heterogeneity of the disease process and drug- and patient-specific characteristics. In particular, the unique functionality of the blood-brain and blood-cerebrospinal (CSF) barrier, and therewith drug transport into and out of the brain, are not elucidated. Thus drug target site concentration (e.g. cerebral drug concentrations) are unknown. Information on the target site concentrations is fundamental in understanding drug action. Therefore assessing target site pharmacokinetics is the primary step before attempting to study the resulting pharmacodynamics.(9, 11, 59)

Bottlenecks in pharmacological research, especially in children, are ethical concerns about performing invasive studies of compounds with unproven benefit in minors, and difficulty obtaining adequate sample size to provide definitive answers. Another obstacle in paediatric drug research is the limited number and volume of blood or cerebral fluid samples which can be obtained per patient due to smaller circulating volumes. This is where 'bench-meets-bedside' research can be of value. Animal-based PBPK models can be translated to humans and thereby serve as templates of what happens to a drug in the body under various clinical conditions. After translation of the animal PBPK model to humans, full drug concentration PK profiles in human brain can be predicted. The PBPK human model can be validated by comparing predicted drug concentration values to a number of observed drug concentrations in the human CNS (e.g. CSF and brain extracellular fluid from microdialysis monitoring). Especially for paediatric PK analysis, obtaining individual plasma PK is crucial to predict a drug-concentration time profile in the CNS due to the various developmental differences that have an impact on PK profiles. Collecting sufficient human samples can be challenging, but 'sparse sampling population-based PK (PPK)-analysis' is an innovative statistical technique that can be used to solve this challenge. Practically, this model requires only a limited number of samples per patient. The samples of various patients are then used as a single 'population' (after corrections of covariates such as age, weight, renal function) providing enough data points to compile drug-specific pharmacokinetic time profiles under different clinical conditions and developmental differences. In other words, the combination of PBPK and PPK modelling allows prediction of drug concentrations at various target sites (e.g. blood plasma, brain extracellular fluid) at different dosing regimens for each paediatric patient. It has been enlightening that drug plasma concentrations do not represent cerebral drug concentrations, highlighting the unique properties of the blood-brain and blood-cerebrospinal fluid barrier.(11, 59-61)

Although focus must shift 'back to basics' with regard to improved pharmacological understanding of frequently used analgesics and sedatives, this does not mean observations from the clinical field should be dismissed. For example, comparative effectiveness research could provide direction as to which drug compounds warrant further PKPD research. Finally, pharmacology is dynamic, complicated and an indispensable part of clinical practice. It is imperative we understand basic principles but also cooperate with experts in the field to optimize our treatment. In this respect, a clinical pharmacologist or hospital pharmacist can be of great value to point out significant drug interactions and provide alternative options as well as dose adjustments based on clinical status. It is becoming increasingly clear that a multifactorial, complex disease like (paediatric) severe TBI warrants a multidisciplinary approach, also as regards pharmacology.



## CONCLUSION

Analgosedation is a crucial part of severe (paediatric) TBI management but evidence-based guidelines are not available leaving the choice of analgesic and sedative drugs to the treating physician. *Practice* is heterogeneous and leads to serious concerns about efficacy and safety. *Pitfalls*, besides the well-known side effects of frequently used drugs, include paediatric-specific concerns in terms of potential neurotoxicity in the developing brain and age-specific differences in drug distribution and metabolism. *Possibilities* to enhance our pharmacological understanding include the implementation of animal-based pharmacokinetic models that enable prediction of drug concentrations at target sites. This combined with multimodal neuromonitoring can link cerebral drug concentrations to drug effect and ultimately lead to more evidence-based analgosedation therapies in (paediatric) TBI.

**Table 1.** Overview analgesic drugs in paediatric severe traumatic brain injury

| Class | Medication | Mode of action | Dosage |
|---|---|---|---|
| *Opioid* | Morphine | Opiate receptor agonist | Bolus 0.05 – 0.1 mg/kg<br>Range 0.01 – 0.04 mg/kg/hour |
| | Fentanyl | Opiate receptor agonist: inhibition of nociceptive neurotransmitters | Bolus 1 – 2 mcg/kg<br>Range 1-2 mcg/kg/hour |
| | Remifentanil | Opiate (specific) mu-receptor agonist<br>Ultra-rapid onset and offset of action | Bolus 0,25 – 1 mcg/kg<br>Range 0,1 – 2 mcg/kg/minute |
| *Other* | Acetaminophen | Inhibition of cyclooxygenase (COX) enzymes involved in prostaglandin synthesis | Loading dose 20 mg/kg i.v.<br>Maintenance 60 mg/kg/dg in 4 doses (maximum 1 gram per dose) |

The abovementioned dosage suggestions are for children aged 0 – 18 years of age, with the exception of neonates (< 1 month old).
BBB = blood-brain-barrier, COX = cyclooxygenase, CNS = central nervous system, i.v. = intravenous, MRP= multidrug resistance-associated protein, PK = pharmacokinetic

**Table 2.** Overview sedative drugs in paediatric severe traumatic brain injury

| Class | Medication | Mode of action | Dosage |
|---|---|---|---|
| *Benzodiazepine* | Midazolam | GABA receptor agonist | Bolus 0.05 – 0.2 mg/kg<br>Range 0.05 – 0.5 mg/kg/hour |
| *Barbiturate* | Pentobarbital | GABA receptor agonist | Bolus 5 mg/kg<br>Range 1 – 2 mg/kg/hour |
| | Thiopental | GABA receptor agonist | Range 12,5 mg/kg/hour (starting dose for 6 hours), then 5 mg/kg/hour and taper to 3 mg/kg/hour depending on EEG and plasma concentration |
| *Other* | Propofol | GABA receptor agonist | Bolus 1-2 mg/kg<br>Range (not recommended but reported up to 4 mg/kg/hour) |
| | Dexmedetomidine | Selective alpha-2-adrenoreceptor agonist | Range 0.1 -2 mcg/kg/hour (loading dose 0.25 mcg/kg optional) |
| | Ketamine | *N*-methyl-D-aspartate receptor antagonist | Bolus 1 – 2 mg/kg |
| | Etomidate | GABA receptor agonist | Bolus 0.3 – 0.5 mg/kg |

The abovementioned dosage suggestions are for children aged 0 – 18 years of age, with the exception of neonates (< 1 month old).
EEG = electroencephalogram, GABA = gamma-aminobutyric acid, PK = pharmacokinetic, PRIS = Propofol Infusion Syndrome.

| T ½ | Side effects | PK points of interest |
|---|---|---|
| 2 – 4 hours | Respiratory depression, hypotension, urinary retention, vomiting, constipation, pruritus | Active metabolite morphine-6-glucuronide (M6G)<br>Direct interaction with opioid binding sites in brain<br>Active efflux mechanism in brain (P-glycoprotein and multidrug resistance-associated protein (MRP)) and active influx transporter (undefined) |
| 7 hours | Sedation, respiratory depression, hypotension, muscle rigidity (thorax), nausea | High lipophilicity leading to easier penetration CNS.<br>Not subjected to active transport across the BBB |
| 1 – 20 minutes | Respiratory depression, muscle rigidity, hypotension, nausea, pruritus | Direct interaction with opioid binding sites in brain |
| 1 – 4 hours | Risk of hepatic necrosis and failure in prolonged or high dosage | Blockage of COX enzymes in the CNS |

| T ½ | Side effects | PK points of interest |
|---|---|---|
| 5.5 hours (±3.5 hours) | Sedation, respiratory depression, hypotension, bradycardia, (paradoxical) emergence delirium | Metabolized to active metabolites 1- and 4 –hydroxy-midazolam<br>Lipophilic |
| 5 – 50 hours (dose dependant) | Sedation, respiratory depression, hypotension, laryngospasm, anaphylactic reactions have been reported | Lipophilic |
| 3 – 8 hours | Sedation, respiratory depression, hypotension, skin reactions (due to histamine release), laryngo- and bronchospasm | Lipophilic |
| 2 – 10 minutes (initial distribution phase) | Hypotension, respiratory depression, hypertriglyceridemia, PRIS | Lipophilic |
| 2 hours | Hypertension, bradycardia | Lipophilic |
| 2.5 – 3 hours | Laryngospasm, tachycardia, dysphoria | Lipophilic |
| 75 minutes | Adrenal insufficiency, hypertension, laryngospasm, dyskinesia | Lipophilic |

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# 3

# Brain microdialysis and applications to drug therapy in severe traumatic brain injury

**Naomi Ketharanathan, Ursula Rohlwink, Anthony Figaji, Enno Wildschut, Dick Tibboel, Elisabeth de Lange (2022)**

*In Rajendram R, Preedy V and Martin C (Ed)*
***Cellular, Molecular, Physiological, and Behavioral Aspects of Traumatic Brain Injury: The Neuroscience of Traumatic Brain Injury***
*(Chapter 19, pp. 231-243)*
*London, United Kingdom: Academic Press (Elsevier Inc)*
*ISBN 9780323991971*

## ABSTRACT

Pharmacotherapy has a fundamental role in the management of severe traumatic brain injury (TBI). Currently limited level evidence supports the use of various agents. Overall, the development of drugs for the central nervous system (CNS) has an extremely high failure rate with an estimated 8% of CNS drug candidates becoming clinically available. This is due to the complexity of unique CNS barriers and transport mechanisms that govern (unbound) CNS drug distribution. Improved understanding of CNS drug concentrations, and their relationship to drug response, is needed for more effective and safe drug dosing strategies. Brain microdialysis enables sampling of extracellular (interstitial) brain fluid to obtain unbound drug concentrations at or close to the target site. This information, combined with pharmacokinetic modeling, provides unique opportunities to investigate which drugs are appropriate for CNS treatment to ultimately improve patient specific drug therapy.

# INTRODUCTION

Pharmacotherapy plays an important role in the treatment of severe traumatic brain injury (TBI). Analgesia and sedation are fundamental in the acute phase of the disease (Carney et al., 2017; Kochanek, Tasker, Bell, et al., 2019). Other drug categories frequently administered include anti-epileptic drugs (AEDs) and antibiotics. Neuroprotective agents are also subject to investigation (Janowitz & Menon, 2010).

Considerable efforts have been made to investigate various substances and prescribing strategies for central nervous system (CNS) diseases, however these failed to account for the unique properties of the CNS with respect to pharmacokinetics, particularly for unbound drug concentrations at or close to the target site. Specific points that require elucidation are the dynamic blood-brain and blood-cerebrospinal fluid (CSF) interfaces with their intricate transport properties, as well as drug distribution within the CNS itself. Moreover, patient specific variables and drug properties are relevant for CNS drug distribution. The high attrition rate in the development of CNS drugs emphasizes the necessity to improve our understanding of CNS drug pharmacokinetics, as extrapolation of drug pharmacokinetic data from blood plasma falls short (Kaitin & Milne, 2011; Kola & Landis, 2004). As such, it is understandable that to date, there is overall limited evidence for currently implemented drugs in severe TBI despite their pivotal role (Carney et al., 2017; Kochanek, Tasker, Carney, et al., 2019)

This chapter describes the challenges of the unique CNS environment as it relates to pharmacotherapy as well as explaining how brain microdialysis and pharmacokinetic modelling will improve our understanding of CNS pharmacokinetics and selection of promising CNS drug candidates, thereby paving the way toward improved TBI pharmacotherapy.

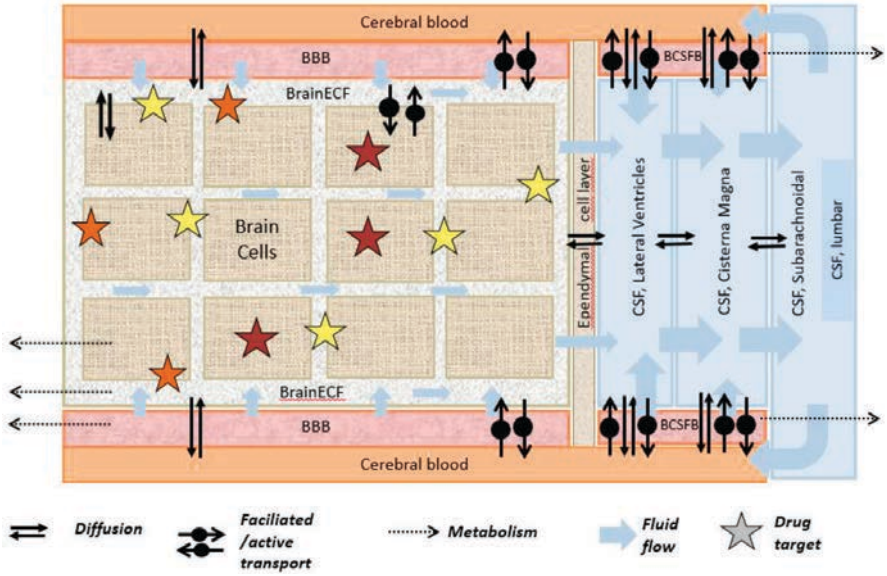
# THE CENTRAL NERVOUS SYSTEM

## Compartments and barriers

Pharmacotherapy of the CNS is distinct and challenging due to the various CNS compartments and compartmental interfaces with unique transport characteristics (Daneman & Prat, 2015; Sharif et al., 2018). Knowledge of these concepts is important to understand CNS drug distribution. The CNS anatomy can roughly be divided into four compartments: the brain intracellular space (ICS), the brain extracellular fluid compartment (ECF), the ventricular and lumbar CSF compartments. Barriers between blood and CNS are formed by the blood-brain-barrier (BBB) and blood-CSF-barrier (BCSFB), which are mostly comparable. However, a distinct difference between these barriers is that the BBB is comprised of cerebrovascular endothelial cells whereas choroid plexus epithelial cells constitute the BCSFB and the expression and activity of transport proteins may differ (Abbott, Patabendige, Dolman, Yusof, & Begley, 2010;

de Lange, 2013a). The brain barrier permeability to substances is mainly influenced by the lipophilicity of a molecule (also expressed as either logP or logD), molecular size and ionization. The degree of molecular ionization is dependent on the pKa of a drug (measure of acidity) and the pH of the specific compartment (Yamamoto, Danhof, & de Lange, 2017). **Figure 1** provides an overview of the various CNS compartments, barrier interfaces and transport mechanisms.

**Figure 1:** Overview of CNS barrier interface transport mechanisms in relation to CNS compartments .




Schematic representation of central nervous system compartments, their interfaces and specific transport mechanisms for molecular substances. From de Lange et al (2013, Fig. 3, p. 318) (de Lange, 2013b) with permission from the Publishers.
BBB = blood-brain-barrier; BCSFB = blood cerebrospinal fluid; CSF = cerebrospinal fluid; ECF = extracellular fluid.

## TRANSPORTATION ACROSS BRAIN BARRIERS

The unbound drug concentration in plasma drives transportation into the brain. Plasma protein binding reduces the unbound drug concentration, and the plasma proteins mostly responsible for drug binding are albumin and α1-acid glycoprotein (Hammarlund-Udenaes, Fridén, Syvänen, & Gupta, 2008; Yamamoto, Danhof, et al., 2017). Small lipophilic drugs can pass the barrier by crossing the lipophilic cell membranes (transcellular) and small hydrophilic drugs can only pass via the spaces between these cells (paracellular), which is highly restricted by so-called "tight

junctions". Besides such passive diffusion, there are various other transport mechanisms across brain barriers. An overview of all transport mechanisms is provided in **Table 1**.

**Table 1**: Transport mechanisms across brain barriers

| Mode of transport | Mechanism |
|---|---|
| ***Simple diffusion***<br>• Paracellular<br>• Transcellular | Passive process that includes *transcellular* and *paracellular* transport, and is driven by the unbound molecule concentration gradient (high to low) between blood and brain sides. Transcellular diffusion of small lipophilic molecules depends on lipophilicity and size. Paracellular transport of small hydrophilic drugs that are not able to diffuse passively through the lipophilic membranes, occurs between the cells through the space left over by the tight junctions, and is limited by molecule size. |
| ***Facilitated diffusion***<br>• Helper molecules | Passive process driven by the concentration gradient (high to low) of the unbound molecule concentrations facilitated by *helper molecules*. The limiting step is helper molecule availability. |
| ***Fluid phase (vesicular) transport***<br>• Pinocytosis<br>• Transcytosis | This transport encompasses bulk flow endocytosis (pinocytosis), adsorptive-mediated transcytosis and receptor-mediated transcytosis. BBB vesicle transport is unidirectional (from blood to brain). Pinocytosis is non-specific uptake of extracellular fluid and is temperature and energy dependent, non-competitive and non-saturable. In BBB cells this only happens to a limited degree under physiological conditions. Adsorptive-mediated transcytosis involves interaction of large charged molecules with the BBB cells, inducing vesicle formation by a non-specific mechanism. Receptor-mediated transcytosis results from the specific binding of large molecules to specific receptors. These transport modes require energy. |
| ***Active transport***<br>• Influx<br>• Efflux | Active transport of molecules may occur by membrane transport proteins with specific binding sites for particular molecules. This transport type is energy dependent, directional (influx and/or efflux) and transport may occur against a concentration gradient. Influencing factors are temperature, transporter capacity, competitive and non-competitive inhibitors and protein kinases that determine transporter protein phosphorylation and thereby activity. The efflux transporters explain in part why many lipophilic drugs have poor CNS distribution. Well-known efflux transporters are P-glycoprotein (P-gp), multidrug-resistance-related proteins (MRPs) and the breast-cancer resistance protein (BCRP) |

BCRP = breast-cancer resistance protein, CNS = central nervous system, P-gp = P-glycoprotein, MRP = multidrug-resistance-related proteins. (de Lange, 2013a)

Other CNS properties relevant to CNS drug distribution are cerebral blood flow (CBF), effective capillary surface, CSF turnover rate, brain tissue binding and drug metabolism. CBF and effective capillary surface area are especially important for drugs with high BBB permeation whereby CBF can become rate-limiting. CBF variables are the

driving blood pressure, intracranial pressure and total number of perfused capillaries. CSF turnover rate may affect drug levels in CSF, but not brain ECF, and therefore influences the ratio between brain ECF concentrations to plasma concentrations. In addition, the ECF bulk flow into the CSF can counteract molecular diffusion from the CSF into brain tissue via the ventricle linings. Brain tissue binding determines drug molecule distribution between the extracellular and intracellular spaces. Thus, not only passive diffusion but also active transport may play a role in governing unbound drug concentrations at either side of the BBB, and therefore the target site. The target may face the ECF (e.g. neurotransmitter receptors) or can reside intracellular (such as nuclear receptors). Apart from active transporters at blood-brain barriers, active transporters may reside at cellular membranes and thereby influence extra-intracellular transport. Moreover, drug metabolism at the BBB and BCSFB could influence CNS drug distribution, acting as 'enzymatic barriers' to drug influx (Yamamoto, Danhof, et al., 2017). Also, drug metabolizing enzymes may be present in the ECF and/or ICS and affect actual drug concentrations at these sites.



In summary, drug molecule transport into and within the CNS is determined by multiple variables including patient characteristics (e.g. the BBB and BSCF permeability, surface area, CNS compartmental pH, transporter activities), and drug-specific properties such as logP, pKa, size, degree of ionization and dependency/affinity for CNS transporters (de Lange, 2013a).

## PHARMACOKINETICS

Pharmacokinetics (PK) describes the processes that determine drug concentrations in the body and encompasses drug absorption, distribution, metabolism and elimination (**Table 2** and **Figure 2**) (Markey, 2012; Starkey & Sammons, 2015). The two primary PK parameters that govern drug PK are the volume of distribution (Vd) and clearance (CL). The combination of Vd and CL determines drug half-life ($t_{1/2}$) and bioavailability. These factors are important for determining drug prescribing practices. The Vd is the hypothetical volume that the total drug concentration in plasma would occupy if distributed evenly over this hypothetical volume. It is relevant to ascertain the drug loading dose to reach target concentrations or conversely to predict an expected plasma drug concentration based on the loading dose. CL describes drug removal from blood plasma and represents the sum of drug CL by each organ although this often equates to hepatic and renal CL. CL is defined as the volume of plasma (or other body fluid) that is completely cleared from the drug per unit of time. CL is used to determine the drug maintenance dose necessary to achieve a certain steady-state plasma concentration. Drug half-life ($t_{1/2}$) reflects the time the drug needs to decrease its concentration by half in the plasma. It is calculated with the formula ($t_{1/2}$) = (0.693 x Vd)/CL and is used to calculate the time required for a drug to achieve steady

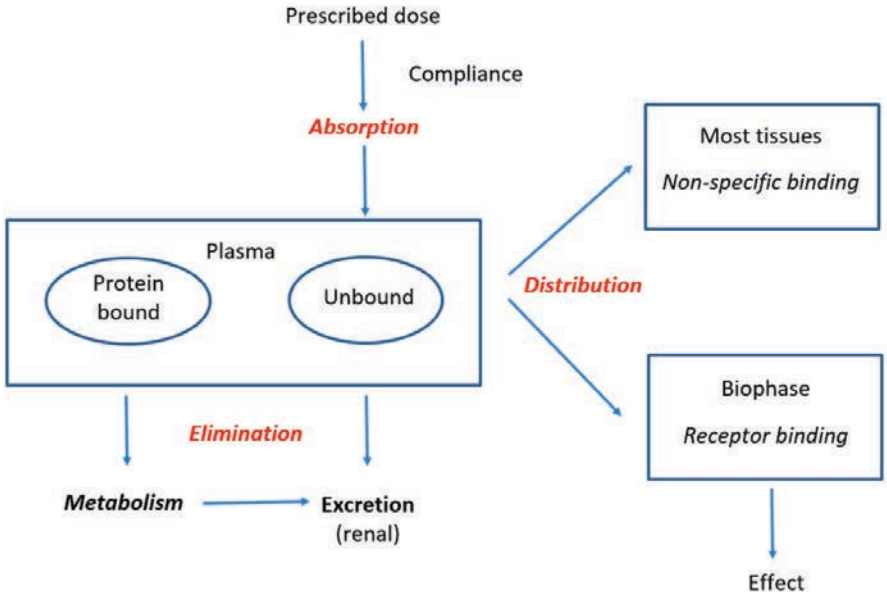
state, in case of a continuous infusion, or to be completely eliminated after injection. In clinical practice, it is applied to determine drug dosing intervals. Bioavailability describes the fraction of the drug dose that reaches the systemic circulation after being administered. It facilitates understanding how drug or human factors influence dose-exposure. Furthermore, CL can affect bioavailability as it might influence the amount of drug that reaches the systemic circulation (Starkey & Sammons, 2015). When considering the multitude of interrelated PK processes and variables, it is clear why extrapolation of plasma PK to brain PK does not suffice and specific CNS PK research is warranted.

**Table 2**: Overview pharmacokinetic processes

| PK process | Description | Variables |
|---|---|---|
| ***Absorption*** | Process of drug movement from the site of administration to the site of measurement (typically plasma) | • Tissue characteristics that separate the body from the external milieu |
| ***Distribution*** | Dependent on patient characteristics and drug physicochemical properties | • Body composition (such as total body water to fat ratio)<br>• Binding to circulating plasma proteins<br>• Hemodynamic status<br>• Acid-base balance<br>• Blood vessel characteristics (cellular permeability, fenestra's)<br>• Tissue cell membrane permeability |
| ***Metabolism*** | Conversion into more water-soluble compounds by means of oxidation and conjugation to facilitate excretion; mainly in the liver by hepatic enzymes (e.g. CYP-dependent enzymes) | • Genetic polymorphism and/or developmental differences in CYP or other types of enzyme activity and conjugation pathways |
| ***Elimination*** | The renal route is the most important pathway of excretion and constitutes glomerular filtration, tubular secretion and reabsorption | • Renal function maturation<br>• Altered renal function in illness<br>• pH of pre-urine and blood |

This table describes the four key processes that constitute drug pharmacokinetics and the variables that influence each process. CYP = cytochrome P450.

**Figure 2**: Schematic representation of the pharmacokinetic processes in the body




The diagram demonstrates the various pharmacokinetic (PK) processes in the body after a drug is prescribed and administered. The four key PK processes encompass: absorption, distribution, metabolism and elimination. The balance between these processes, which is influenced by drug and patient-specific variables, will determine drug concentration at the biophase (i.e. the site where the drug exerts its effect). Adapted from Markey et al (2012, Fig 2.1, p. 14) (Markey, 2012) with permission from the Publisher.

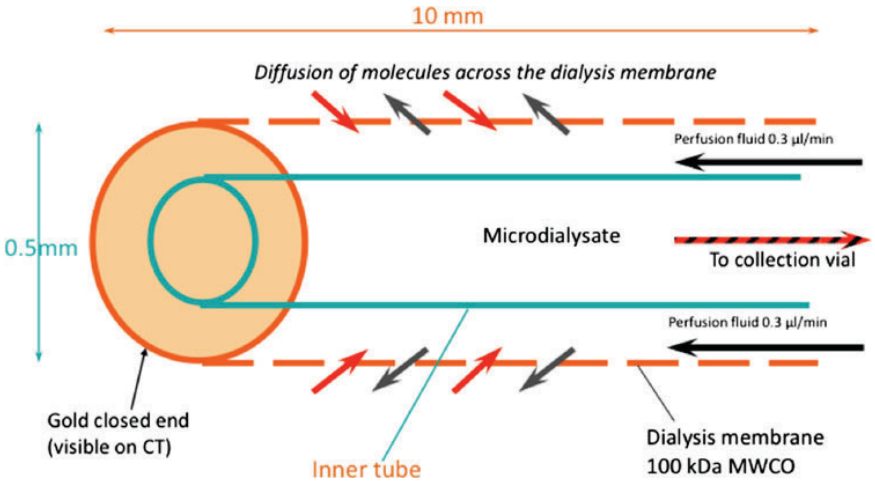


## BRAIN MICRODIALYSIS

Microdialysis (MD) is a technique that measures extracellular concentrations by sampling soluble molecules from the interstitial space of body tissue (so-called extracellular fluid, ECF) through a semipermeable membrane. In brain MD the dialysis catheter is inserted into the brain tissue. Due to the invasive nature of monitoring, this technique is predominantly employed as part of multimodality monitoring in neurocritical care patients, such as severe TBI patients. The microdialysis catheter consists of two concentric tubes: the outer wall is a semi-permeable microdialysis membrane allowing diffusion of molecules between the brain ECF and perfusion fluid of the MD catheter. The perfusion rate is usually set at 0.3 microL/min, although this can be adjusted. The perfusion fluid flows back up the central catheter tube and is collected in a vial (**Figure 3**). The molecule size that can be investigated depends on the brain catheter membrane pore size which can range from 20 to 100 kDa molecular weight cut-off (MWCO) (Charalambides, Sgouros, & Sakas, 2010; Mdialysis, 2020; Shannon, Carpenter, Guilfoyle, Helmy, & Hutchinson, 2013; Wang et al., 2020).

The applications of brain MD are multifold and include metabolic monitoring (glucose, lactate, pyruvate), neurotransmitters (glutamic acid, aspartic acid, GABA), markers of membrane damage (glycerol), biomarkers (e.g. cytokines) and drug monitoring (Shannon et al., 2013). Metabolic monitoring is an analysis that can be performed at the bedside and trends can assist in clinical decision making (Le Roux et al., 2014).

**Figure 3:** Schematic representation of the microdialysis probe




Schematic representation of a microdialysis catheter tip which is implanted in brain tissue. Diffusion of particles and substances in the extracellular fluid surrounding the catheter tip is possible through the dialysis membrane and collected for analysis. From Shannon et al (2013, Fig 2, p.345) (Shannon et al., 2013) with permission from the Publishers.
CT = computed tomography; kDa = kiloDalton; MWCO = molecular weight cut-off.

## Application of brain microdialysis in CNS drug therapy

There is a paucity of data on CNS drug concentrations due to the challenge of determining these at accessible locations that best approximate the brain target site and reflect time-dose relationships. Brain MD is the only available technique that collects samples from the CNS compartment with direct contact with astrocytes and neurons, the ECF compartment, and which most closely represents the intracellular brain concentrations. Furthermore, importantly, brain MD provides a temporal profile of ECF concentrations with MD vials collected hourly. (Azeredo, Dalla Costa, & Derendorf, 2014; Shannon et al., 2013) The unbound CNS drug concentrations obtained using brain MD provides a unique opportunity to determine the net result of CNS drug distribution secondary to the interplay of CNS barriers and compartments, barrier transport mechanisms, and patient and drug specific factors.

However, there are important considerations regarding the interpretation of MD sample concentrations (**Table 3**). First, drug recovery from brain ECF into the catheter may not be 100%. Reasons include incomplete equilibration of drug concentrations on either side of the catheter membrane due to dilution by continuous perfusion through the catheter, as well as sticking of compounds to the catheter and tubing. This can be investigated under in vitro conditions, and when drug recovery is adequate, be used to determine in vivo concentrations. For drugs that do not stick, the concentration equilibration in human MD catheter fluid is often close to 100% due to the large MD membrane surface and relatively slow perfusion flow rate. Drug concentrations measured in serial MD samples may then be used for understanding drug CNS distribution as a function of time (drug CNS PK) (de Lange, Danhof, de Boer, & Breimer, 1997; de Lange, de Boer, & Breimer, 2000).



CNS PK may differ between patients, despite the same drug dosing strategy, because of differential intra-patient BBB integrity at different brain locations and/or times (Sharif et al., 2018), inter-patient variability in the degree of CNS injury, age specific factors (differences in CNS maturation) and patient specific factors (e.g. disease state, CBF variation). (Ketharanathan et al., 2019; Shannon et al., 2013; Thelin, Carpenter, Hutchinson, & Helmy, 2017)

Moreover, brain MD samples reflect focal drug CNS PK, i.e. at the position of the MD catheter (de Lange, Bouw, et al., 1995). Hence it is important to consider MD catheter positioning carefully for the intended purpose. For general drug CNS PK investigations, positioning of the MD catheter in relatively un-injured brain would offer the best approximation of 'healthy' brain tissue. To provide a more global picture, it is possible to use various modalities that combine dynamic, focal (e.g. brain MD) and global/cross-sectional monitors with better spatial coverage of the intracellular environment (e.g. magnetic resonance imaging, magnetic resonance spectroscopy or positron emission tomography) (de Lange, 2013a; Shannon et al., 2013; Thelin et al., 2017). Brain MD is an invasive technique and pericatheter tissue damage has been reported in (pre-)clinical settings although there are no reported traumatic complications in patients (de Lange, Danhof, Zurcher, de Boer, & Breimer, 1995; Thelin et al., 2017). Furthermore, over time the MD pores can become clogged and restrict adequate dialysis of solutes or catheter dislocation may occur (> 10% in selected reports) (Thelin et al., 2017).

**Table 3**: Overview brain microdialysis properties in clinical monitoring and research applications

| Advantages | Challenges |
|---|---|
| Closest approximation of monitoring target site concentrations (unbound PK in brain ECF) | Invasive, potential peri-catheter damage<br>Expensive monitoring modality |
| High frequency sample collection<br>Temporal profile drug recovery (unbound drug concentration) for dose-response relationships | Focal area of monitoring with limited spatial resolution<br>Time consuming<br>Current application only in patients requiring invasive monitoring for clinical care |
| Concurrent monitoring of brain chemistry could serve as PD markers of drug efficacy | Non-specific binding to tubing<br>Molecule size dependent |
| Less intra-patient heterogeneity due to direct measurement of concentrations achieved | Catheter dysfunction and/or dislocation |

ECF = extracellular fluid, PD = pharmacodynamic, PK = pharmacokinetic

## PHARMACOKINETIC MODELING

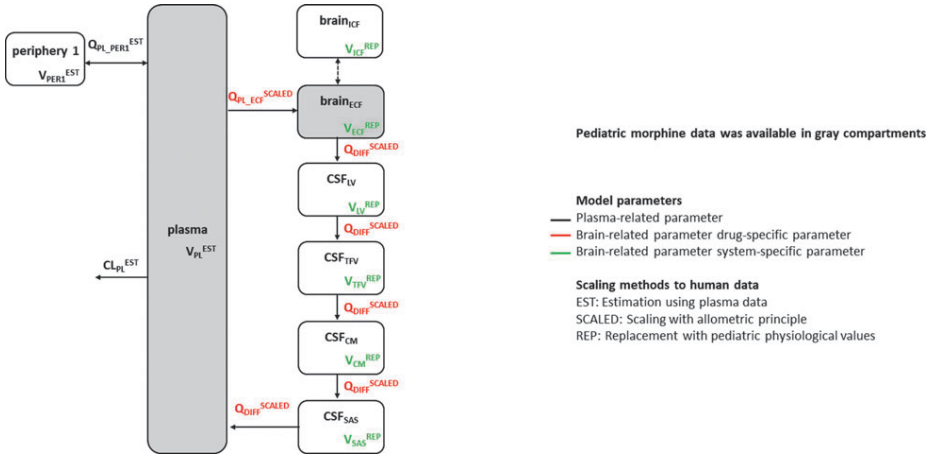
The cornerstone for improving CNS pharmacotherapy is understanding and predicting CNS drug distribution as this determines CNS target site drug concentrations, which drive drug effect. Plasma and CNS drug concentrations are required to adequately study PK processes and gain insight into variations between patient characteristics and drug properties, and interdependencies of individual PK processes. However, measurement of human CNS target concentrations is limited. Therefore, a method to predict CNS drug concentrations is crucial to further our understanding of overall drug PK and drug effect.

Translational PK models can predict drug concentrations in body compartments by using pre-clinical animal data. Physiology-based PK (PBPK) modelling is a mathematical approach which combines biological systems properties (which can vary) and drug properties (which are fixed). The biological system (e.g. the human body) has physiological variables that include volumes, surfaces, pH, and enzyme and transporter functionality of specific compartments in the system. Drug variables are properties such as logP/logD (descriptions of lipophilicity), pKa and how the drug is prescribed (dosing, formulation and route of administration).

It is the combination of the system and the drug variables that determines PK (in plasma and elsewhere in the body), in terms of absorption, distribution and clearance, and active transport. By adjusting specific values of system and drug parameters in the PBPK model, the PBPK model may be used to predict PK in all defined body compartments for that particular individual and (patho-)physiological situation (**Figure 4**). Subsequent comparison of measured and predicted drug concentrations can

validate the PBPK model, which then can be used as a PBPK model template for that drug without the need for further patient samples, as recently shown (Ketharanathan et al., 2019; Yamamoto, Välitalo, et al., 2017; Yamamoto et al., 2018).

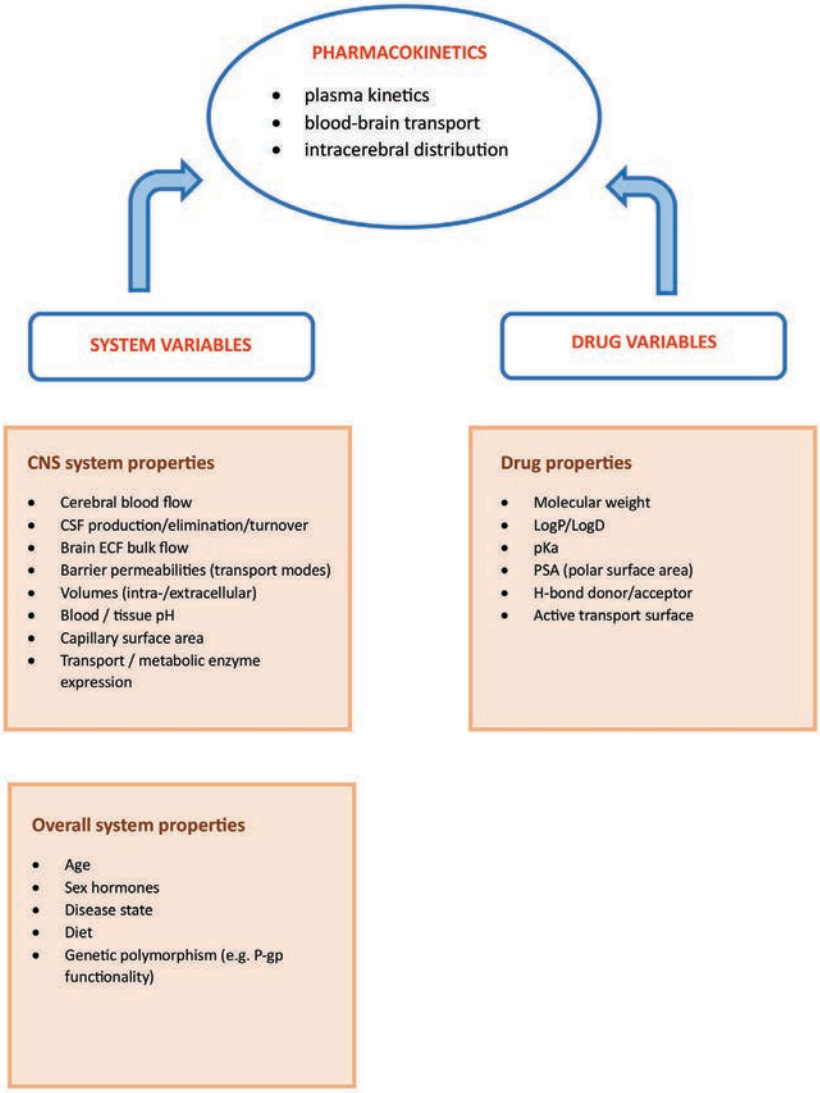
**Figure 4**: A comprehensive physiologically-based pharmacokinetic model for the CNS




A comprehensive multi-compartmental CNS physiologically-based pharmacokinetic model structure which displays various body compartments and inter-compartmental exchange mechanisms. From Ketharanathan et al Fig. 1, p. 113 of (Ketharanathan et al., 2019) with permission from the Publishers.
V = volume, CL = clearance, Q = flow, CSF = cerebrospinal fluid, CNS = central nervous system, DIFF = diffusion, EST = estimated, PL = plasma, PER = periphery, ICF = intracellular fluid, ECF = extracellular fluid, LV = lateral ventricle, TFV = third and fourth ventricle, CM = cisterna magna, SAS = subarachnoidal space.

System specific variables are multifold. Firstly, the CNS is subject to maturational differences depending on age which may influence variables like compartment weight, size or actual volume, cerebral blood flow and active transport (e.g. P-gp) and functionality (de Lange, 2013a; Figaji, 2017). Active transporter functionality can also be influenced by genetic polymorphisms. Altered P-gp functionality at the BBB, for example, can impact brain efflux activity of P-gp substrates and therefore their distribution in brain ECF (de Lange, 2013a; Hammarlund-Udenaes, Paalzow, & de Lange, 1997). Genetic variations account for a large degree of system variations in drug enzyme and transporter activities (Starkey & Sammons, 2015). Further, disease state is an important system variable as it can influence (regional) BBB and/or BCSFB integrity and cerebral blood flow. Other variables described include sex hormones, which influence cerebral circulation, and diet, which may trigger changes under specific systems conditions (de Lange, 2013a). An overview of PK (CNS) system and drug variables of importance in PK (modeling) is provided in **Figure 5**.

**Figure 5**: Overview system and drug specific properties that influence CNS pharmacokinetics




Abovementioned variations in system and drug specific variables explain the different PK of the same dose of (CNS) drug in different subjects, and can therefore lead to different effects. CNS = central nervous system, CSF = cerebrospinal fluid, ECF = extracellular fluid, P-gp = P-glycoprotein. Adapted from Yamamoto et al (2017, Fig 1, p. 892) (Yamamoto, Danhof, et al., 2017) with permission from the Publishers.

## PHARMACODYNAMICS

Pharmacodynamics (PD) describe the effect(s) of a drug on the body (Markey, 2012; Starkey & Sammons, 2015). This can be the intended effect but also a (beneficial) side effect, adverse effect, or toxicity. Ultimately the goal of (CNS) pharmacotherapy is to provide effective and safe treatment. Titrating pharmacotherapy to the individual patient is a dynamic process and challenging, especially when appreciating the variability between individuals and the heterogeneity of disease processes that influence drug PK. In TBI the primary goal is to prevent secondary injury, PD markers should therefore reflect (potential) signs of impending secondary injury. This can be on both a micro (cellular) and macro (organ system) level and serve as a guide to evaluate efficacy and safety of the drug administered.



Brain MD provides valuable PD data by concomitantly offering insight into the temporal trends of PK distribution (ECF drug concentrations) and metabolic markers indicative of oxidative stress or cellular membrane damage, particularly the lactate-pyruvate ratio (Shannon et al., 2013; Thelin et al., 2017). Other PD markers include reductions in (episodic) intracranial hypertension (Welch et al., 2016), variations in electro-encephalography (EEG) monitoring and high-frequency monitoring of physiological parameters in general (Grinspan, Pon, Greenfield, Malhotra, & Kosofsky, 2014; Le Roux et al., 2014). However, linking specific drug PK to PD in a multifactorial and dynamic disease process (such as severe TBI) with polypharmacy is a challenging process. Furthermore, one must also be aware of the role that active metabolites of a prescribed drug may have on the overall drug effect. An example is morphine-6-glucunoride (M6GG), which is an active metabolite of morphine (Ketharanathan et al., 2019). Nonetheless, advances in multimodality (neuro-)monitoring on multiple system levels (micro and macro organ function) together with high-frequency data analysis could provide the infrastructure needed to tease out drug-specific PD effects.

## APPLICATIONS TO OTHER AREAS OF NEUROSCIENCE

Brain MD is currently the only available technique to provide insight into temporal brain drug distribution closest to the target site (Ederoth et al., 2004). This is imperative in CNS drug development as it enables improved CNS drug study design by better selection of promising CNS drug candidates in an early pre-clinical phase.

A specific mention is warranted about the application of brain MD in pediatric CNS pharmacotherapy. Sampling is highly restricted in children due to medical-ethical issues and lower circulating volumes. However, extrapolation of adult drug PK data to children is inappropriate due to considerable differences in physiological development and maturation, which could potentially compromise both the efficacy and safety of

drug dosing (Figaji, 2017; Starkey & Sammons, 2015). The combination of population-based PK statistical analysis, which allows for sparse sampling per individual, and a predictive PBPK model can yield a PBPK drug template which can be adjusted to the specific individual in pediatric pharmacotherapy investigations (Ketharanathan et al., 2019; Knibbe & Danhof, 2011; Starkey & Sammons, 2015).

Other neurological pathologies which could benefit from improved CNS pharmacokinetic profiling are (refractory) epilepsy, neuro-oncology, neurodegenerative diseases, CNS infections, stroke and subarachnoid hemorrhage (Alves, Doyle, Clausen, Gilman, & Bullock, 2003; Clinckers et al., 2009; de Lange, de Vries, et al., 1995; Notkina, Dahyot-Fizelier, & Gupta, 2012; Shannon et al., 2013; Thelin et al., 2017; Ulrich et al., 2013). The differing pathophysiology of these neurological conditions demonstrates how brain MD could be applied to various ends in CNS drug development. For example, optimizing drug dosing strategies in CNS infections would benefit from information regarding the minimum inhibitory concentration (MIC) attained in the brain tissue of which the brain ECF is the closest representation. In neurodegenerative conditions, such as Alzheimer's disease, brain MD can be useful in obtaining biomarkers (apolipoprotein E) important in monitoring the response to therapeutic drug interventions (Shannon et al., 2013; Ulrich et al., 2013).

Nasally administered drugs might provide a direct route into the CNS target site which is non-invasive yet enhances CNS target site bioavailability and CNS drug selectivity (Bahadur & Pathak, 2012). Brain MD could provide insight into target-site concentrations of nasally administered substances (Ruigrok & de Lange, 2015; Stevens, Suidgeest, van der Graaf, Danhof, & de Lange, 2009). Further, brain MD can also facilitate CNS drug delivery to focal lesions by means of retrodialysis, a process whereby the MD catheter is used to deliver a substance to the brain ECF (Jalloh et al., 2017; Thelin et al., 2017).

Finally, the invasive nature of brain MD is an important barrier as it is not routine clinical care for most patients requiring CNS pharmacotherapy and thus limits the number of patients from whom samples can be obtained. Population-based PK statistical analysis can provide a solution by still providing the opportunity to develop a PBPK model. Furthermore, the focal nature of monitoring is a limitation. However, it is possible to monitor the CSF compartment with MD by inserting the MD catheter via an external ventricular drain into the ventricular CSF compartment. This enables a higher temporal resolution of metabolite and drug level measurements in CSF in a larger group of patients, although there are concerns about the sensitivity due to the relatively large size of the measured compartment and high CSF turnover rate (approximately four times a day) (de Lange, 2013b; Thelin et al., 2017).

Increased knowledge of CNS (unbound) drug distribution by means of brain MD together with PBPK modelling plays a crucial part in enabling prediction of CNS drug concentrations. This will ultimately facilitate the development of patient-specific CNS therapies and precision medicine. To this end, close collaboration is necessary between preclinical and clinical investigations, multi-modality monitoring and the provision of platforms for data-sharing given the urgent need for improved CNS therapies.

## Mini-Dictionary of Terms

- Biophase: the site in the body where the drug exerts its effect
- In vitro: the process(ses) that are studied or take place outside a living organism
- In vivo: the process(ses) that are studied or take place in a living organism
- Microdialysis: a technique that measures extracellular soluble molecules from the interstitial space of body tissue (so-called extra-cellular fluid, ECF) through a semipermeable membrane
- Pharmacokinetics: describes the processes a drug undergoes in the body and which can be subdivided into absorption, distribution, metabolism and elimination.
- System: refers to the biological system of a PBPK model, such as the animal or human body.
- Physiologically based pharmacokinetic model: a pharmacokinetic model that is based on the parameters of the drug and the physiological system (e.g. animal), and that can be translated to another system's parameters (e.g. of human).
- P-glycoprotein (P-gp): a transporter in the brain that actively pumps a substance out of the brain (efflux). Also termed multidrug resistance protein (MDR-1).
- Pharmacodynamics: describes the effect of the drug on the body in terms of efficacy and safety
- Retrodialysis: the ability to deliver a substance via the microdialysis catheter when the molecule concentration is higher in the perfusate than in the extracellular fluid.

## Key Facts of brain microdialysis and applications to drug therapy in traumatic brain injury

- Knowledge of CNS drug pharmacokinetics at the target site is crucial to CNS drug development as blood plasma pharmacokinetics cannot be extrapolated due to the unique barrier and transport characteristics of the CNS.
- CNS drug pharmacokinetics are governed by multiple system and drug specific properties and their dynamic interplay.
- Brain microdialysis is currently the only modality available to measure temporal concentration profiles of drugs in the extracellular fluid of the brain.
- Brain microdialysis can be used to perform feasibility studies of CNS drug candidates in humans prior to extensive and costly clinical trials.
- Physiologically-based pharmacokinetic (PBPK) modelling is an approach to combine system and drug variables, translate preclinical data to humans and predict CNS drug target concentrations.

- Genetic polymorphisms of BBB transporters (P-gb in particular) need specific consideration in CNS PK studies and explain a large degree of inter-individual observed PKPD variability.
- Pediatric CNS pharmacology is an important subgroup in CNS drug development that could benefit from improved understanding of CNS system physiology and CNS drug PK by means of brain MD due to significant developmental and maturational differences compared to adults.

## SUMMARY POINTS

- CNS drug distribution is the result of the interplay between system variables such as blood-brain and blood-CSF barrier, brain tissue and fluid space anatomy characteristics, patient-specific (patho-)physiological processes, as well as drug-specific properties.
- The dynamic combination of drug-specific properties and patient-specific variables determines drug concentrations in specific CNS regions, including the unbound concentrations at the target site, which drives drug effect.
- The major advantage of brain microdialysis is that it represents the only modality that can measure unbound drug concentrations in the brain ECF in a temporal manner. This enables compilation of a temporal PK profile of a drug.
- A potential disadvantage of brain microdialysis is the focal nature of sampling in the context of a heterogeneous disease such as severe TBI. Inclusion of more global diagnostic modalities such as MRI/MRS or PET scan can improve overall understanding of CNS drug distribution.
- PBPK modelling facilitates PK investigations by predicting CNS drug concentrations and thus enables CNS PK drug analysis without the need for multiple, repeated patient samples.
- The application of brain MD in the context of CNS drug therapy allows improved characterization of CNS drug PK of various CNS pathologies (TBI, neuro-oncology, CNS infections and neuro-degenerative diseases) which could ultimately lead to individualized pharmacotherapy with the aid of PBPK modelling

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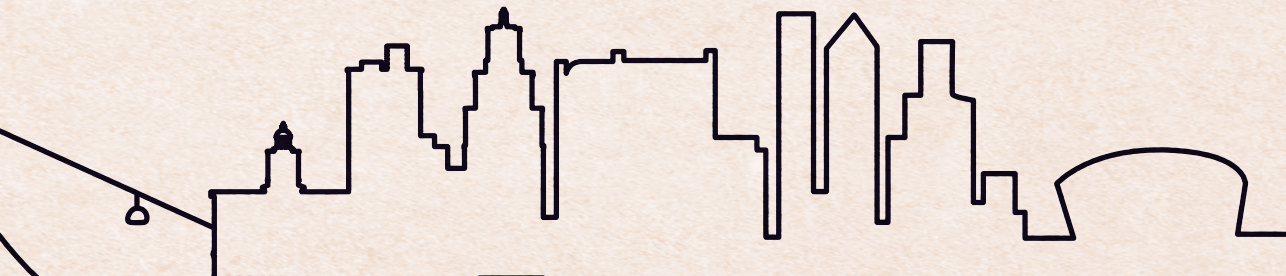
# PART II

# Pharmacotherapy in pediatric severe TBI



# 4

# Combining brain microdialysis and translational pharmacokinetic modeling to predict drug concentrations in pediatric severe traumatic brain injury: the next step towards evidence-based pharmacotherapy?

**Naomi Ketharanathan N, Yumi Yamamoto, Ursula Rohlwink, Enno Wildschut, Ron Mathôt, Elisabeth de Lange, Saskia de Wildt, Andrew Argent, Dick Tibboel, Anthony Figaji**

***J Neurotrauma*** *2019; 36(1): 111-117*

## ABSTRACT

Evidence-based analgosedation in severe pediatric traumatic brain injury (pTBI) management is lacking and improved pharmacological understanding is needed. This starts with increased knowledge of factors controlling the pharmacokinetics (PK) of unbound drug at the target site (brain) and related drug effect(s). This prospective descriptive study tested a pediatric physiology-based pharmacokinetic software model by comparing actual plasma and brain extracellular fluid ($brain_{ECF}$) morphine concentrations with predicted concentration time profiles in severe pTBI patients (Glasgow Coma Scale ≤ 8).

Plasma and $brain_{ECF}$ samples were obtained after legal guardian written consent and were collected from eight pTBI patients (75% male, median age 96 months [34 – 155.5], median weight 24 kg [14.5-55]) with a need for intracranial pressure monitoring (GCS ≤ 8) and receiving continuous morphine infusion [10 - 40 mcg/kg/hour]. $Brain_{ECF}$ samples were obtained by microdialysis. $Brain_{ECF}$ samples were taken from 'injured' and 'un-injured' regions as determined by microdialysis catheter location on computed head tomography. A previously developed physiology-based software model to predict morphine concentrations in the brain was adapted to children using pediatric physiological properties. The model predicted plasma morphine concentrations well for individual patients (97% of data points within the 90% prediction interval). In addition, predicted $brain_{ECF}$ concentration-time profiles fell within a 90% prediction interval of microdialysis $brain_{ECF}$ drug concentrations when sampled from an *'un-injured'* area. Prediction was less accurate in *'injured'* areas.

This approach of translational physiology-based PK modeling allows prediction of morphine concentration-time profiles in 'un-injured brain' of individual patients and opens promising avenues towards evidence-based pharmacotherapies in pTBI.

## INTRODUCTION

As trauma continues to be a leading cause of mortality and morbidity worldwide, research into effective and safe therapies is imperative to improve patient outcome.[1] Analgosedation plays a crucial role in the supportive therapy of traumatic brain injury (TBI); however, evidence-based guidelines are lacking in both adults and children.[2,3] The latter is especially disturbing as this concerns a vulnerable population still undergoing brain development. The significant physiological and anatomical changes that take place, especially until the age of 8 years, emphasize why extrapolation of studies from adult populations does not suffice and could even be detrimental in children.[4]

In pharmacological terms, it is imperative one first understands the *pharmacokinetics* (PK) of a drug, i.e. 'what the body does to the drug' in terms of absorption, distribution, metabolism and elimination. These processes are influenced by the half-life of the drug, the volume of distribution and total body clearance. The net effect results in a dose and time dependent drug concentration in a certain body compartment. The following step in pharmacological research is to correlate drug concentration (PK) to drug effect or *pharmacodynamics* (PD; i.e. 'what the drug does to the body').[5] As analgosedative drug effects are related to the unbound drug concentration at the site of action (i.e. the brain as target site), knowledge of unbound brain concentrations in TBI patients could help predict drug effect(s).[6,7] To date, such information is limited. Innovative developments in the field of preclinical and clinical pharmacology research are promising and provide tools which could be utilized to improve our pharmacological understanding of commonly used drugs in (pediatric) TBI.

In the clinical setting, measuring drug concentrations in the human brain is challenging. However, parenchymal microdialysis catheters as part of clinical brain monitoring in severe TBI patients allows high frequency sampling of the brain extracellular fluid ($brain_{ECF}$).[3,8] This enables the acquisition of data on unbound drug concentrations in the $brain_{ECF}$,[7,9,10] while human plasma drug concentrations can be obtained by serial blood sampling. In the context of this article, it must be emphasized that $brain_{ECF}$ refers to the interstitial brain fluid, not cerebrospinal fluid, and reflects the closest representation of *intra*cellular brain fluid which ultimately is the target site for drug action.

Acquiring sufficient plasma samples for pharmacological research can be challenging in the pediatric population due to lower circulating volumes. An approach to solve this issue is population-based PK analysis that uses the often sparse samples of various individual patients and analyzes them as a single 'population' (after taking covariates such as age, weight, renal function and severity of illness into account). This approach provides sufficient data points to develop a drug-specific PK model which can subsequently be used as a template for that drug in the individual patient. The identification of covariates improves the model fit per patient and explains PK

differences between individual patients.[11 12] This approach (top-down) does not take into account our knowledge on physiology parameters (e.g. blood flow, organ sizes, drug metabolism enzyme activity, renal function, blood brain barrier function) which could be used to predict drug concentration in previously unstudied populations. The approach presented in this study: physiology-based modeling (bottom-up) has increasingly been used and has been approved by the European Medicines Agency and the USA Federal Drug Agency to extrapolate adult and/or animal pharmacokinetics to children after adapting them to pediatric physiological parameters.

A physiology-based, multi-compartmental PK model that was recently developed on the basis of preclinical data in the rat allowed prediction of drug concentrations in multiple brain compartments for 9 highly diverse compounds (including: morphine, acetaminophen, phenytoin and methotrexate).[13] Replacement of rat with human brain physiological parameter values in the model allowed prediction of the brain PK, i.e. unbound drug concentrations, of each of the 9 compounds in multiple brain compartments for adult humans.[13] Using the same approach, we hypothesized that it would be possible to adapt this physiology-based PK model to the *pediatric* human brain and predict unbound drug concentrations in $brain_{ECF}$. This is the first step in pharmacological research: finding a method to adequately predict specific drug concentrations at the target site (in this case: the brain) which can then be correlated to pharmacodynamic parameters in the clinical setting.



The aim of our study was to determine if the physiology-based pediatric brain PK model could adequately predict actual plasma and $brain_{ECF}$ unbound morphine concentrations obtained from pTBI patients.

If successful, this approach could ultimately lead to predicting brain PK profiles in individual pTBI patients.[10 13 14] This is a novel and promising approach in pharmacological TBI research, especially for children, as it could ultimately lead to more evidence-based and tailored TBI treatment.

## MATERIALS AND METHODS

### Study design and population

This was a single center, prospective, descriptive pilot study performed in the pediatric intensive care unit (PICU) of Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa from March 2014 until April 2015. Patients admitted with severe TBI (aged 0 – 13 years, GCS≤ 8, requiring invasive neuromonitoring) were eligible for inclusion. Standard care for pediatric TBI patients at this institution consisted of intracerebral monitoring of intracranial pressure and brain oxygenation. In general, patient care was directed by a local algorithm based on the current recommendations

for the management of severe TBI in children, including intracranial pressure (ICP), cerebral perfusion pressure (CPP) and brain oxygenation ($PbtO_2$) targets.[15] Microdialysis was being used for clinical monitoring of brain metabolism by the bedside. Specifically, metabolites such as lactate, pyruvate, glucose, glycerol and glutamate were analyzed hourly by the bedside and were used to adapt clinical care based on temporal changes. Exclusion criteria were no parental/legal guardian written informed consent, severe hemorrhagic disease as contraindication for intracerebral monitoring and unavailability of microdialysis consumables or expertise. This study was initiated after approval from the University of Cape Town's Human Research Ethics Committee (HREC reference 060/2011). The study protocol complied with the Declaration of Helsinki (2013).

## Clinical data collection

Data collection included age, estimated weight, gender and mechanism of injury. Pharmacological data collected included morphine infusion concentration and rate as well as timing and dose of morphine boluses. Intracerebral catheters are routinely placed (by the neurosurgical team) in the frontal white matter away from known areas of contusion and damage. Radiological findings were recorded and the position of the microdialysis catheter was noted on follow up head computed tomography (CT) scans and its location relative to any contusions (i.e. 'injured brain'). Typically all patients have a globally diffuse brain injury: however, areas close to contusions may demonstrate differing blood brain characteristics. For these reasons we defined the position of the catheter, based on the CT scans as follows: 'Un-injured' brain referred to positioning in diffusely injured brain with no visible contusion close to the catheter; 'injured' brain referred to positioning near to a contusion.[9 16] Note that these terms are relative. Finally, the duration of PICU and hospital stay were collected.

## Sample collection

Plasma samples were retrieved from remnant blood taken during routine laboratory rounds. A minimum volume of 0.5 mL was required, which was immediately centrifuged at 4000 rpm for 5 minutes to obtain plasma, which was separated from the precipitate. Brain microdialysis catheters were placed in the brain parenchyma via a separate burrhole at the time of ICP monitoring. We used M Dialysis 71 High cut-off brain microdialysis catheters (shaft diameter 0.9 mm, pore size 100kDa) with a bedside CMA 106 pump infusing sterile and artificial CNS perfusion fluid at a set flow rate of 0.3 µL/min (M Dialysis, Sweden). Microdialysate was collected hourly in capped microvials. When hourly dialysate was less than 10 µL, the time interval between vial change was increased to two hours to guarantee this minimum volume for drug concentration analysis. $Brain_{ECF}$ and plasma samples were frozen at -80 degrees Celsius until drug analysis was performed.

### Analysis of concentrations in plasma and dialysate

Drug concentrations in plasma and microdialysate were determined at the clinical pharmacology laboratory of the Academic Medical Center in Amsterdam, The Netherlands. Morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations were analyzed using LC-MS/MS in the positive ionization mode on a Shimadzu LC-30 (Nishinokyo-Kuwabaracho, Japan) system coupled to an AB SCIEX 5500 QTRAP mass spectrometer (Framingham, MA, US). To 10 µL of sample, 75 µL acetonitril/methanol 84:16 (v/v%) containing the internal standard morphine-d3, morphine-3-glucuronide-d3 and morphine-6-glucuronide-d3 was added to precipitate proteins. Samples were vortexed, stored at -20 degrees Celsius for 30 minutes, vortexed again and centrifuged. For the determination of morphine, morphine-3-glucuronide and morphine-6-glucuronide, 3 µL was injected onto a Thermo Scientific Hypersil Gold HILIC (50x 2.1mm, 1.9 µm) column. A stepwise chromatographic gradient was applied using acetonitril and water with a constant 5% addition of 1% ammonium formate / 2% formic acid in water. The flow was 600 µL/min for the HILIC method, column-oven temperature was 40 degrees Celsius. Morphine, morphine-3-glucuronide and morphine-6-glucuronide were measured as [M+H+], using the mass transition of 286.1/165.1, 462.2/286.2 and 462.2/286.2 respectively. The method was validated over a range of 2 to 500 ng/mL. The accuracies ranged from 93.5% to 105.5%, the intra-day precisions were below 9.6% and the inter-day precisions were below 12.9%.



### Translational modeling methods

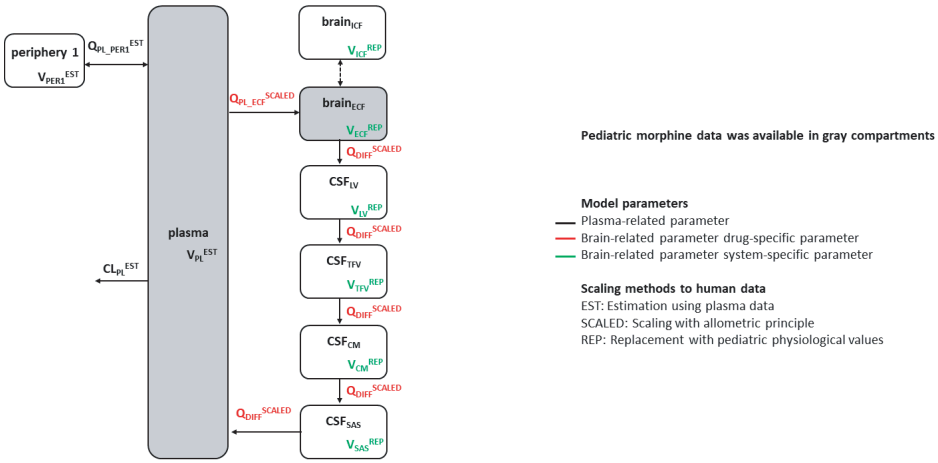
A physiology-based PK model consists of 3 parts that each contain variables which can be measured and entered into the model. These are variables from the 'system' (i.e. the biological system, such as the human body, and relate to weight and age), plasma variables (i.e. the measured concentration of drug in the blood which is influenced by plasma volume and rate of clearance) and finally variables concerning the drug itself (i.e. drug dosing, drug characteristics such as lipophilicity which influence diffusion characteristics). Subsequently, modeling assumptions are made to predict how the drug will spread to other compartments in the body (or 'system') such as the brain. These assumptions are based on the expected volume of these (brain) compartments and factors that govern drug distribution and clearance (i.e. brain transport mechanisms). The validity of the physiology-based PK model can be tested by comparing prediction to observed concentrations. If these correlate, then the PK model can be used as a template for that specific drug.

The previously published physiology-based multi-compartmental brain PK model used in this pilot study was based on healthy rat central nervous system (CNS) physiological parameters and PK information of multiple CNS compartments.[13] The CNS compartments in this model encompassed brain extracellular and intracellular fluid (ECF and ICF respectively) and the cerebrospinal fluid (CSF) compartments of the lateral ventricle (LV), third- and fourth ventricle (TFV), cisterna magna (CM) and

subarachnoid space (SAS). This model was developed and subsequently translated to humans (adults) for 9 compounds, including morphine. The details of the model structure and translational methods are described in Yamamoto et al.[13]

Ultimately, the $brain_{ECF}$ can be seen as the best representation of the target site for drug therapy, as sampling of human *intra*cellular fluid ($brain_{ICF}$) is not feasible. Therefore, the Yamamoto generic multi-compartmental CNS distribution model was translated to predict morphine plasma and $brain_{ECF}$ concentrations for each *pediatric* patient in four steps: 1) development of a plasma PK model using individual plasma PK data; 2) replacing system-specific parameters by individual pediatric patient's values (e.g. age and weight), 3) applying allometric scaling to the drug-specific parameters, and 4) predicting the $brain_{ECF}$ concentrations using estimated human plasma PK parameters, replacing system-specific parameters and scaling drug-specific parameters. The specific parametric scaling is detailed in supplement A. The scaling method of each parameter (plasma-, drug- or system specific) is indicated with color coding and the entire model is illustrated in **Figure 1**. Simulation was performed using NONMEM version 7.3 (ICON Development Solutions, Hanover, MD, USA). The plots were conducted using R (R Foundation for Statistical Computing, Vienna, Austria). This approach enabled prediction of $brain_{ECF}$ morphine concentrations for each individual pTBI patient, based on a few individual plasma data points. The predicted morphine $brain_{ECF}$ concentrations could then be visually compared to the observed morphine $brain_{ECF}$ concentrations.

**Figure 1.** The multi-compartmental brain pharmacokinetic model structure




V = volume, CL = clearance, Q = flow, CSF = cerebrospinal fluid, DIFF = diffusion, PL = plasma, PER = periphery, ICF = intracellular fluid, ECF = extracellular fluid, LV = lateral ventricle, TFV = third and fourth ventricle, CM = cisterna magna, SAS = subarachnoidal space

### Statistical analysis

This study was descriptive with exploratory aims (no interventions yielding comparison of patient groups) and as such no formal power analysis was performed. Given the small study population, clinical data are presented as median with range and categorical variables presented as proportions (%).

## RESULTS

Eight patients were included in this pilot study during the one year study period. The median age was 8 years (range 2,8 to 13), median weight 24 kilograms (range 14.5 to 55) and 75% were male. All patients survived to hospital discharge. Morphine infusion was commenced on admission to the PICU as per local protocol. **Table 1** provides an overview of the patient characteristics.



**Table 1.** Patient characteristics

| Patient | Age (years) | Gender | Weight (estimated kg) | Injury mechanism | Morphine infusion range (mcg/kg/hour) | PICU LS (days) | HLS (days) |
|---|---|---|---|---|---|---|---|
| 1 | 4.2 | M | 16 | Pedestrian – MVA | 20 – 40 | 23 | 35 |
| 2 | 9.5 | F | 28 | Pedestrian – MVA | 20 – 40 | 30 | 48 |
| 3 | 8.3 | M | 26 | Gunshot | 20 – 40 | 11 | 18 |
| 4 | 3.5 | F | 15 | Gate crush | 0 – 40 | 6 | 8 |
| 5 | 13 | M | 30 | Passenger – MVA | 20 – 40 | 7 | 15 |
| 6 | 7.7 | M | 22 | Pedestrian - MVA | 20 – 40 | 6 | 8 |
| 7 | 2.8 | M | 14.5 | Pedestrian - MVA | 10 – 40 | 6 | 22 |
| 8 | 11.7 | M | 55 | Pedestrian - MVA | 0 - 40 | 2 | 5 |

PICU LS = PICU length of stay, HLS = Hospital length of stay, MVA = motor vehicle accident

**Table 2** describes the various intracerebral injuries of the head CT scan at admission to hospital and the positioning of the MD catheter.

**Table 2.** Overview of intracerebral injuries on admission head CT scan and MD catheter position

| Patient | CT scan on admission | MD catheter location | MD sample location |
|---|---|---|---|
| 1 | Left frontal lobe hemorrhage, intraventricular bleeding and subarachnoid hemorrhage | Right frontal lobe | 'un-injured' |
| 2 | Subarachnoidal bleeding, contusions, intraventricular bleeding and generalized swelling | Right frontal lobe | 'un-injured' |
| 3 | Right parietal subdural hematoma (max. 7 mm) with right hemispheric swelling and midline shift to left (max 10 mm) | Right frontal lobe | 'injured' |
| 4 | Right fronto-parietal subdural hematoma (max. 7 mm), left frontal hemorrhagic contusion, midline shift to left (4 mm) with cerbral edema (R>L) | Left frontal lobe | 'un-injured' |
| 5 | Right frontal lobe hemorrhagic contusion, generalized swelling | Right frontal lobe | 'injured' |
| 6 | Small punctate hemorrhagic contusions at right grey-white matter interface, suggestive of DAI | Right frontal lobe | 'injured' |
| 7 | Diffuse axonal injury, subarachnoidal bleed and interventricular bleed | Right frontal lobe | 'injured' |
| 8 | Small frontal subdural hematoma | Right frontal lobe | 'injured' |

CT = computed tomography, MD = microdialysis, DAI = diffuse axonal injury

## MICRODIALYSIS BRAIN$_{ECF}$ SAMPLING

### Feasibility

The first step of this study was to determine whether brain$_{ECF}$ sampling with microdialysis for analysis of brain$_{ECF}$ morphine concentrations was feasible in pTBI patients. We were able to determine morphine concentrations in low-volume microdialysis samples (volume ≥ 10 µL) as detailed in the Methods section. It was necessary to adjust the brain$_{ECF}$ sampling time from one to two hours in 5 patients to obtain the minimum volume of 10 µL (patients 1, 2, 4, 5 and 6).

Of the 8 patients included in this study, we were able to use 6 patient's data to investigate the translated multi-compartmental brain pharmacokinetic model: in one patient the MD catheter failed to yield dialysate, in another no blood samples were collected and no further modeling was possible. The total duration of brain

microdialysis sampling for morphine PK varied per patient with a median collection time of 90 hours (n = 6, range 57 to 128 hours). **Table 3** illustrates the number of samples collected per patient and the median unbound morphine concentration in blood and brain$_{ECF}$.

**Table 3.** Overview of patient samples and unbound morphine concentrations

| Patient | Blood samples | Brain$_{ECF}$ samples | Unbound morphine concentration blood | Unbound morphine concentration brain$_{ECF}$ |
|---|---|---|---|---|
| | (n) | (n) | (µg/L) | (µg/L) |
| 1 | 11 | 31 | 43,6 [18,8 – 60,2] | 13,1 [1,0 – 17,5] |
| 2 | 5 | 15 | 36,5 [31,1 – 40,1] | 6,7 [2,6 – 8,8] |
| 3 | 1 | 0 | 3,5 | NA |
| 4 | 5 | 19 | 47,6 [22,3 - 209] | 6,9 [2,1 – 13,1] |
| 5 | 4 | 11 | 7,6 [7,5 – 7,7] | 6,8 [2,1 – 19,7] |
| 6 | 5 | 23 | 26,5 [16,6 – 53,9] | 15,0 [10 – 37,5] |
| 7 | 4 | 29 | 30,7 [21,1 – 32,4] | 3,6 [2,4 – 6,9] |
| 8 | 0 | 4 | NA | 33,7 [28,7 – 42,3] |

The unbound morphine concentrations are demonstrated as the median concentration and [range].
NA = not applicable, n = number of samples

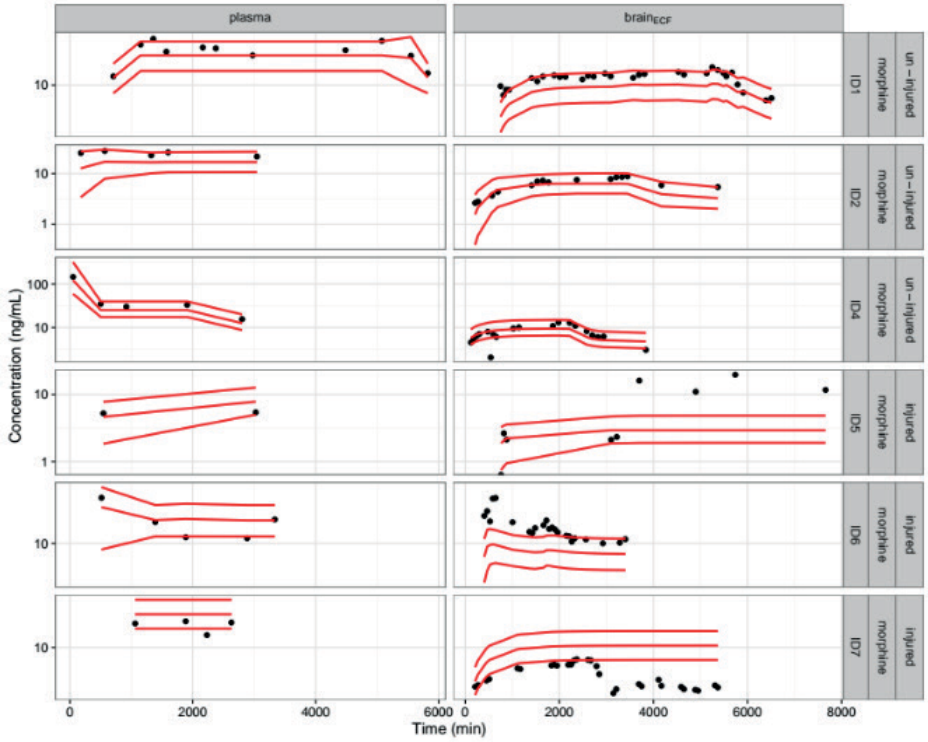


## PHYSIOLOGY-BASED PK MODELING

### Comparison of predicted and observed pediatric morphine concentrations

The plasma PK parameters were estimated with good precision and the developed plasma PK model described pediatric plasma PK of morphine well in all patients, with 97% of the morphine plasma sample concentrations falling within the 90% prediction interval (**Figure 2**). As for the brain$_{ECF}$ morphine concentrations, the model captured the observed values more accurately (i.e. within the 90% prediction interval) when sampling was from relatively 'un-injured' brain (patients 1, 2 and 4).This was not the case for brain$_{ECF}$ morphine concentrations sampled from relatively more injured brain regions (patients 5, 6 and 7). Plotting of the measured concentrations in the 90% prediction interval for these patients, demonstrated diverse patterns ranging from diffuse scattering to a trend on the upper or lower limit respectively.

**Figure 2:** Observed vs. predicted morphine concentrations in plasma and brain$_{ECF}$




The red lines represent the 5th, 50th and 95th percentile respectively of predicted morphine concentrations for that specific patient. The black dots represent the observed morphine concentrations over time. ECF = extracellular fluid.

## DISCUSSION

This study demonstrates that collecting brain$_{ECF}$ samples to determine drug concentrations is possible in pTBI patients. Using these data we also show that a physiology-based PK model can be used to adequately predict morphine concentrations in plasma and brain$_{ECF}$ in the 'un-injured' brain regions of pediatric TBI. The importance of this finding is that it enables prediction of morphine PK in the target site (i.e. the brain) and holds the potential of developing a model-based approach from which further research into evidence-based pharmacotherapy in (pediatric) TBI is possible.

Analgosedation is one of the pillars of supportive therapies in protocols for TBI and other acute brain injury conditions worldwide.[2 3 17] Frequently used drugs include midazolam, pentobarbital, fentanyl, morphine, and propofol with the aim of providing adequate sedation to reduce secondary brain injury and relieve pain and anxiety.

However, evidence-based dosing regimens are lacking, which raises concerns about efficacy and safety of drugs currently used, due to under- and overdosing. Current guidelines provide level 2 (adults) and level 3 (children) evidence at best and, although disturbing, it is no surprise the recommendation still reads: *"...the choice of sedative, analgesics and neuromuscular blocking agents ...should be left to the treating physician"*.[3] Inevitably, this leads to diverse analgosedation regimens in TBI patients dependent on clinician experience and preference. This is often guided by the effect on hemodynamic stability, further hampering constructive comparison of such treatment regimens. Furthermore, there is a general paucity of pharmacokinetic and pharmacodynamic understanding of the CNS drugs at target sites.[10] These factors, together with ongoing poor outcome post-TBI and the high failure rate in CNS drug development, have sparked renewed interest in unraveling the mechanisms of drug passage across the blood-brain-barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) to improve our pharmacological understanding and ultimately develop evidence-based, adequate therapies.[7 9 10 14 18 19] Combining innovative techniques from both preclinical and clinical research enables us to take the next step in determining PK properties of commonly-used drugs and holds the promise of developing individualized analgosedation.



As a future implication of our data, it will be feasible to use a translated ('humanized') preclinical multi-CNS compartment PK model, combined with population-based PK statistical analysis, to develop a pediatric template for prediction of morphine PK in $brain_{ECF}$. In addition, our findings underline the necessity of knowledge about $brain_{ECF}$ morphine concentrations to understand morphine PK in total. This pilot study shows that a given drug dose with similar plasma morphine concentration can lead to *different* brain morphine levels dependent on whether the $brain_{ECF}$ sampling was from 'injured' of 'un-injured' brain. This confirms the important role of BBB and BCSFB drug passage mechanisms in drug distribution at the target site of the brain as other covariates (such as weight and age) are accounted for in the model.

The successful development and validation of a physiology-based PK model could enable further pharmacological research without the need for large patient numbers requiring invasive procedures and numerous samples per patient. This is important because microdialysis studies, particularly in children, are rare. These are currently some of the obstacles that are especially relevant in pediatric pharmacological research and account for the paucity of evidence-based drug dosing data in this patient group. If using the physiology-based PK model as a template for predicting pediatric morphine PK profiles is successful in linking brain PK to pharmacodynamics (PD), it may open new avenues for determining evidence-based dosing regimens for other analgosedative drugs in (pediatric) TBI.

## Limitations

There are various limitations and learning points from this study. This is a small patient group from a single center. Larger patient numbers, included from multiple centers, would be necessary to further validate this (pediatric) morphine PK model. Furthermore, this pilot study focuses solely on drug PK and as such, no assumptions can be made about clinical outcome measures (PD) at this stage.

The pooling of samples over two-hour intervals could be seen as a suboptimal measurement, yet the overall trend is important, which in general remained within the 90% predicted interval for samples derived from relatively 'un-injured' brain. The median duration of sampling was 90 hours in this pilot study. Given the natural history of secondary brain injury, which evolves over the course of days, it is of interest to assess whether the currently observed correlation between model prediction and measured drug concentrations remains consistent over time due to changes in blood-brain-passage mechanisms secondary to variations in brain swelling and evolving infarction. Furthermore, biofouling of the MD catheter membrane (e.g. clogging of the membrane pores) within 5 days potentially affects catheter recovery rate, which may affect sample integrity. These are some mechanisms that might influence sampling and the $brain_{ECF}$ morphine concentrations over time and need further investigation.

The distinction between 'un-injured' and 'injured' brain is relative, given the global nature of traumatic head injury, but is a well-established practice in microdialysis TBI studies for brain chemistry.[9 16] The reason for this distinction was to determine how accurate the physiology-based PK model was as this is currently based on 'un-injured' animals. Contusions and peri-contusional regions of the traumatized brain may behave in a dysregulated manner in which regulatory mechanisms affecting hemodynamic and BBB characteristics are different from 'un-injured' brain. We hypothesized the physiology-based PK model would therefore provide better prediction of those samples collected from relatively 'un-injured' brain which seemed to be the case as illustrated in **figure 2**. This finding is in accordance with the $brain_{ECF}$ morphine concentrations found in adult TBI patients by Ederoth et al. which demonstrated both lower and higher $brain_{ECF}$ morphine concentrations in 'injured' brain compared to relatively 'un-injured' brain.[20] Their suggestion was that the injured brain shows altered efflux mechanisms and BBB permeability for morphine. In our study, patients 5, 6 and 7 had values above and below the outer percentiles for observed vs. predicted cerebral morphine concentrations. This may be the result of a new balance between BBB in- and efflux mechanisms and permeability as a result of localized brain injury. This finding is important as it demonstrates that only measuring drug plasma levels can over- or underestimate drug levels in the brain. Subsequent PKPD studies could lead to misinterpretations of drug efficacy and safety, if only *plasma* PK is taken into account in pharmacological studies that focus on clinical outcome measures such as depth of sedation and pain control. In addition, it also demonstrates that the current

physiology-based PK model dose not fully capture the local PK changes that take place in injured brain. Therefore, it is important to translate this physiology-based PK model for injured brain by changing system-specific parameter values according to alterations in injured brain. Hypothetically, this could enable better prediction of morphine PK in injured regions. However, potential regional differences in cerebral drug target site concentrations within patients raise the question of what the focus for adequate drug dosing should be (i.e. injured vs. un-injured brain). This is similar to questions about targeting physiological parameters in clinical care.

Finally, we have only focused on predicted and observed morphine concentrations in this pilot study. It is imperative to also determine if (active) metabolites of morphine, such as morphine-6-glucunoride (M6G), can be predicted accurately. This is of importance for future PKPD modeling. Preliminary data, not presented in this paper, show that it is possible to determine morphine metabolites in both blood and brain$_{ECF}$ in pediatric TBI.



Future steps towards compiling an evidence-based dosing regimen for morphine in pediatric TBI patients include adding other centers in data acquisition to validate the physiology-based PK model. In addition, a physiology-based PK model for 'injured' brain will be developed to assess whether this predicts drug concentrations from 'injured' brain more precisely. Once the physiology-based PK model has been validated, the next step will be to compile a PD profile for morphine with the aid of multimodal neuromonitoring.[8] This approach will enable defining more PD markers such as brain-oxygenation levels, lactate/pyruvate ratio and the presence of seizures which together with ICP may better reflect local dynamics of cerebral blood flow and metabolic demand as well as establish both efficacy and safety of CNS drugs used in (pediatric) TBI.

## CONCLUSION

Level 1 evidence-based dosing regimens for commonly used drugs in analgosedation in pediatric TBI currently do not exist. Modalities such as brain microdialysis combined with physiology-based PK modeling and population-based PK statistical analysis are promising tools in designing a PK template for a variety of drugs that could assist in developing evidence-based dosing strategies for effective and safe therapy in vulnerable patient groups. Our data demonstrate the feasibility of this concept and warrant further studies, which are currently in progress.

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# 5

# A Population Pharmacokinetic Model of Pentobarbital for Children with Status Epilepticus and Severe Traumatic Brain Injury

**Naomi Ketharanathan N*, Anastasia Lili*, Julia Penning de Vries, Enno Wildschut, Matthijs de Hoog, Brenda de Winter*, Birgit Koch***

* authors contributed equally

***Submitted***

## ABSTRACT

### Background
Pentobarbital pharmacokinetics (PK) remain elusive and the therapeutic window narrow. Administration is frequent in critically ill children with refractory status epilepticus (SE) and severe traumatic brain injury (sTBI).

### Objectives
To investigate pentobarbital PK in SE and sTBI patients admitted to the pediatric intensive care unit (PICU) with population-based PK modelling and perform dosing simulations.

### Methods
To develop a population PK model with non-linear mixed-effects modeling (NONMEM®) with retrospective data from 36 patients (median age 1.3 years; median weight 10 kg; 178 blood samples) treated with continuous intravenous pentobarbital. An independent dataset was used for external validation (n=4). Dosing simulations were performed with the validated model to evaluate dosing regimens.

### Results
A one-compartment PK model with allometrically scaled weight on clearance, (CL; 0.75) and volume of distribution (Vd; 1) captured data well. Typical CL and Vd values were 3.59 L/h and 142 L respectively. Elevated serum creatinine and C-Reactive Protein (CRP) levels significantly correlated to decreased CL, explaining 84% of interpatient variability, and were incorporated in the final model. External validation using stratified visual predictive checks showed good results. Simulations demonstrated patients with elevated serum creatinine and CRP failed to achieve steady state yet progressed to toxic levels with current dosing regimens.

### Conclusions
The one-compartment PK model of intravenous pentobarbital described data well and demonstrated serum creatinine and CRP significantly correlated with pentobarbital CL. Dosing simulations formulated adjusted dosing advice in patients with elevated creatinine and/or CRP. Prospective PK studies in combination with pharmacodynamic endpoints, are imperative to further optimize pentobarbital dosing in terms of both safety and clinical efficacy in critically ill children.

## KEY POINTS

- Pentobarbital demonstrates high PK variability which is challenging in the clinical context given its narrow therapeutic window which serves mainly to prevent toxicity than it does to achieve efficacy.
- The population-based pentobarbital PK model demonstrated that creatinine and C-reactive protein significantly influence pentobarbital clearance in critically ill children with SE and sTBI and could explain the majority of the variability. The significance of creatinine as a marker of renal function or overall severity of illness requires further prospective investigation.
- Dosing simulations with the population-based pentobarbital PK model suggest weight-based dosing in children with SE and sTBI should be lower in children with elevated serum creatinine and C-reactive protein values given their failure to achieve steady-state and progress to toxic levels instead.

## INTRODUCTION

Pentobarbital is an oxybarbiturate analog of barbituric acid and a potent Central Nervous System (CNS) depressant mediating its action via γ-aminobutyric acid-sensitive chloride channels (1-3). This short-acting barbiturate has a half-life ranging from 5 to 50 hours (3, 4). Similar to all barbiturates, pentobarbital is metabolized by the hepatic microsomal enzyme system to inactive metabolites (2, 3). Elimination is by urinary excretion and less commonly in feces (2, 3). Intravenously administered pentobarbital quickly distributes into the CNS due to its relatively high lipophilicity (log P 2.16), allowing rapid onset of action (3, 5). After prolonged infusions, pentobarbital may accumulate in adipose tissue due its lipophilicity, resulting in decreased drug elimination and protracted sedative effects (3, 5).

Pentobarbital has traditionally been used as a sedative-hypnotic and anticonvulsant agent as well as premedication in anesthetic procedures (1). Pentobarbital exhibits a dose-dependent effect producing all sedation levels, from drowsiness to deep coma (2, 3). High-dose pentobarbital administration induces cardiorespiratory depressive effects. As such, pentobarbital intoxication is associated with severe morbidity and mortality (3).

Pentobarbital prescription has been restricted to specific therapeutic applications given its narrow therapeutic window and toxicity profile (1, 3). In intensive care settings, pentobarbital remains a therapeutic option for the emergency control of refractory seizures in status epilepticus (SE) and refractory intracranial hypertension after severe traumatic brain injury (sTBI) (2, 3, 5-11). The therapeutic endpoint of pentobarbital can vary depending on the underlying disease and its course. For example, the goal

in refractory SE is burst suppression on electroencephalogram (EEG) whereas in sTBI improved intracranial pressure control (ICP) does not necessarily equate to burst suppression on EEG. High-dose pentobarbital can cause loss of brainstem reflexes and an isoelectric EEG pattern in combination with reduction in cerebral metabolic rate (3, 12). The latter reduces oxygen demand and cerebral blood flow resulting in ICP decrease, albeit the exact mechanisms of ICP-reduction are unknown (3, 13).

Limited pediatric pharmacokinetic (PK) data are available to guide pentobarbital dosing in pediatric SE and sTBI. The clinical application of pentobarbital in this population is debatable, given safety issues including systemic hypotension, feeding intolerance and propylene glycol toxicity that may counterbalance its clinical benefit, or even lead to multiorgan failure and death (6, 14). For SE, recommendations for inducing and maintaining adequate plasma pentobarbital levels have been published, however these are based solely on adult data (6). In pediatric sTBI, evidence for refractory ICP treatment with pentobarbital is limited, low-level and dated (15, 16).

Children pose unique pharmacological challenges because of significant physiological differences due to rapid growth and developmental changes in comparison to adults (17). In addition, SE and sTBI pediatric patients are critically ill and have significant PK alterations secondary to illness-related issues, of which inflammation is an increasingly recognized factor (2, 18, 19). These dynamic developmental and illness-related changes could significantly impact pentobarbital PK. Understanding pentobarbital PK is essential for rational drug dosing in this particularly vulnerable patient group. The aim of this study was to describe pentobarbital PK in critically ill children with SE and sTBI, and to explore how to optimize individual pentobarbital dosing in this population by means of dosing simulations.



## METHODS

### Study design and population

This is a single-center, retrospective study (January 2007 - September 2021) at a 28-bed university-based pediatric intensive care unit (PICU) of the Erasmus MC, Sophia Children's Hospital in Rotterdam, The Netherlands. Patients admitted were less than 18 years of age. Inclusion criteria: refractory SE or sTBI defined by a Glasgow Coma Scale (GCS) of ≤ 8 with refractory intracranial hypertension requiring pentobarbital infusion. Exclusion criteria: pentobarbital infusion for another diagnosis, incomplete documentation of pentobarbital administration or no documented pentobarbital concentrations in blood serum. PK model external validation was performed on an independent patient dataset (n=4) treated with pentobarbital from October 2019 to September 2021 in our hospital. These children were selected with the same inclusion criteria and not included in the initial model building dataset. Study approval was

granted by the institutional review board (IRB) with waiver of signed consent (MEC-2019-0072).

## Data collection

Demographic and clinical data were derived from hospital electronic medical records. Patients who received pentobarbital were identified from the pharmacy database. Demographic data included diagnosis, gender, age, weight, height and PICU length of stay. Missing values for height were resolved using the P50 value for gender-based height-for-age validated growth curves. Laboratory data consisted of documented renal function (serum creatinine and urea), liver assays (albumin, bilirubin, aspartate transaminase (ASAT), alanine transaminase (ALAT), gamma-glutamyltransferase (γ-GT), alkaline phosphatase (ALP)) C-Reactive Protein (CRP) and blood serum pentobarbital concentrations. Renal function was evaluated by calculating glomerular filtration rate (GFR) using the Schwartz formula: eGFR = k x $L/S_{cr}$, whereby eGFR is the estimated GFR in ml/min/1.73m$^2$, L is height in centimeters, $S_{cr}$ is serum creatinine in milligrams per deciliter and k is an empirical constant that is determined by comparing the $L/S_{cr}$ ratio against measured GFR (20). A value of 0.365 is used as the k constant in our Clinical Chemistry department and therefore used for our calculations. The other method of assessing renal function was by KDIGO (Kidney Disease Improving Global Outcomes) criteria (a staging system for renal disease that incorporates creatinine change and diuresis over time; **Supplement Table 1**) (21). Data collected on pentobarbital administration included number and amount of pentobarbital boluses as well as amount and duration of pentobarbital infusion.

## Laboratory analysis

Pentobarbital was analyzed in 100 µL plasma. UV detection was performed at 220 nm. Pentobarbital was measured using a high-performance liquid chromatography with diode-array detection (HPLC-DAD) method which was validated according to Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. The lower limit of quantification (LLOQ) was 0.5 mg/L and the upper limit of quantification (ULOQ) was 90 mg/L. Internal standard was secobarbital. All validation parameters were within the requirements (amongst all of e.g. precision/accuracy <15%).

## Population PK Modeling

PK analysis was performed by non-linear mixed-effects modeling using NONMEM® Version 7.2.0 (ICON Development Solutions, Ellicott City, MD, USA) and PsN ® Version 4.6.0. Pirana ® software (version 2.9.5) was used as an interface between NONMEM®, R (version 4.2.1) and Xpose (version 4). Data were analyzed using the first-order conditional estimation method with interaction (FOCE-I).

**Base Model Development**

One- and two- compartment models were tested to fit the pentobarbital plasma concentration data based on visual data inspection, objective function value (OFV) and literature review. Typical values for clearance (CL), volume of distribution (Vd) and inter-compartmental clearance (Q) were estimated. Inter-individual variability (IIV) for each PK parameter was evaluated using an exponential model and residual variability was described as an additive and proportional error. PK parameters were allometrically scaled with fixed exponents (0.75 for CL and 1 for Vd) to account for variability due to bodyweight differences in a pediatric population (22). Exponents for allometric scaling were also further estimated during covariate analysis. Shrinkage was calculated for all model parameters with estimated IIV and residual error. A shrinkage below 25% was considered acceptable (23). Model selection was based on minimum OFVs, parameter precision, error estimates, shrinkages and visual inspection of the goodness-of-fit plots.

**Covariate Model Development**

Demographic and laboratory characteristics were evaluated as potential model covariates after base model selection. Covariates tested: diagnosis, age, gender, urea, creatinine, eGFR, albumin, bilirubin, ASAT, ALAT, γ-GT, ALP, CRP and KDIGO criteria. The relationship between covariates and eta distribution was first examined graphically, albeit all covariates were singly added to the model. Continuous covariates were described using an exponential model normalized to population median values or cut-off values when used. Categorical covariates were described using a proportional model (24). The forward inclusion-backward elimination method was used (25). Covariates that significantly improved the model with an OFV decrease ≤ 3.84 ($p$ <0.05 with 1 degree of freedom) were added to the full model. A backward elimination process was performed with a statistical significance of $p$ <0.001 (OFV>10.83). Covariate effect on IIV of the PK parameter involved was also evaluated to assess covariate significance.

**Model Validation**

Firstly, a bootstrap analysis was performed whereby 1000 bootstrap datasets were generated by randomly sampling from the original dataset with replacement (26). The model was evaluated for its robustness and validity by comparing median values and their corresponding 95% confidence intervals (CI) of the bootstrap samples with the estimates from the original dataset. Secondly, the model was evaluated using the visual predictive check (VPC) by simulating 1000 datasets (27). Finally, an independent dataset consisting of 4 children treated with pentobarbital for SE or sTBI was used for external validation using a VPC. The VPCs for internal and external validation were stratified for final model covariates.

### Dosing simulations

Simulations were performed based on covariate value variations included in the final pharmacokinetic model and stratified by body weight. Different dosing scenarios were explored for each diagnosis in different clinical conditions whereby the goal was to reach a pentobarbital concentration of 25 mg/L. The time interval between loading doses (5 mg/kg) was 5 minutes and repeated a maximum of 6 times (within a 30 minute time span).

## RESULTS

### Patient characteristics

Forty-two patients received intravenous pentobarbital for SE or sTBI at our PICU between January 2007 and September 2021. Two patients were excluded from PK analysis: one patient had an unrealistic documented pentobarbital dose compared to normal dosing reference and one patient had pentobarbital infusion whilst receiving extracorporeal membrane oxygenation (ECMO). No patient had hypothermia (targeted temperature management <35 degrees Celsius) during pentobarbital infusion. Of the 40 included patients, 36 patients were used for the base model development group of which 22 and 14 received pentobarbital for SE and sTBI respectively. The external validation group consisted of 4 patients: SE (n=1) and sTBI (n=3). Patient characteristics for each model group are presented in **Table 2**.

A total of 178 blood samples were used for the population PK model, and 21 blood samples for external validation. Pentobarbital concentrations excluded from PK analysis were from patients receiving concurrent hemodialysis or if it was unclear which barbiturate was administered at the time of a documented pentobarbital concentration (e.g., pentobarbital vs phenobarbital). The median measured pentobarbital concentration was 27.5 mg/L [range 0.1 to 106 mg/L] in the model building group and 24 mg/L [range 5 to 56 mg/L] in the model validation group. SE median infusion dose was 3 mg/kg/h (range 0.5 to 10 mg/kg/h) and the sTBI median infusion dose was 2 mg/kg/h (range 0.05 to 5 mg/kg/h). Three patients from the external validation group had sTBI, reflecting similarities in loading and infusion dose with the sTBI cohort of our PK model.

**Table 2.** Patient characteristics for the model building and the model validation group

| | Model building group | | Model validation group[a] |
|---|---|---|---|
| | **SE (n=22)** | **sTBI (n=14)** | **(n=4)** |
| **Age** (years)* | 0.31 [0.05-3.73] | 12 [0.3-16] | 14[0.3-16] |
| **Gender**, n (%) | | | |
| Male | 14 (64%) | 7 (50%) | 3(75%) |
| Female | 8 (36%) | 7 (50%) | 1(25%) |
| **Weight** (kg)* | 6.3[3-19] | 40[5-87] | 60[6-75] |
| **Pentobarbital*** | | | |
| Loading dose (mg/kg) | 15[0-40] | 1[0-20] | 0.85[0.2-5] |
| Min Infusion (mg/kg/h) | 2[0.5-3] | 0.55[0.05-3] | 1.25[0.3-2] |
| Max Infusion (mg/kg/h) | 5[2-10] | 3[2-5] | 2[1.4-4.5] |
| Duration of infusion (days) | 4[1.5-11] | 4[1-15] | 2.5[2-6.5] |
| **PICU length of stay** (days)* | 12.5[0-33] | 17.5[8-44] | 10.5[5-46] |
| **Mortality**, n (%) | 7(32%) | 2(14%) | 2(50%) |
| **Laboratory measurements*** | | | |
| Urea (mmol/L) | 2.9[0.9-15.2] | 3.1[0.4-9.9] | 3.5[1.3-9.3] |
| Creatinine (µmol/L) | 23[13-94] | 49[12-109] | 51[14-102] |
| eGFR (mL/min/1.73m²) | 95[30-199] | 96[33-195] | 83[54-151] |
| CRP (mg/L) | 32.5 [10.8-77.3] | 131.5 [39.5-312.8] | 207 [153-274] |
| Albumin (g/L) | 25[19-37] | 27[13-38] | 21[18-25] |
| ASAT (U/L) | 70[20-382] | 38[17-245] | 60[38-113] |
| ALAT (U/L) | 23[2.5-738] | 28[12-90] | 20[13-65] |
| γ-GT (U/L) | 43[6-430] | 22[5-271] | 25[12-37] |
| ALP (U/L) | 171[103-290] | 170[61-297] | 95.5[73-164] |
| Bilirubin (µmol/L) | 3[0.5-49] | 7[0.5-37] | 25[16-25] |

* Values presented as median and interquartile range for continuous variables.
[a] The model validation group consisted of 3 severe traumatic brain injury patients and 1 status epilepticus patient.
ALAT: Alanine Aminotransferase; ALP: alkaline phosphatase; ASAT: Aspartate Aminotransferase; CRP: C-Reactive Protein; eGFR: estimated Glomerular Filtration Rate; γ-GT: gamma-glutamyl transferase; PICU: Pediatric Intensive Care Unit

## Base Model

Data were equally well-described by a one- or two-compartment model. For the simplicity of modelling, a one-compartment model was chosen for further model refinement. The model fit was improved after including an IIV on CL. The residual error was described as an additive error, as the proportional error was estimated close

to zero. Allometric scaling with fixed exponents (0.75 for CL and 1 for Vd) significantly improved the model ($p$ <0.001) compared to no allometric scaling. Parameter estimates of the base and final model with their respective standard errors are presented in **Table 3**.

**Table 3.** Parameter estimates for the base model, final model and bootstrap analysis

| Parameter | Base model | Final model | Bootstrap of the final model | |
|---|---|---|---|---|
| | | | Median | 95% CI |
| OFV | 1039.1 | 930.1 | | |
| CL (L/h/70kg) | 2.78 (19) | 3.59 (11) | 3.69 | 2.80 to 4.74 |
| Vd (L/70kg) | 151 (6) | 142 (6) | 143 | 120 to 158 |
| Creatinine effect on CL | | -0.919 (21) | -0.909 | -1.192 to -0.242 |
| C-Reactive Protein effect on CL* | | -0.883 (14) | -0.923 | -1.25 to -0.613 |
| IIV (%) | | | | |
| CL | 88.1 (18) [14] | 34.8 (24) [23] | 32.1 | 15.8 to 49.6 |
| Residual variability | | | | |
| Additional | 8.93 (10) [8] | 7.22 (10) [6] | 7.11 | 5.72 to 8.54 |

The relative standard error (expressed as percentages) is depicted in round brackets, and the shrinkage (expressed as percentages) is depicted in square brackets. CI: confidence interval; CL: clearance; IIV: inter-individual variability; OFV: objective function value; Vd: volume of distribution. *if CRP>70 mg/L

## Covariate Analysis

The base one-compartment model with allometric scaling was used as a reference for covariate analysis. Estimation of the exponent for allometric scaling of bodyweight was taken into account as covariate. After visual inspection of the covariates with the PK parameters, the univariate analysis resulted in the following significant covariates: diagnosis, age, creatinine, γ-GT, CRP, KDIGO criteria and bodyweight as presented in **Table 4**. Regarding CRP, relative lower pentobarbital CL was seen in the higher range of CRP. To describe this effect several cut-off values were evaluated, of which a cut-off value of >70 mg/L resulted in the best correlation and highest decrease in OFV. Creatinine and CRP significantly correlated with CL ($p$ <0.001) after backward elimination and hence incorporated in the final model. Using this covariate model, no trends in covariates were found. IIV on CL decreased by 84% in the final model with incorporation of creatinine and CRP when compared to the base model. The following equation described the final model for estimation of pentobarbital CL (L/h), whereby the effect of CRP was only included for patients with increased CRP >70 mg/L:

$$CL\ (l/h) = 3.59 \times \left(\frac{Weight}{70}\right)^{0.75} \times \left(\frac{Creatinine}{36}\right)^{-0.919} IF\ CRP > 70: \times \left(\frac{CRP}{70}\right)^{-0.883}$$

**Table 4.** Covariate effects in the univariate analysis compared with the base model

| Covariate | ΔOFV | Covariate effect | Included after backward elimination |
|---|---|---|---|
| Age | 7.8 | -0.242 | No |
| Gender | 1.574 | 1.53 | No |
| Diagnosis | 12.8 | 3.3 | No |
| Urea | 5.235 | -0.254 | No |
| Creatinine | 75.4 | -1.47 | **Yes** |
| CRP | 66.4 | -1.12 | **Yes** |
| eGFR | 51.377 | 1.39 | No |
| Albumin | 0.953 | 0.736 | No |
| ASAT | 0.633 | -0.102 | No |
| ALAT | 0.106 | -0.0376 | No |
| γ-GT | 14.5 | 0.441 | No |
| ALP | 1.692 | -0.423 | No |
| Bilirubin | 6.628 | -0.488 | No |
| KDIGO criteria: | 15 | | No |
| Stage 1 | | 0.419 | |
| Stage 2 | | 0.489 | |
| Stage 3 | | 0.063 | |

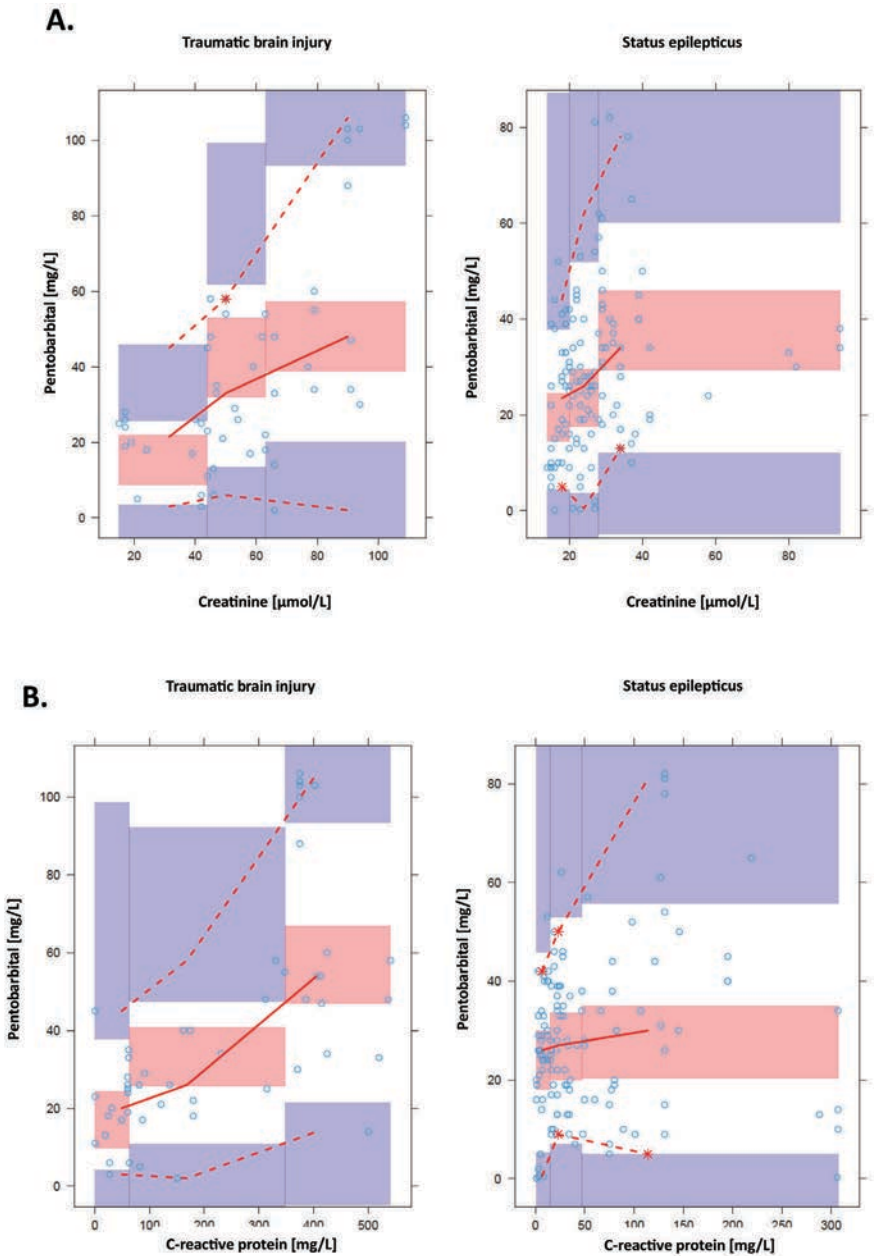
ALAT: Alanine Aminotransferase; ALP: alkaline phosphatase; ASAT: Aspartate Aminotransferase; CRP: C-Reactive Protein; eGFR: estimated Glomerular Filtration Rate; γ-GT: gamma-Glutamyltransferase; KDIGO: Kidney Disease Improving Global Outcomes. OFV: Objective Function Values.

Goodness-of-fit plots of the final model showed good model performance (**Supplement, Figure 1**) whereby population and individual predictions were evenly distributed around the unity line when plotted against the observations. Trends in interpatient variability of pentobarbital clearance, as seen in the base model, were no longer present after incorporation of the covariates (**Supplement, Figure 2**).

## Model validation

Bootstrap results showed that the model-based parameter estimates were similar to median values and within the 95% CIs of the bootstrap analysis, indicative of final model stability (**Table 3**). The VPCs in **Figure 3** demonstrate that observed pentobarbital concentrations (median and variability) fall within the corresponding simulations when stratified by diagnosis with creatinine or CRP respectively. Some small deviations in variability were seen, which can be explained by the sample size. External validation using stratified VPCs showed good results (**Supplement, Figure 4**). Variability of the external validation VPCs was wide and secondary to the limited number of patients in the model validation group (n=4).

**Figure 3.** Visual predictive check (VPC) of the final model. The VPC's illustrate how the average trend (*solid red line*) and variability (*two dashed red lines*) of the pentobarbital observed concentrations fall within the model-based simulations average trend (*red semi-transparent area*) variability (*blue semi-transparent areas*) represented as a 95% confidence interval (CI). (**A)** VPC of the final model per diagnosis for Creatinine (**B)** VPC of the final model per diagnosis for C-Reactive Protein.

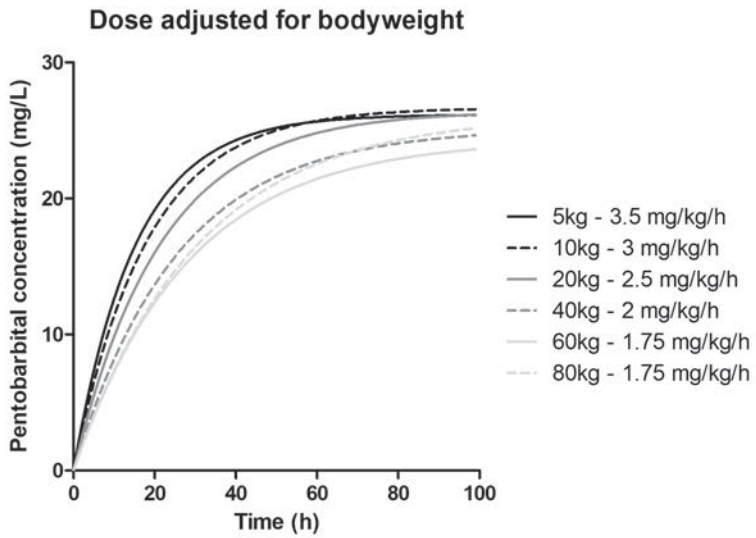


## Dosing simulations

Different dosing regimens were simulated using the final pentobarbital PK model developed in this study for a 6 kg SE patient and a 40 kg sTBI patient as these were the median weight per diagnosis for our study cohort. Initial creatinine and CRP values for these simulations were kept at a value of 26 µmol/L and ≤ 70 mg/L respectively.

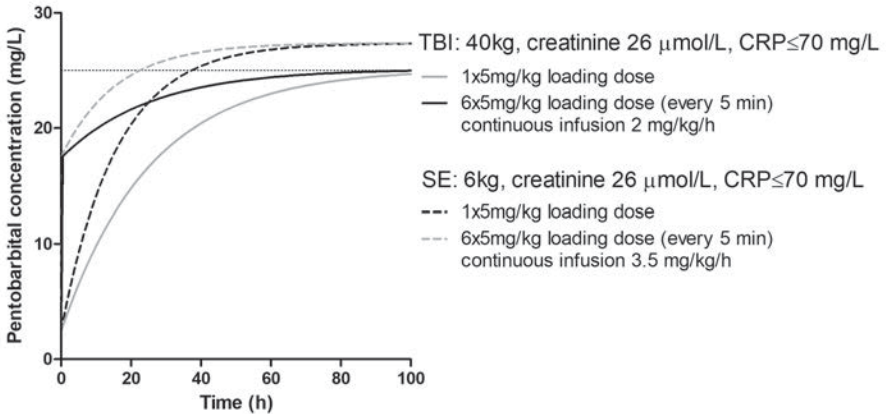
First of all, dosing simulations of continuous pentobarbital infusion (without a loading dose) led to the following pentobarbital dosing advice based on body weight as shown in **Figure 5**. CL was lower in patients with a higher body weight. Therefore lower pentobarbital continuous infusion doses were required to achieve concentrations around 25 mg/L. At the same time, steady state took longer to reach in higher weight categories. Overall, it took at least 48 hours to reach steady state in all patients. This could be shortened using loading doses.

**Figure 5.** Pentobarbital dose adjusted for bodyweight. Dosing simulations were performed to reach a target pentobarbital concentration of 25 mg/L (simulations performed with creatinine values 26 µmol/L and CRP ≤ 70 mg/L).




The effect of loading doses on achieving pentobarbital steady state for each diagnosis and its respective median weight is visualized in **Figure 6**. A single loading dose (5 mg/kg) did not contribute substantially to achieving steady state. Repeated loading doses with a minimum time interval of 5 minutes facilitated a more rapid achievement of steady state. The median weight difference between the SE and sTBI patient categories resulted in a different continuous pentobarbital infusion dose between diagnosis groups. This was to ensure the desired steady state concentration (25 mg/L) was not exceeded in the higher weight group (sTBI).

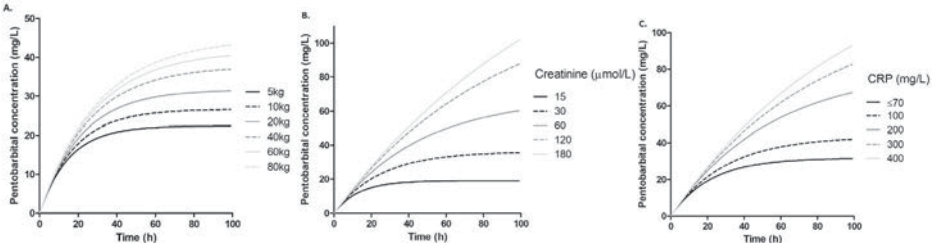
**Figure 6.** Effect of pentobarbital loading dose simulations on achieving steady state per diagnosis.




CRP: C-Reactive Protein; SE: Status Epilepticus; TBI: Traumatic Brain Injury

The effect of body weight, creatinine and CRP on pentobarbital concentration is depicted in **Figure 7**. In this simulation a pentobarbital maintenance infusion of 3 mg/kg/h without loading dose was used to evaluate the effect on reaching a pentobarbital steady state concentration of 25 mg/L. **Figure 7** demonstrates that the effect of elevated creatinine [range 15 to 180 μmol/L] and CRP [range ≤ 70 to 400 mg/L] on pentobarbital concentrations is more pronounced than weight-based dosing: instead of reaching a steady state, pentobarbital concentrations progress to toxic levels.

**Figure 7.** Effect of bodyweight, creatinine and C-reactive protein (CRP) on pentobarbital concentrations using a continuous infusion of 3 mg/kg/h. Simulations were performed for a median patient of 20kg, creatinine 26 μmol/L and CRP ≤70 mg/L, of which (**A**) bodyweight, (**B**) creatinine or (**C**) CRP was adjusted each time to evaluate the effect on pentobarbital concentrations.



**Dose adjustment recommendations**

The simulations yield the following suggestions for dose adjustment to keep pentobarbital concentrations within the *safety* margin of 20-40 mg/L: a *doubling* of creatinine results roughly in *halving* of pentobarbital clearance. Thus, *halving* of the pentobarbital dose seems necessary. As for CRP, no dose adjustments seem required for a CRP value ≤70 mg/L. Dose adjustments are recommended for a CRP> 70 mg/L as presented in **Table 5**. It must be noted these dose adjustments are based solely on safety targets with the goal to prevent toxicity and do not reflect clinical efficacy.

**Table 5.** Dose adjustment for Pentobarbital infusion rate based on C-Reactive Protein > 70 mg/L

| C-Reactive Protein value [mg/L] | Pentobarbital dose adjustment (% of original dose) |
|---|---|
| 100 | 73 |
| 200 | 40 |
| 300 | 28 |
| 400 | 21 |

The following formula can be used to calculate optimal dosing for pentobarbital continuous infusion whereby two items must be noted: if CRP ≤ 70 mg/L then do not include the CRP part of the equation or use a CRP value of 70 mg/L. Secondly, the dose is noted in (mg/h) thus still needs to be divided by bodyweight (BW; kilograms) to provide continuous infusion rates (mg/kg/h):

$$Dose\ (mg/h) = 89.75 \times \left(\frac{BW}{70}\right)^{0.75} \times \left(\frac{Creat}{36}\right)^{-0.919} \times \left(\frac{CRP\ *}{70}\right)^{-0.883}$$

* if C-Reactive Protein (CRP) > 70 mg/L

## DISCUSSION

To our knowledge, this is the first pentobarbital population-based PK study in PICU patients with refractory SE or sTBI. A one compartment PK model including allometric scaling and IIV on CL described data well. Our pentobarbital PK model demonstrated that serum creatinine and CRP (> 70 mg/L) significantly influence pentobarbital CL requiring pentobarbital dose adjustments based on simulations. Importantly, dosing simulations demonstrated that patients with elevated serum creatinine and CRP failed to reach a pentobarbital steady state and progressed to toxic concentrations without dose adjustments.

The following observations were made concerning pentobarbital metabolism based on our pentobarbital PK model. First of all, the identification of creatinine and CRP as significant covariates on pentobarbital CL which has not been previously documented. Regarding CRP, there is an increasing body of evidence that inflammation significantly

impacts cytochrome P450 (CYP450) activity leading to alterations in drug clearance (18, 19, 28). Our findings concerning elevated CRP and decreased pentobarbital CL mirror these results. In the context of pentobarbital CL, the liver has a pivotal role in metabolism. Pentobarbital is subject to low hepatic intrinsic CL and hence its systemic CL would not be primarily sensitive to fluctuations in hepatic blood, which usually occur in critical illness, but rather to alterations in intrinsic enzyme activity or plasma binding (13). Pentobarbital is mainly metabolized by the hepatic microsomal enzyme system (2), therefore alterations in the activity of hepatic enzymes, such as CYP450, secondary to inflammation, may explain the altered pentobarbital CL of our population (18, 19). Another indirect marker of a decrease in hepatic function could be reflected by protein synthesis, such as albumin levels. Hypothetically this could influence pentobarbital protein binding which can range from 35% to 70% (3). However, hepatic markers were not significant covariates in our study. Thus we hypothesize that pentobarbital protein binding alterations are not of clinical significance in the context of pentobarbital CL. As for serum creatinine, this has been reported as a significant covariate on CL in children receiving phenobarbital for seizure management (29). Phenobarbital is a barbiturate often compared to pentobarbital when administered for refractory SE, thus our findings could reflect these barbiturate PK similarities. The question remains whether creatinine as a significant covariate solely represents a marker for kidney dysfunction or severity of critical illness in general. To explore this hypothesis, we tested our pentobarbital PK model with other estimates of renal function by estimating eGFR using the Schwartz formula and categorizing patients with the KDIGO criteria. However, these proved to have limited value as a marker of renal function in this retrospective study given the need to estimate most anthropometric data (height) in combination with missing diuresis data. Furthermore, the use of one *k*-coefficient for all pediatric ages, such as in our clinic, is debatable as it might overestimate eGFR in younger children as proposed by de Souza *et al*. (30). In addition, neonates and infants show steady GFR increase up to 18 months of age when full maturity is reached (31). This is of interest, as the median age of our SE cohort was 0.3 years. Thus, eGFRs based on standard creatinine-based equations could be misleading in specific populations, not only based on age but also gender, dietary factors, catabolic and disease state (32).

Secondly, in terms of pentobarbital CL we identified no dose-dependent effect on pentobarbital CL and half-life within the known range of 5 to 50 hours (24.68 hours) as described in the literature (2, 15). The CL values we determined (3.59 L/h/70kg) were higher than values reported in a pediatric population PK study in patients that received pentobarbital after open heart surgery (2.96L/h/70kg) (2). A possible reason for this observed CL variation was the younger age in the post-cardiac surgery cohort (median age 6.3 months, range 3.0 days – 4.4 yrs) which could relate to substantial variation in body weight and/or kidney maturation (2, 31). Analogous to Zuppa *et al.* allometric scaling significantly improved our PK model. However, their study also

suggested an age effect on CL remained for subjects <12 months after accounting for difference in body weight. We tested this hypothesis by using an age cut-off (< and ≥12 months) to assess kidney maturation and this did not result in further improvement of our pentobarbital PK model.

Thirdly, pentobarbital is a highly lipophilic drug with a rapid blood brain barrier (BBB) penetration and CNS distribution after intravenous administration, ensuring its rapid onset of action (3, 5). However, continuous infusions lead to rapid drug redistribution into peripheral tissues and result in pentobarbital storage in adipose tissue (3, 5). Despite this knowledge, it was remarkable to find that a two-compartment model did not provide superior data fit in our study. However, we observed a large Vd (142L) reflecting the high lipophilicity of pentobarbital. Interestingly, we did observe Vd differences between lean and obese children of the same age (defined as weight-for-age ≥ 2 standard deviations), with the Vd 71% higher in the latter group, probably secondary to the lipophilic nature of pentobarbital. Moffet *et al.* developed a population PK model for children receiving phenobarbital for seizure treatment and demonstrated that the model with allometrically scaled CL and Vd using fat-free mass was superior to body weight (29). This observation could be applicable for pentobarbital too despite not finding a superior PK model fit with two compartment analysis. Further exploration of body composition effect on pentobarbital PK, using body mass index (BMI) or standardized weight-for-height growth curves, is warranted in a prospective manner.



Finally, the dosing simulations yielded important and clinically applicable findings. First of all, from a safety point of view, it could be necessary to prescribe a lower continuous infusion rate for increasing body weight (**Figure 4**). This is to prevent exceeding the upper limit of the desired pentobarbital range. Secondly, further dose reductions of the continuous pentobarbital infusion are required in patients with elevated creatinine and CRP as these patients fail to attain a steady state and progress to toxic levels. Overall, the effect of elevated creatinine and CRP is more pronounced than the effect of body weight. Therefore, elevations of these values should alert the clinician and clinical pharmacist to perform timely dose reductions in an effort to prevent toxic pentobarbital levels. Thirdly, the actual clinical effect of the loading dose (i.e. rapid control of epileptic activity or raised intracranial pressure) was not evaluated in this study although simulations with loading doses demonstrated a more rapid achievement of pentobarbital concentrations within desired safety margins. It is conceivable that titration to clinical effect could be achieved by additional loading doses on top of a fixed continuous infusion rate determined by body weight during concurrent therapeutic drug monitoring (TDM) and pharmacodynamic monitoring by EEG and/or ICP trends.

To our knowledge, this is the largest study on pentobarbital PK in critically ill children admitted to the PICU. In addition, our PK model was comprehensively validated with

several methods as well as an external validation. Finally, it is the first PK study to describe a significant association between creatinine, CRP and pentobarbital CL. These findings were translated to bedside dosing adjustment recommendations in an effort towards safer pentobarbital dosing practices. The main study limitation is its retrospective nature leading to inherent challenges in data collection. Especially challenging, was obtaining reliable markers of renal function whereby anthropometric data (weight and height) often have to be estimated upon admission of the patient due to clinical instability. Furthermore, estimating equations, such as the Schwartz formula, are often associated with limitations when estimating eGFR due to the k values that deviate based on age, gender and creatinine assay [18]. Our clinic used a single k value for all ages which may not properly reflect developmental and gender variability (30). Another limitation is that our observations reflect a single center experience. Also, drug-drug interactions were not tested as variables that influence pentobarbital pharmacokinetics in our model. Finally, we studied two distinct patient groups who received pentobarbital for different indications with different dosing protocols. The rationale to combine these groups was to provide a wide spectrum for age and variability in dosing practice. Although the pentobarbital model incorporates patient-specific covariates, it must be noted that this might not cover all disease specific factors of influence on pentobarbital PK even though using the diagnosis itself as a covariate was not significant.

Our observations in the development and subsequent dosing simulations of our pentobarbital PK model for pediatric SE and sTBI suggest high PK variability. We recommend future studies aiming at improving this PK model by prospective data collection in addition to multicenter involvement to enhance patient and sample numbers. In addition, dosing simulations with prospective data will further improve model informed precision dosing. Furthermore, the incorporation of other renal markers such as cystatin-C and neutrophil gelatinase-associated lipocalin (NGAL), which are less influenced by factors like muscle mass, age, ethnicity and dietary factors (20, 33), could provide more insight into the role of kidney function in pentobarbital CL. In addition, data regarding degree of overall (critical) illness such as additional markers of inflammation (e.g. interleukin-6) and illness severity depending on disease (eg. Glasgow Coma Scale, Injury Severity Score, Vasoactive-Inotropic Score, and Pediatric Logistic Organ Dysfunction Score).

Given the current insights provided by this PK model, we want to raise awareness for potential pentobarbital intoxication when dosing pentobarbital in critically ill patients with elevated creatinine and CRP levels. We advise adjusting the dose in accordance with our dose recommendations, combined with routine and frequent TDM during pentobarbital treatment, due to this high PK variability. This assists in reaching and maintaining pentobarbital concentrations within the safety margin. Based on our experience, we suggest daily pentobarbital TDM after initiation of

pentobarbital infusion and daily creatinine and CRP measurements to promptly identify elevated levels and thus facilitate timely pentobarbital dosing adjustments. In addition, to optimize individualized pentobarbital dosing, defining and correlating pharmacodynamic (PD) endpoints to PK data is necessary. Additional PD studies are warranted to further provide meaningful dosing guidance in this complex population, with special focus on measures of pharmacological efficacy such as EEG or sedation scores/ICP trends and measures of safety, such as hemodynamic stability in terms of vasopressor index score.

## CONCLUSION

A population PK model of pentobarbital for pediatric SE and sTBI was developed that successfully describes the concentration-time profile of pentobarbital. Serum creatinine and CRP were significantly correlated with pentobarbital clearance. Dosing simulations incorporating bodyweight, creatinine and CRP yielded significant dose adjustments regarding pentobarbital maintenance infusion. Thus, our PK model demonstrates high pentobarbital PK variability, which can be explained for 84% by creatinine and CRP. This underlines the importance of model informed precision dosing and TDM. Further prospective pediatric pentobarbital PK/PD studies, including dosing simulations, are required that will incorporate renal biomarkers, markers of inflammation and illness severity scores depending on the underlying disease. These covariates in combination with end points of efficacy and safety will advance our understanding of pentobarbital pharmacology and guide individualized dosing.

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# SUPPLEMENT

**Table 1.** KDIGO acute kidney injury guidelines

| Stage | Serum creatinine change | Urine production |
|---|---|---|
| 1 | Elevation of 27 umol/l or 1.5-2x baseline. | 0.5ml/kg/hour during 8 hours |
| 2 | 2-3x baseline | 0.5ml/kg/hour during 16 hours |
| 3 | >3x baseline, indication for dialysis, eGFR<35mL/min/1.73m$^2$, creatinine > 350umol/l | 0.5ml/kg/hour during 24 hours or anuria during 12 hours |

eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes(21)

**Figure 1.** Goodness-of-fit plots of the final model. Observed concentrations plotted against population predicted concentrations (**A**) and individual predicted concentrations (**B**) of pentobarbital (mg/L). Dashed lines represent the line of identity.

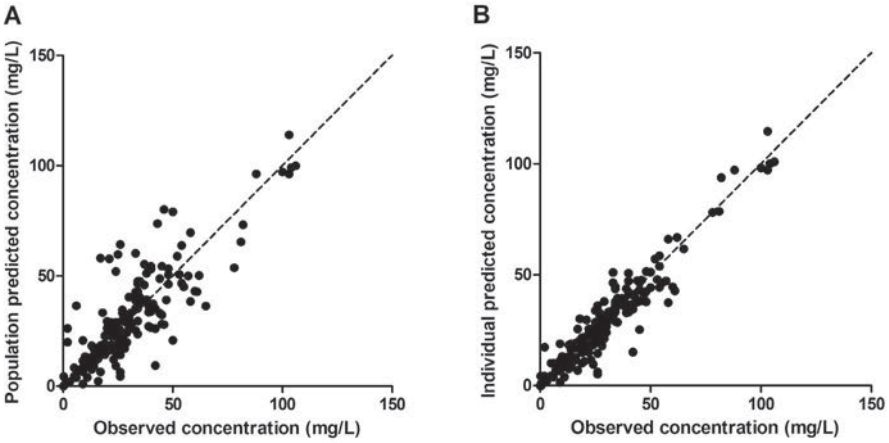


**Figure 2**. Interpatient variability of pentobarbital clearance. The variability in pentobarbital clearance (Y-axis) in relation to creatinine values (µmol/L) or C-Reactive Protein (CRP) values (mg/L) respectively (X-axis), decreased with model refinement from base to final model (figures **3A** and figures **3B** for serum creatinine and CRP respectively). The final model shows how increased values for Creatinine and CRP decrease pentobarbital clearance (L/hr) (figures **3A** and figures **3B** upper and lower right plots).

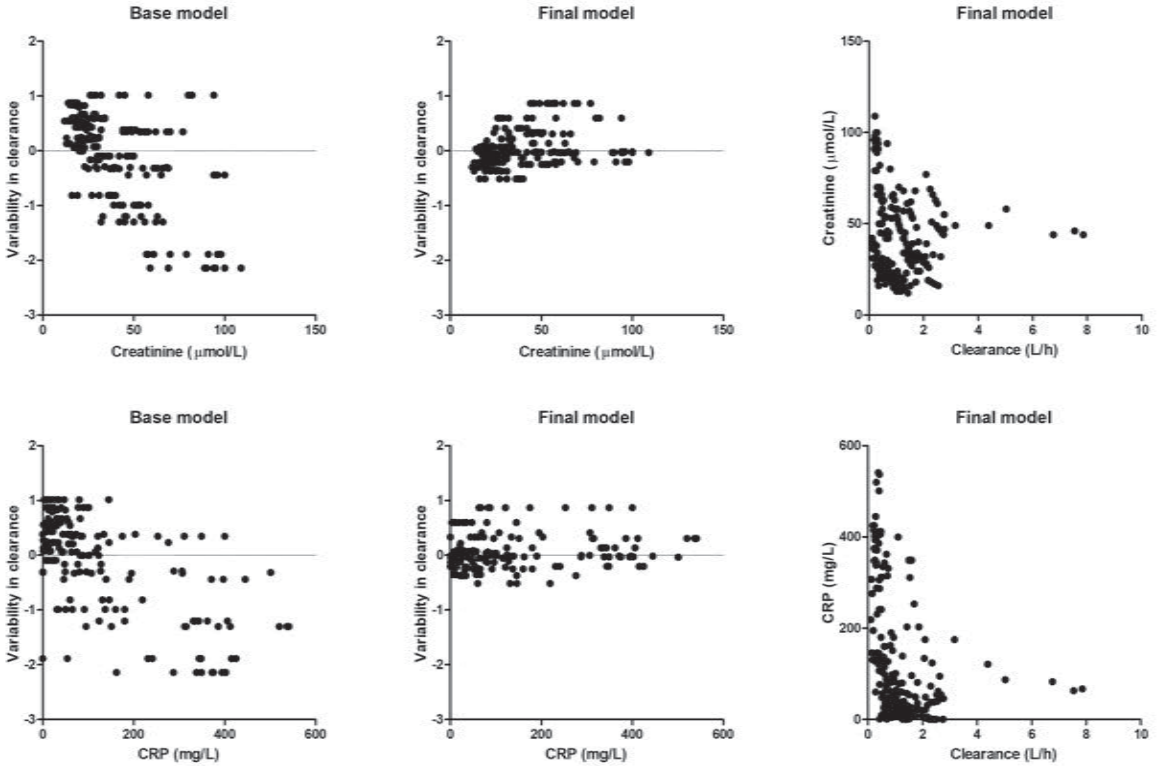
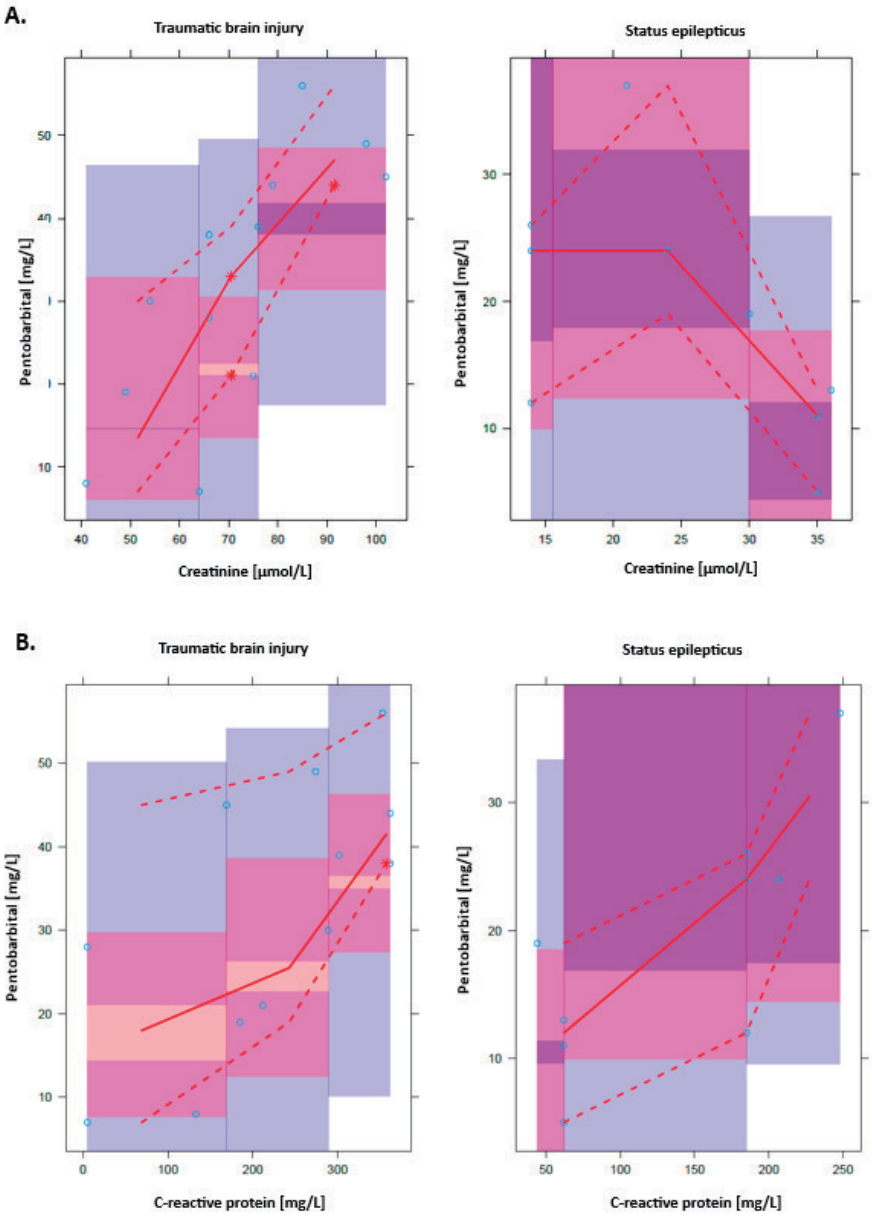
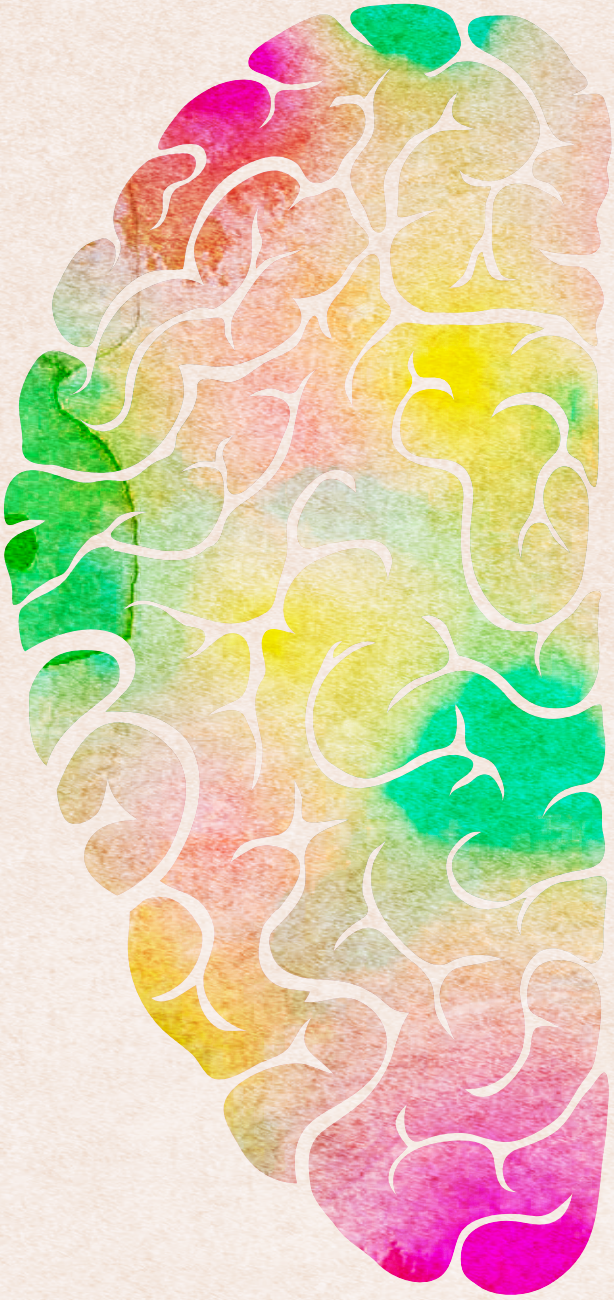


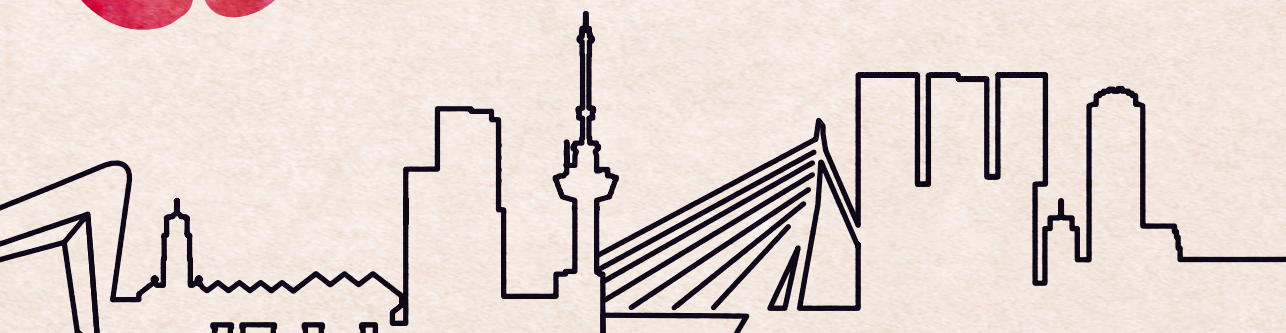
**Figure 4.** Visual predictive check (VPC) of the final model with the external validation cohort (n=4). The VPC's illustrate how the average trend *(solid red line)* and variability *(two dashed red lines)* of the pentobarbital observed concentrations fall within the model-based simulations average trend *(red semi-transparent area)* variability *(blue semi-transparent areas)* represented as a 95% confidence interval (CI). **(A)** VPC of the final model per diagnosis for Creatinine **(B)** VPC of the final model per diagnosis for C-Reactive Protein.



# PART III



# Outcome in pediatric severe TBI



# 6

# **Hyperoxia in pediatric severe traumatic brain injury:** a comparison of patient classification by cutoff versus cumulative (area-under-the-curve) analysis

**Naomi Ketharanathan, Rogier de Jonge, Ilse Klouwen, Enno Wildschut, Irwin Reiss, Dick Tibboel, Iain Haitsma, Corinne Buysse**

***Brain Inj*** *2020; 2: 1-7.*

# ABSTRACT

## Objective

Hyperoxia is associated with adverse outcome in severe traumatic brain injury (TBI). This study explored differences in patient classification of oxygen exposure by $PaO_2$ cutoff and cumulative area-under-the-curve (AUC) analysis.

## Methods

Retrospective, explorative study including children (< 18 years) with accidental severe TBI (2002 – 2015). Oxygen exposure analysis used three $PaO_2$ cutoff values and four $PaO_2$ AUC categories during the first 24 hours of Pediatric Intensive Care Unit (PICU) admission.

## Results

Seventy-one patients were included (median age 8.9 years [IQR 4.6 – 12.9]), mortality 18.3% (n=13). Patient hyperoxia classification differed depending on $PaO_2$ cutoff vs AUC analysis: 52% vs. 26% respectively were classified in the highest hyperoxia category. Eleven patients (17%) classified as 'intermediate oxygen exposure" based on cumulative $PaO_2$ analysis whereby they did not exceed the 200 mmHg PaO2 cutoff threshold. Patient classification variability was reflected by Pearson correlation coefficient of 0.40 (p-value 0.001).

## Conclusions

Hyperoxia classification in pediatric severe TBI during the first 24 hours of PICU admission differed depending on $PaO_2$ cutoff or cumulative AUC analysis. We consider $PaO_2$ cumulative (AUC) better approximates (patho-)physiological circumstances due to its time and dose dependent approach. Prospective studies exploring the association between *cumulative* $PaO_2$, physiological parameters (e.g. ICP, $PbtO_2$) and outcome are warranted as different patient classification of oxygen exposure influences how its relationship to outcome is interpreted.

## INTRODUCTION

It is well known that hypoxemia is associated with worse outcome in TBI [1-4]. The influence of hyperoxia on outcome remains controversial. Suggested mechanisms of potential negative effects include cerebral vasoconstriction in a similar manner as hypocarbia, oxidative stress and inflammation [2, 5-7].

Most studies investigating hyperoxia and outcome in TBI and other patient groups used (arbitrary) cutoff values for hyperoxia such as 200, 250 or 300 mmHg respectively [2, 8-11]. Whether the analysis of different cutoff values adequately approximates oxygen exposure is questionable due to the multifactorial and dynamic nature of oxygen physiology in combination with continuous supplemental oxygen exposure in the majority of cases. A study in pediatric post cardiopulmonary resuscitation (CPR) patients by van Zellem et al introduced a new innovative method in defining and measuring hyperoxia and oxygen exposure: the cumulative analysis using the area under-the-curve (AUC) $PaO_2$ calculation, which is a commonly used approach to estimate drug exposure in pharmacological studies [12-14]. Although each method of oxygen exposure analysis has its limitations, our hypothesis is that the longitudinal, cumulative approach better addresses the (patho-)physiology of cerebral hyperoxia as it takes time and dose dependent factors into account [15].

The aim of our study was to compare hyperoxia classification of pediatric severe traumatic brain injury patients during the first 24 hours of Pediatric Intensive Care Unit (PICU) admission by using conventional $PaO_2$ cutoff analysis and area-under-the-curve (AUC) $PaO_2$ cumulative analysis. The rationale being that patient classification is crucial to how we subsequently associate hyperoxia to outcome measures, such as morbidity and mortality.

## MATERIAL AND METHODS

### Study design and setting

This is a retrospective observational study with exploratory aims. The study was performed at PICU of the Erasmus MC - Sophia Children's Hospital, a tertiary-care hospital providing regional pediatric health care for the southwest of The Netherlands (estimated regional population of 4.2 million inhabitants). This population is a representative sample of the Dutch population. Waiver of consent was granted by the ethical review board of the Erasmus MC due to the non-invasive matter of the study (MEC 2015-583).

## Study aim

The aim of this observational study was to explore two methods of analyzing oxygen exposure (cutoff vs. cumulative AUC $PaO_2$) per patient. The importance of comparing these two methods, is to ascertain if the type of analysis leads to differences in hyperoxia patient classification.

## Subjects

All children admitted to the PICU of the Erasmus MC- Sophia Children's Hospital with severe TBI between January 2002 and July 2015 were evaluated for study eligibility. Inclusion criteria were severe TBI defined as a Glasgow Coma Scale (GCS) of eight or less requiring ICP-monitoring in the PICU and the presence of an arterial line for acquisition of $PaO_2$ values. Treatment of severe TBI in our hospital is conform international guidelines for acute medical management of severe traumatic brain injury [16]. Exclusion criteria were non-accidental TBI, such as child battering and no arterial line in situ for $PaO_2$ sampling.

## Data collection

Data were derived from ambulance registration forms, electronic medical records and our Patient Data Management System (PDMS) and collected for the first 24 hours after the event (T=0). Due to inadequate documentation of the precise time of event in the majority of cases, this had to be approximated. Therefore, we chose to define T=0 as the PICU admission time. This is deemed a reasonable solution because of a rapid response time of medical emergency services in our region with relatively little time between the estimated time of event (based on ambulance registration forms, ER admission forms) and PICU admission (median 1.7 hours, IQR [0.1-22.3]).

The following data were collected: (1) basic patient characteristics (e.g., gender, age, PIM3 and PRISM scores), (2) TBI characteristics (e.g. etiology, first recorded GCS (at the scene or, if unknown, GCS at the Emergency Room) and radiological findings), 3) outcome (mortality during PICU admission), 4) laboratory values (Arterial Blood Gas (ABG): arterial pH, lactate, $PaO_2$, $PaCO_2$) and 5) values of ICP, Fraction of inspired Oxygen ($FiO_2$) and Mean Airway pressure (MAP). The Oxygenation Index (OI) was calculated as follows: ($FiO_2$ x MAP) / $PaO_2$.

## Statistical analysis

Data are presented as frequencies (%), mean (standard deviation, SD) for normally distributed variables or median (interquartile range, IQR) for continuous variables that were not normally distributed. Correlation between $PaO_2$ max and total $PaO_2$ AUC in the first 24 hours of PICU admission was calculated using Person correlation coefficient (95% confidence interval). It was pre-defined that the correlation was excellent with a coefficient above 0.80, good between 0.61 and 0.80; fair to moderate when between 0.21 and 0.60; and poor when below 0.20. Univariable logistic regression was used

to explore the differences in association between the two approaches to define hyperoxia and the outcome measure 'mortality'. A two-sided p-value of ≤ 0.05 was considered statistical significant for all analyses. Data analysis was performed with IBM SPSS Statistics 25.0.0 (IBM Inc.) and GraphPad Prism 8.30 for Windows (Graphpad Software, Inc.).

### Oxygen exposure analysis

The presence of hyperoxia during the first 24 hours of PICU admission was investigated using two different methods of analyzing $PaO_2$: the traditionally used cutoff value analysis and secondly the cumulative analysis of $PaO_2$ using the trapezoidal method. Both methods were used in each individual patient from the cohort. Subsequently a comparison was made on how patients were categorized dependent on the type of oxygen exposure analysis (cut-off vs AUC). No correction of patient specific variables was necessary as comparison of the type of analysis was per patient and not patient subgroups.

*$PaO_2$ cutoff analysis:* Three different cutoff values of hyperoxia (>200, >250 and >300 mmHg) were used as proposed in the literature [2, 8-11]. The highest $PaO_2$ value for each individual patient was determined for the first 24 hours of PICU admission. Patients were categorized in 1 of these 3 cutoff groups based on which of the aforementioned cutoff values was surpassed.

*$PaO_2$ cumulative area-under-the-curve (AUC) analysis:* The AUC of $PaO_2$ was calculated to determine the *cumulative* $PaO_2$ of each patient during the first 24 hours of PICU admission. A minimum of four $PaO_2$ measurements within the first 24 hours was required for this analysis. The actual number of available $PaO_2$ samples per patient in this 24 hour time frame was dependent on how frequently an arterial blood gas was drawn for routine clinical care. One step of the AUC calculation included a correction for the time of $PaO_2$ measurement for patients who did not have a 24 hour time period in which $PaO_2$ was measured (e.g. the patient died within 24 hours). This resulted in a cumulative $PaO_2$ per hour, which was converted into the cumulative $PaO_2$ by multiplying by 6, 18, or 24 respectively.

*Exploratory analyses of cutoff and cumulative $PaO_2$:* To enable comparison of $PaO_2$ AUC patient classification to $PaO_2$ cutoff categories, we divided AUC values into the following 4 groups: AUC value < 2000, 2001-4000, 4001-6000 and > 6000. These groups are based on evaluation of individual case analysis whereby an AUC value < 2000 reflected 'physiological' oxygen exposure, an AUC value between 2000 – 4000 'intermediate' oxygen exposure and AUC values > 4000 'high' oxygen exposure. The values for $PaO_2$ AUC and $PaO_2$ max are continuous and are exploratively compared in univariable regression analyses. In the literature $PaO_2$ max is (mostly) used in combination with cutoff values, thus creating different hyperoxia categories.

# RESULTS

## Patient and TBI characteristics

Seventy-one patients met the inclusion criteria for this study between the study period of January 2002 and July 2015. The median age was 8.9 years [IQR 4.6 – 12.9] and 51 (72 %) patients were male. The mortality rate was 18.3% (N=13) of which seven patients (54%) died within 24 hours. The etiologies of death were: brain death (n=6, all of which had an apnea test), withdrawal of life-sustaining treatment (n=6) and cardiac arrest (n=1). The cause of the cardiac arrest was unclear and post-mortem examination did not reveal a specific etiology. Withdrawal of life-sustaining treatment because of unfavorable neurological prognosis was based on repeated neurological examination, brain imaging, and electroencephalography. The majority of patients had been involved in traffic accidents (53%) and displayed multiple injuries on cerebral computed tomography (CT) scan. **Table 1** displays the patient characteristics of the total study cohort.

**Table 1.** Overview patient characteristics

| | **N (%) or median [IQR] when applicable** |
|---|---|
| ***Demographics (N=71)*** | |
| Age (years) | 8,9 [4,6 – 12,9] |
| Male | 51 (72) |
| GCS (first recorded) | 6 [4 – 8] |
| Pupils fixed and dilated (at presentation) | 10 (14) |
| Etiology TBI | |
| *Fall* | 24 (33) |
| *Hit by motorvehicle* | 16 (23) |
| *Passenger motorvehicle accident* | 21 (30) |
| *Hit by object* | 10 (14) |
| ***Radiological findings (N=71)*** | |
| Fracture | 51 (72) |
| Subdural hematoma | 26 (37) |
| Epidural hematoma | 13 (18) |
| Subarachnoidal hematoma | 19 (27) |
| Contusion | 39 (55) |
| Diffuse axonal injury | 22 (31) |
| Midline shift | 18 (25) |
| Hydrocephalus | 5 (7) |

**Table 1.** Overview patient characteristics (continued)

| | N (%) or median [IQR] when applicable |
|---|---|
| ***Surgical intervention (N= 71)*** | |
| Decompressive craniotomy | 13 (18) |
| Extraventricular drain | 3 (4) |
| ***Severity scores (N=71)*** | |
| PIM3 probability | 0.034 [0.028 – 0.068] |
| PRISM3 | 17 [11-22] |
| ***Arterial blood gas values (N= 62)*** | |
| Lowest pH | 7.24 [7.19 – 7.32] |
| Highest lactate, mmol/L | 2.7 [1.9 – 3.8] |
| Lowest $PaO_2$, mmHg | 72 [51 – 90] |
| Highest $PaO_2$, mmHg | 289 [202 – 405] |
| Lowest $PaCO_2$, mmHg | 29 [26 – 31] |
| Highest $PaCO_2$, mmHg | 46 [40 – 61] |
| Cumulative $PaO_2$ AUC 0-24 hrs (N= 66) | 3105 [2547 – 4015] |
| ***Ventilator settings (max value per patient, N= 61)*** | |
| Oxygenation index | 4 [2 – 9] |
| $FiO_2$ | 46 [35 – 78] |
| Mean airway pressure | 11 [9 – 14] |
| ***ICP values (N=70)*** | |
| Median ICP | 16 [ 11 – 18] |
| Minimum ICP | 0 [ 0 – 9] |
| Maximum ICP | 34 [24 – 58] |

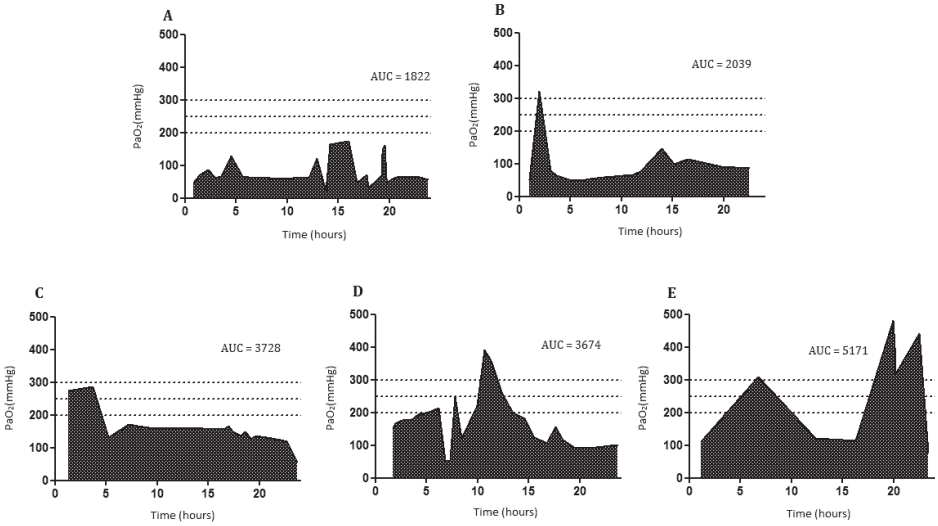
All presented values were determined for the first 24 hour of PICU admission. AUC = area-under-the-curve, GCS = Glasgow Coma Scale, ICP = intracranial pressure, PICU = Pediatric Intensive Care Unit, PIM = Pediatric Index of Mortality, PRISM = Pediatric Risk of Mortality Score, TBI= traumatic brain injury.

## Oxygen exposure analysis

**Figure 1** visually demonstrates the difference in how oxygen exposure can be viewed when defined by a single $PaO_2$ cutoff value versus $PaO_2$ cumulative value (AUC) for the first 24 hours of five different patients in our cohort. The individual patients have varying $PaO_2$ cumulative (AUC) values (presented as increasing values from low to high in patient A and patient E respectively). However this does not mean that a single, absolute $PaO_2$ value necessarily crosses a cut-off threshold. Examples of this difference are patients C and D who have similar cumulative (AUC) $PaO_2$ values (approx. 3700 each) but only patient D crosses the 300 mmHg $PaO_2$ threshold. This illustrates how

different methods of oxygen analysis might lead to different interpretations of oxygen exposure.

**Figure 1.** Oxygen exposure of five patients comparing $PaO_2$ cutoff versus $PaO_2$ cumulative analysis (area-under-the-curve, AUC)




**(A)** Low AUC values, no $PaO_2$ above cutoff values. **(B)** Low AUC value, $PaO_2$ above cutoff values. **(C)** Intermediate AUC value, $PaO_2$ above 2 cutoff values but not highest cutoff value. **(D)** Intermediate AUC, $PaO_2$ fluctuates yet crosses all cutoff values. **(E)** High AUC values, $PaO_2$ above highest cutoff value.

Comparison of $PaO_2$ cutoff and $PaO_2$ AUC classification is represented in **Table 2**. This showed heterogeneity in patient classification whereby some patients could be categorized as both 'hyperoxic' as well as relatively physiological oxygen exposure depending on which analysis was used. Furthermore, patients classified as 'intermediate' oxygen exposure based on $PaO_2$ AUC cumulative analysis showed a wide distribution over the various $PaO_2$ cutoff values.

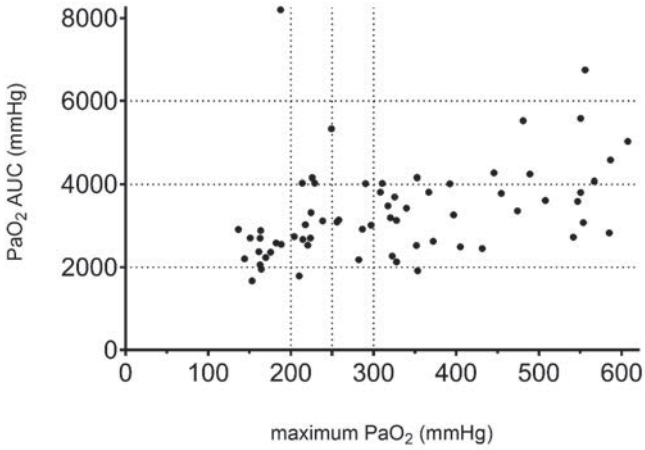
**Table 2.** Patient classification based on $PaO_2$ cutoff versus $PaO_2$ cumulative (AUC)

| | $PaO_2$ AUC | | | | |
|---|---|---|---|---|---|
| | **≤ 2000** | **2001-4000** | **4001-6000** | **≥6001** | **Total** |
| **$PaO_2$ cut off (mmHg)** | | | | | |
| **≤200** | 2 | 11 | 0 | 1 | 14 |
| **201-250** | 1 | 7 | 4 | 0 | 12 |
| **250-300** | 0 | 5 | 1 | 0 | 6 |
| **≥ 301** | 1 | 22 | 10 | 1 | 34 |
| **Total** | 4 | 45 | 15 | 2 | 66 |

All presented values were determined for the first 24 hours of Pediatric Intensive Care Unit admission.
AUC = area-under-the-curve.

**Figure 2** illustrates the variation in patient hyperoxia classification based on the type of analysis and is underlined by a Pearson's correlation coefficient for $PaO_2$ max and $PaO_2$ cumulative AUC of 0.40 (95% CI 0.17-0.58), p-value < 0.001, which reflects fair to moderate correlation.

**Figure 2.** Correlation patient classification based on $PaO_2$ cutoff versus $PaO_2$ AUC




All presented values were determined for the first 24 hours of Pediatric Intensive Care Unit admission. The dotted lines represent the various hyperoxia categories. AUC = area-under-the-curve.PaO2 cutoff categories: > 200, >250 and > 300 mmHg respectively.PaO2 AUC categories: 2001-4000, 4001-6000, > 6000 respectively. Pearson's correlation coefficient is 0.40 (95% CI 0.17 - 0.58), p-value < 0.001.

**Table 3** reflects an exploratory univariable logistic regression analysis of $PaO_2$ cutoff versus cumulative (AUC) and mortality. This yielded a possible association with cumulative $PaO_2$ during the first 24 hours of PICU admission (OR 1.059, CI 1.005-1.117), p-value 0.032. No association was found with the three $PaO_2$ cutoff values or the (continuous) maximum $PaO_2$ value.

**Table 3.** Univariable logistic regression analyses of cutoff vs. area-under-the-curve (cumulative) $PaO_2$ and mortality

| | OR | (95% CI) | p-Value [a] |
|---|---|---|---|
| ***Cutoff $PaO_2$ values*** | | | |
| Max. $PaO_2$ >200 mmHg | 1.791 | (0.353-9.074) | 0.482 |
| Max. $PaO_2$ >250 mmHg | 2.796 | (0.695-11.241) | 0.148 |
| Max. $PaO_2$ >300 mmHg | 1.778 | (0.518-6.097) | 0.360 |
| Max $PaO_2$ in mmHg | 1.003 | (0.999-1.007) | 0.171 |
| ***Cumulative $PaO_2$ value*** | | | |
| AUC $PaO_2$ 0-24h mmHg [b] | 1.059 | (1.005-1.117) | 0.032 |

AUC = area under the curve, CI = confidence interval, max.= maximum, OR= odds ratio, $PaO_2$= partial pressure of arterial oxygen
a two-sided P-value of ≤0.05 was deemed significant.
b Value was rescaled by dividing by 100 in advance of interpretable regression analysis.



## DISCUSSION

This study compared two different types of oxygen exposure analysis ($PaO_2$ cutoff versus cumulative area-under-the curve analysis) and showed major differences in patient classification of hyperoxia and in the association between hyperoxia and mortality. This is an important finding as it could influence our understanding of the relationship between hyperoxia and outcome measures and subsequent therapeutic targets we formulate for clinical care.

The importance of improving our understanding of oxygen physiology in TBI is emphasized by the established harmful effect of hypoxia resulting in international guidelines advocating brain tissue oxygenation tension ($PbtO_2$) monitoring [3, 17]. However, the effects of hyperoxia remain controversial. No formal definition for hyperoxia exists and different modes of analysis have been applied leading to reports of both beneficial and adverse effects of hyperoxia in critical illness in general and TBI specifically [2, 4, 8, 10, 11, 18-25]. To further compound the complexity of this debate, there are reports that suggest the *timing* of arterial hyperoxia, at admission and during the first 24 hours, could influence outcome measures [2, 26, 27]. Potential harmful effects of hyperoxia (e.g. oxygen toxicity due to reactive oxygen species

and vasoconstriction) could be accentuated in the (severe) TBI patient due to higher susceptibility for inflammation and cardiovascular instability thus potentially contributing to increased morbidity and mortality [2, 5-7].

The majority of studies on hyperoxia and TBI use a single value to describe oxygen exposure: either a $PaO_2$ value above an arbitrary cut-off or a maximum $PaO_2$ value used as a continuous value in analysis [2, 4, 8-11, 18-20, 22, 28-30]. However, fluctuations in $PaO_2$ levels are common in critical illness and TBI. The biological rationale for considering an alternative approach to oxygen exposure analysis other than cutoff methodology is that the $PaO_2$ cumulative (AUC) analysis incorporates time and dose dependent factors. This could yield a more realistic description of overall oxygen exposure in comparison to a single cut-off value. In this context, oxygen can be seen as one of the most commonly prescribed drugs in the pre-hospital, emergency room and critical care setting [24, 31]. This could warrant an analytic approach of its exposure similar to other pharmacological agents whereby the clinician attempts to navigate dosage between the margins of efficacy and safety, so-called 'therapeutic drug monitoring' [32]. Parallels can be drawn from pharmacological studies on optimal dosing strategies for antibiotics. Comparison of cutoff versus cumulative (AUC) methodology in this context has demonstrated that cumulative (AUC) analysis could lead to adequate exposure/efficacy for the intended purpose, often at a lower dosage than initially calculated, and subsequently with less toxicity than dosing schemes based on peak and trough levels alone [13, 14]. Applying the same methodology to evaluate (cumulative) oxygen exposure could improve our understanding of oxygen pathophysiology in terms of safety and efficacy [12, 15, 33]. Therefore we found it of interest to explore this methodology in pediatric TBI, an especially vulnerable group where improved understanding of oxygen physiology may be one of the tools to improve overall outcome.

In essence, **Figure 1** illustrated the core finding of our study where oxygen exposure and subsequent hyperoxia classification depended on which analysis method was used. Patient B would be classified as 'high oxygen exposure' based on the fact that one $PaO_2$ value exceeded the cut-off yet the AUC-value is low. On the other hand, patients C and D both have an 'intermediate' AUC value but would be scored differently as far as potential harmful oxygen exposure is concerned when classified by cut-off values. From a clinical point of view, this might mean that supplemental oxygen therapy with $PaO_2$ values consistently on the upper range of what is considered normal could be as harmful as a few moments with very high values of $PaO_2$ and fits the pharmacological concept of a time and dose dependent effect of oxygen when viewing it as a drug. The visual observations represented in **Figure 1** where further underlined in **Table 2** where the differences in patient classification for the total cohort became apparent and demonstrated the extent of the discrepancy in patient classification based on type of analysis. This was also reflected by a fair to moderate correlation between

maximum $PaO_2$ and cumulative $PaO_2$ (Pearson's correlation coefficient of 0.40 (95% CI 0.17-0.58, p-value < 0.001) in **Figure 2**.

Awareness of such potentially large differences in patient classification secondary to methodology, is crucial when attempting to associate oxygen exposure to clinical outcome measures. Therefore we explored patient classification based on cutoff or cumulative $PaO_2$ analysis to mortality (**Table 3**) and interestingly the cumulative $PaO_2$ of the first 24 hours of PICU admission suggested an association with mortality. No conclusions can be drawn from this finding given the retrospective, small sample size. However, it is of interest given previous observations made about oxygen exposure *timing* and outcome measures [26, 27, 34, 35].

There are various limitations which need to be addressed. Obviously a retrospective cohort study with a relatively small patient sample size, variable $PaO_2$ sampling and a short time frame (first 24 hours of PICU admission) makes it impossible to establish superiority of one method of analysis over the other. However, this cohort provided the opportunity to explore two methods of oxygen exposure analysis in a hypothesis generating manner.

From a data collection point of view, this study has an inclusion period of 24 hours after PICU admission because of its explorative nature. This time period does not represent the full scope of TBI pathophysiology and in future studies it would be interesting to investigate the entire PICU admission period, especially given reports on the timing of arterial hyperoxia and outcome [26, 27].



When discussing limitations in the AUC method analysis, we must acknowledge that the AUC method might not be ideal in measuring $PaO_2$ fluctuations. The trapezoidal rule to estimate cumulative $PaO_2$ is commonly used in pharmacokinetic research to measure total drug exposure [12]. An important assumption of calculating the AUC using this trapezoidal rule, is the predictability of the measured concentrations (such as in drugs with a substantial half life time value). This is not the case for oxygen and fluctuations in $PaO_2$ levels are common in critical illness and TBI, resulting in no pattern or predictability in $PaO_2$ levels. Nonetheless, we conclude that the $PaO_2$ cumulative AUC method better captures exposure variability in combination with the time and dose dependent factors than a single $PaO_2$ cutoff approach. Therefore, to optimize the granularity of the cumulative $PaO_2$ AUC approach in future studies, we advocate standardized, frequent $PaO_2$ sampling. Modalities such as transcutaneous $PaO_2$ monitoring might be considered for this type of analysis as it would yield high-frequency, continuous $PaO_2$ data [36]. In general, it must be noted, that systemic arterial oxygenation ($PaO_2$) might not be an adequate surrogate of regional cerebral oxygenation, such as $PbtO_2$. Thus, concomitant $PbtO_2$-monitoring and microdialysis would enable a better understanding in which patients higher supplemental oxygen

administration (and subsequent $PaO_2$ levels) might be justified, but these modalities are currently not available in most clinical settings. Therefore guidelines for supplemental oxygen titration on the basis of $PaO_2$ values would be practical in the clinical context which have been defined based on consensus in the most recent management guidelines of pediatric severe TBI [16].

TBI pathophysiology is complex, multifactorial and dynamic. Our study focuses on only one element in this complex cascade of events. We suggest further prospective studies to investigate the context of cumulative $PaO_2$ in relationship to other physiological parameters, such as intracranial pressure (ICP) and cerebral blood flow (CBF) as well as cerebral oxygen exposure ($PbtO_2$) and cerebral metabolism (microdialysis). This could facilitate establishing which method of oxygen exposure analysis might be most appropriate to define hyperoxia and its subsequent association with clinical outcome measures.

## CONCLUSION

Our study findings are hypothesis-generating and demonstrate that patient classification of oxygen exposure shows major differences based on the analytic method used (cutoff versus cumulative AUC). In our opinion, the cumulative $PaO_2$ (AUC) analysis better accounts for the time and dose dependent nature of supplemental oxygen therapy and deserves further exploration using large, prospective data collection to determine which method of oxygen exposure analysis might be most appropriate before attempting to establish potential causality between hyperoxia and outcome in (pediatric) TBI and the critically ill (pediatric) patient in general. Until more definite answers can be provided on the manner to analyze and interpret oxygen exposure in critically ill (pediatric) patients and titrate this appropriately to the individual patient, awareness that oxygen is the most commonly used 'drug' in the PICU, with the potential for toxicity, should trigger more stringent titration of supplemental oxygen where possible to suggested $PaO_2$ values (90-100 mmHg) conform the most recent international guidelines on the management of pediatric traumatic brain injury [16].

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# 7

# Withdrawal of life sustaining therapies in pediatric severe traumatic brain injury

Naomi Ketharanathan, Maayke Hunfeld, Marcus de Jong, Lineke van der Zanden, Jochem Spoor, Enno Wildschut, Matthijs de Hoog, Dick Tibboel, Corinne Buysse

*J Neurotrauma accepted for publication*

## ABSTRACT

Neuroprognostication in severe traumatic brain injury (sTBI) is challenging and occurs in critical care settings to determine withdrawal of life sustaining therapies (WSLT). However, formal pediatric sTBI neuroprognostication guidelines are lacking, brain death criteria vary and dilemmas regarding WLST persist which lead to institutional differences. We studied WLST practice and outcome in pediatric sTBI to provide insight into WLST-associated factors and survivor recovery trajectory ≥ 1 year post-sTBI. This retrospective, single center observational study included patients < 18 years admitted to the Pediatric Intensive Care Unit (PICU) of Erasmus MC-Sophia (a tertiary university hospital) between 2012 and 2020 with sTBI defined as a Glasgow Coma Scale (GCS) ≤ 8 and requiring intracranial pressure (ICP) monitoring. Clinical, neuroimaging and electroencephalogram (EEG) data were reviewed. Multidisciplinary follow-up included the Pediatric Cerebral Performance Category (PCPC) score, educational level and commonly cited complaints. Seventy-eight children with sTBI were included (median age 10.5 years; IQR 5.0 – 14.1; 56% male; 67% traffic-related accidents). Median ICP monitoring was 5 days [IQR 3-8], 19 (24%) underwent decompressive craniectomy. PICU mortality was 21% (16/78): clinical brain death (cBD, 5/16), WLST due to poor neurological prognosis (WLST_neuro, 11/16). Significant differences ($p$ < 0.001) between survivors and nonsurvivors: first GCS score, first pupillary reaction and first lactate, Injury Severity Score (ISS), pre-hospital cardiopulmonary resuscitation and Rotterdam CT score. WLST_neuro decision timing ranged from 0 to 31 days [median 2 days, IQR 0-5]. WLST_neuro decision (n=11) was based on neurologic examination (100%), brain imaging (100%) and refractory intracranial hypertension (5/11; 45%). WLST discussions were multidisciplinary with 100% agreement. Immediate agreement between medical team and caregivers was 81%. The majority (42/62, 68%) of survivors were poor outcome (PCPC score 3 to 5) at PICU discharge, of which 12 (19%) in a vegetative state. One year post-injury no patients were in a vegetative state and the median PCPC score had improved to 2 [IQR 2-3]. No patients died after PICU discharge. Twenty percent of survivors could not attend school two years post-injury. Survivors requiring an adjusted educational level increased to 45% within this timeframe. Chronic complaints were headache, behavioral and sleeping problems. In conclusion, two thirds of sTBI PICU mortality was secondary to WLST_neuro and occurred early post-injury. Median survivor PCPC score improved from 4 to 2 with no vegetative patients one year post-sTBI. Our findings show the WLST decision process was multidisciplinary and guided by specific clinical features at presentation, clinical course and (serial) neurological diagnostic modalities of which the testing combination was determined by case-to-case variation. This stresses the need for international guidelines to provide accurate neuroprognostication within an appropriate timeframe whereby overall survivor outcome data provides valuable context and guidance in the acute phase decision process.

## INTRODUCTION

Severe traumatic brain injury (sTBI) is a devastating disease with a high rate of mortality and morbidity in mostly previously healthy children.[1] Neuroprognostication in sTBI is especially challenging given the fundamental role and worldwide use of sedation in supportive therapy that hampers neurological clinical examination which is an essential part of neuroprognostication practice. Furthermore, technical aspects of commonly used invasive monitoring systems (eg. metal bolts) limit the application of certain diagnostic modalities, such as brain magnetic resonance imaging (MRI), for detailed information on the extent and evolution of injury. An additional factor to take into account is the potential for significant improvement in pediatric sTBI (both on the level of consciousness and overall functionality) whereby the recovery trajectory can span ≥ 10 years.[2-6] As such, doubt can remain regarding the estimation of poor neurological prognosis and subsequent decision to withdraw life sustaining therapies (WLST). On the one hand, WLST implementation early in the disease course could lead to mortality where an acceptable degree of recovery might have been attainable. Alternatively, delay in a WLST decision could lead to disproportionate and unnecessary burden to the patient, family and society as a whole.[4,7,8] The latter is often more in keeping with the situation wherein WLST is being considered, yet how to balance this against the small chance of a meaningful recovery? It is a dilemma clinicians and families can find difficult to navigate, especially in the absence of international pediatric sTBI neuroprognostication guidelines. Other factors that influence the WLST decision process include professional, personal and cultural beliefs as well as societal factors.[9] The combination of the abovementioned factors account for pronounced differences between centers and regions in WLST practice. This variation accounts for a large variation in WLST associated adult and pediatric TBI death ranging from 40 to almost 90%.[10-18]

It is crucial to evaluate long-term outcome in survivors to better understand the role of WLST within the entire outcome spectrum of (pediatric) sTBI. In this respect, survivors with poor functional outcome at PICU discharge (eg. vegetative state) might provide insight into discriminating clinical and radiological factors in comparison to WLST patients based on poor neurological prognosis.

The primary aim of this study is to describe our single center experience regarding modes of death and WLST timing in pediatric sTBI. Our secondary aim was to review survivor outcome data from this cohort up to two years post-injury.

# MATERIALS AND METHODS

## Study design and participants

We conducted a single center, retrospective cohort study in a Dutch Level 1 trauma center and specialized university children's hospital incorporating a 28 bed PICU (1500 admissions annually, 25% nationwide coverage; Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands). We reviewed all admissions from January 2012 to December 2020 at our PICU for sTBI which was defined as a Glasgow Coma Scale (GCS) of ≤ 8 in patients aged 0 to 18 years and requiring intracranial pressure (ICP) monitoring. ICP-monitoring is performed with an intra-parenchymal catheter as per local protocol. Our institution adheres to current international pediatric TBI treatment guidelines with a tiered approach to treat raised ICP and maintain adequate cerebral perfusion pressure according to age.[19] Follow-up data of survivors were prospectively collected in our standardized, multidisciplinary follow-up program consisting of repeated outpatient clinic visits that include physical and neuropsychological assessments by a pediatric intensivist, neurologist and psychologist.[20]

## Data collection

Data was acquired from electronic medical files after permission was granted from the local medical ethics committee (MEC-2020-0265). Demographic data included age, sex and clinical characteristics such as trauma mechanism, first recorded GCS score and pupillary reactions, injury severity and risk of mortality scores, occurrence of cardiopulmonary resuscitation (CPR), radiological findings and neurosurgical interventions, length of stay in the PICU and hospital. ICP data was one-hourly and analyzed for the first 7 days of PICU admission. Refractory intracranial hypertension (ICH) was defined as ICP > 40 mmHg for longer than 1 hour.[21] All medication is prescribed electronically at our institution. Analgosedation type and dosage was extracted from this electronic medication database. Co-morbidities during PICU admission were reviewed such as (infections, seizures, paroxysmal sympathetic hyperactivity, delirium, renal insufficiency and diabetes insipidus which was defined as polyuria necessitating desmopressin acetate). Radiology reports were used to review brain computed tomography (CT) and magnetic resonance imaging (MRI) results. The Rotterdam CT score was calculated with admission CT scan images by a radiologist for the purpose of this study.[22,23] The radiologist (M.J.) was blinded to clinical outcome. Electrophysiology reports were obtained to determine EEG results during PICU admission. Neurological examination findings around the WLST decision time were reviewed as documented in physician and nursing electronic medical records.

**Outcome measures**

Outcome measures were mortality and functional scores as defined by the Pediatric Cerebral Performance Category (PCPC) 1 year after sTBI as part of our routine outpatient clinic standardized follow-up program. Additional follow-up data (PCPC score, educational level and commonly cited complaints) were incorporated at 2-years post-injury to provide a longer term clinical picture on disease course. The PCPC-data at 2-years post-injury were not used for outcome categorization in statistical analysis due to a higher percentage of missing data (10% vs 3%) and no significant change in PCPC categorization compared to one year post-injury. Mode of deaths were clinical brain death (BD) or WLST based on expected poor neurological prognosis (WLST_neuro). Clinical BD was defined as: GCS score of 3 without brainstem reflexes, no sedation (≥24 hours) or possible effect of neuromuscular blockade administration at the time of neurologic examination by using the train-of-four (a peripheral nerve stimulator to assess neuromuscular transmission), no CPR ≤ 12 hours of neurological examination and a body core temperature of ≥32°C. The WLST decision-making process (decision rationale and timing in relation to the primary event as well as time of actual WLST and time duration to death) were retrieved whereby PICU admission was noted as day 0. Documentation concerning prognosis and WLST decision making were independently reviewed by an experienced (≥ 5 years clinical experience) pediatric intensivist (N.K.) and pediatric neurologist (M.H.). Consensus was reached on mode of death (clinical BD or WLST-neuro) if this was not specifically stated in the medical records. Regarding the survivor outcome measure, the PCPC score ranges from 1 to 6 which respectively represents normal functioning, mild, moderate, severe disability, vegetative state, or death.[24] A 'good' functional outcome was defined as a PCPC score of 1 or 2 whereas a 'poor' was defined as a PCPC score of 3 to 5 and mortality/non-survivor as a PCPC score of 6.

### Statistical analysis

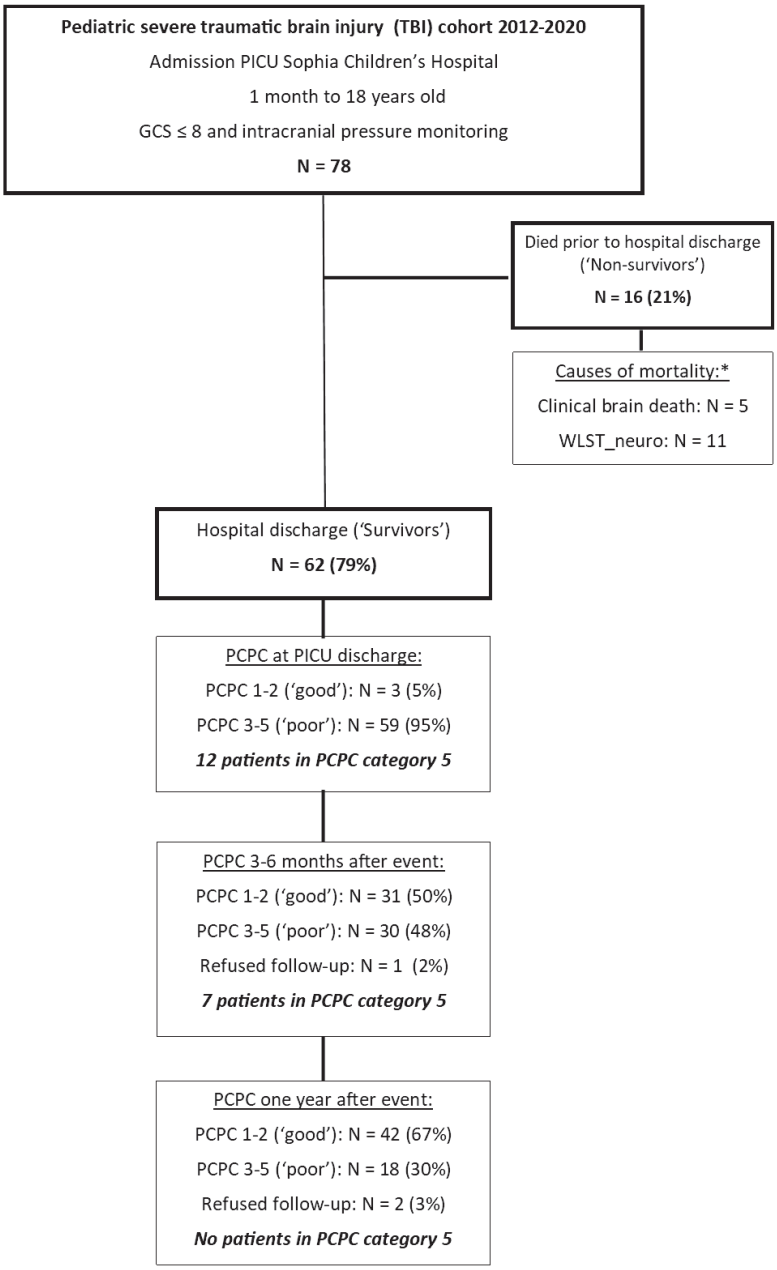
Categorical data are presented as counts (n) and frequencies (%). Continuous data are described as mean and Standard Deviation (SD) or as median [interquartile range, IQR] if not normally distributed. Comparison of good and poor outcome survivors with mortality was studied with chi-square, Fisher's exact test of linear-by-linear association tests for categorical data. Continuous data were studied with the Kruskal Wallis test. ICP value modelling was attempted in a linear mixed model. Repeated measurements analysis was not possible with an ANOVA due to missing values. Logistic regression (with the forward Wald entry method) was used to evaluate the best predictor(s) of mortality and PCPC (values 1-2 vs. 3-5 and values 1-2 vs. 3-6). Gender, age, mechanism of injury, other injuries, CPR, laboratory values, PRISM3, PIM3, ISS, GCS, first pupillary reaction, Rotterdam CT score (individual items and total score), and additionally basal cisterns (open vs. obliterated) were entered into the logistic regression analysis. A 2-sided p-value of ≤ 0.05 was considered statistically significant. Analysis was performed with IBM SPSS Statistics 25.0.0 (IBM Inc.).

## RESULTS

### Patient characteristics

Seventy-eight children were admitted to the PICU of the Erasmus Medical Center, Sophia Children's Hospital, after sustaining sTBI between January 2012 and December 2020. **Figure 1** provides an overview of patient inclusions. The median age was 10.5 years [IQR 5.0 – 14.0]. The most common cause of sTBI were traffic-related accidents (67%) and the majority of patients were male (56%). Overall mortality was 21% (N = 16) and all non-survivors died in the PICU. Six of the 16 non-survivors received CPR at the scene (38%) versus 3 of the 62 survivors (5%).

**Figure 1.** Flowchart of pediatric severe traumatic brain injury cohort (2012-2020)

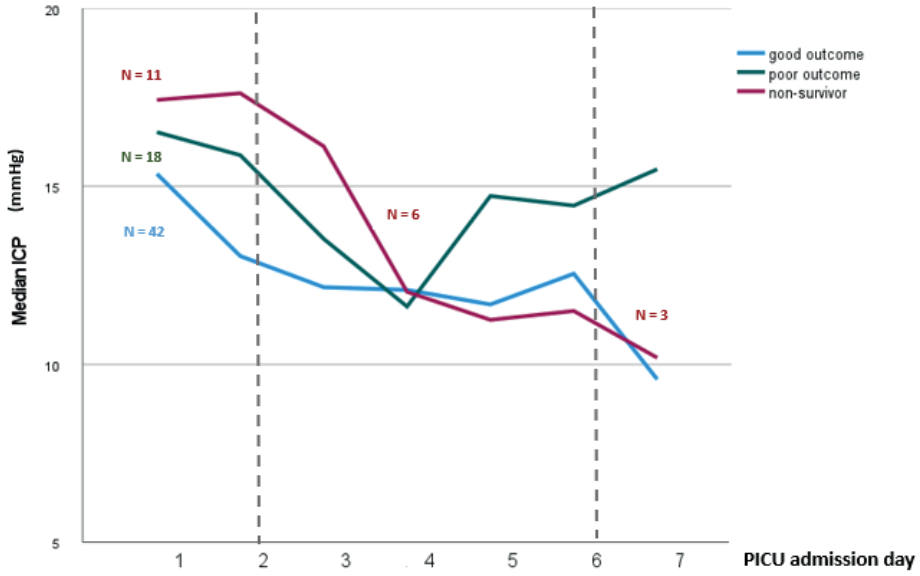



TBI = traumatic brain injury; PICU = Pediatric Intensive Care Unit; GCS = Glasgow Coma Scale; CPR = cardiopulmonary resuscitation; PCPC = Pediatric Cerebral Performance Category, WLST_neuro = withdrawal of life sustaining therapies based on expected poor neurological prognosis.

## Survivors versus Nonsurvivors

The basic and central nervous system (CNS) specific characteristics of survivors one year post-sTBI ( 'good' outcome: n=42; 'poor' outcome: n = 18) and nonsurvivors (n= 16) are presented in **Table 1a** and **Table 1b** respectively. The total cohort number depicted in these tables is 76 patients because 2 patients declined to participate in the follow-up program and therefore could not categorized as 'good' or 'poor' outcome survivor at one year post-injury. **Figure 2** depicts the median ICP trend per outcome category during the first week of PICU admission.

**Figure 2** depicts the median ICP trend per outcome category during the first week of PICU admission.




The median intracranial pressure (ICP) trend per Pediatric Cerebral Performance Category (PCPC) outcome group per day is depicted for the first 7 days of Pediatric Intensive Care Unit (PICU) admission. The PCPC outcome categorization is at one year post-injury and defined as: 'good' for PCPC scores 1 and 2, ' poor' for PCPC scores 3 to 5 and 'non-survivor' is PCPC score 6. It must be noted there was substantial missing data for the non-survivor group (5/16, 31%) and 45% (5/11) of the non-survivors died ≤ 48 hours.

**Table 1a.** Basic characteristics of survivors versus non-survivors

| | | Survivors (good) |
|---|---|---|
| | | **PCPC score 1 and 2 at one year (N=42)** |
| | | Median [IQR] or frequencies (%) |
| | **N** | |
| Age (years) | 42 | 10.0 [6.8-15.0] |
| **Gender (%)** | | |
| Male | 24 | 57 |
| Female | 18 | 43 |
| **Mechanism of injury (%)** | | |
| Bicycle accident | 14 | 33 |
| Passenger | 6 | 14 |
| Fall | 7 | 17 |
| Pedestrian vs motor vehicle | 10 | 24 |
| Other | 5 | 12 |
| **Other injuries (%)** | | |
| Fractures | 12 | 29 |
| Soft tissue/organ | 18 | 43 |
| **CPR** (%) | 1 | 2 |
| **Laboratory values** | | |
| First recorded lactate [mmol/L] | 42 | 1.5 [1.2 – 2.1] |
| **Comorbidities (%)** | | |
| Infection | 21 | 50 |
| VAP | 31 | 74 |
| **PRISM3** | 42 | 16.0 [10.5 – 20.0] |
| **PIM3** | 42 | 11.4 [4.1 – 24.0] |
| **ISS** | 42 | 16.0 [16.0 – 25.0] |
| **PLS** (days) | 42 | 9.5 [7.0 – 18.3] |
| **HLS** (days) | 42 | 25.0 [15.8 – 36.5] |

Subdivision survivor group (one year post injury): Good outcome defined as PCPC score 1 and 2, poor outcome defined as PCPC score 3, 4 and 5. Missing data: 2 patients did not participate in the follow-up program. Data are presented as median ([IQR] or frequencies (%). A 2-sided p-value of ≤ 0.05 was considered significant. PCPC: Pediatric Cerebral Performance Category. NS: not significant. CPR: cardiopulmonary resuscitation, VAP: ventilator acquired pneumonia, PRISM: Pediatric Risk of Mortality Score, PIM: Pediatric Index of Mortality, ISS: Injury severity score, PLS: pediatric intensive care length of stay, HLS: hospital length of stay. A distinction was made between either a VAP or infection otherwise requiring intravenous antibiotics, such as line sepsis.

| | Survivors (poor) | | Non-survivors | |
|---|---|---|---|---|
| | **PCPC scores 3,4 and 5 at one year (N=18)** | | **(N=16)** | |
| | Median [IQR] or frequencies (%) | | Median [IQR] or frequencies (%) | |
| **N** | | **N** | | ***p*** |
| 18 | 11.0 [2.8-14.3] | 16 | 10.5 [2.0-13.9] | 0.71 |
| | | | | 0.639 |
| 11 | 61 | 7 | 44 | |
| 7 | 39 | 9 | 56 | |
| | | | | 0.989 |
| 4 | 22 | 5 | 31 | |
| 3 | 17 | 3 | 19 | |
| 5 | 28 | 3 | 19 | |
| 4 | 22 | 3 | 19 | |
| 2 | 11 | 2 | 13 | |
| | | | | 0.110 |
| 8 | 44 | 8 | 50 | |
| 6 | 33 | 4 | 25 | |
| 2 | 11 | 6 | 38 | **0.001** |
| 18 | 1.8 [1.4 – 2.0] | 15 | 5.7 [2.7 – 8.8] | **<0.001** |
| 13 | 72 | 4 | 25 | 0.34 |
| 15 | 83 | 2 | 13 | **<0.001** |
| 18 | 20.5 [14.0 – 22.3] | 15 | 31.0 [27.0 – 35.0] | **<0.001** |
| 18 | 14.8 [6.6 – 31.4] | 15 | 19.5 [15.0 – 39.7] | 0.07 |
| 18 | 25.0 [16.0 – 41.0] | 16 | 34.0 [26.0 – 39.5] | **<0.001** |
| 17 | 22.0 [17.0 – 28.5] | 16 | 2.0 [1.0 – 5.8] | **<0.001** |
| 18 | 43.0 [34.0 – 48.0] | 16 | 2.0 [1.0 – 5.8] | **<0.001** |

**Table 1b.** CNS characteristics survivors versus non-survivors

| | | Survivors (good) |
|---|---|---|
| | | **PCPC score 1 and 2 at one year** |
| | | **(N=42)** |
| | | Median [IQR] or frequencies (%) |
| | **N** | |
| **GCS score** | | |
| Total at scene | 42 | 6 [5 – 8] |
| M-score at scene | 42 | 4 [2 – 5] |
| **First pupillary reaction (%)** | | |
| Isocoric | 28 | 67 |
| Anisocoric/unilaterally fixed | 13 | 31 |
| Bilaterally fixed, dilated | 1 | 2 |
| **Head CT findings at presentation (%)** | | |
| Skull fracture | 29 | 69 |
| EDH | 8 | 19 |
| SDH | 22 | 52 |
| SAH | 11 | 26 |
| Contusion | 20 | 48 |
| Midline shift | 11 | 26 |
| Diffusely swollen | 6 | 14 |
| Herniation | 2 | 5 |
| **Rotterdam CT score** | 42 | 2 [2-3] |
| **Intervention (%)** | | |
| Decompressive craniotomy | 8 | 19 |
| Extraventricular drain | 2 | 5 |
| **Barbiturate infusion (%)** | 12 | 29 |
| **Intracranial pressure (ICP)** | | |
| Duration monitoring (days) | 42 | 5 [4 – 7] |
| ICP values (mmHg) | 42 | 12 [10-15] |
| **Comorbidities (%)** | | |
| Seizures[a] (acute) | 5 | 12 |
| Seizures (late) | 0 | 0 |
| PSH | 1 | 2,4 |
| DI | 4 | 10 |
| Delirium | 21 | 50 |
| **PRISM3_neuro** | 42 | 5.0 [3.8 – 12.0] |
| **AIS-head** | 42 | 4.0 [3.0 -4.0] |

| Survivors (poor) | | Non-survivors | | |
|---|---|---|---|---|
| PCPC scores 3, 4 and 5 at one year (N=18) | | (N=16) | | |
| Median [IQR] or frequencies (%) | | Median [IQR] or frequencies (%) | | |
| **N** | | **N** | | ***p*** |
| | | | | |
| 18 | 3 [3 – 4] | 16 | 3 [3 – 3] | **<0.001** |
| 18 | 1 [1 – 2] | 16 | 1 [1-1] | **<0.001** |
| | | | | **<0.001** |
| 6 | 33 | 4 | 25 | |
| 7 | 39 | 1 | 6 | |
| 5 | 28 | 11 | 68 | |
| | | | | |
| 13 | 72 | 10 | 63 | 0.71 |
| 2 | 11 | 2 | 13 | 0.46 |
| 11 | 61 | 12 | 75 | 0.12 |
| 14 | 78 | 6 | 38 | 0.11 |
| 8 | 44 | 8 | 50 | 0.93 |
| 4 | 22 | 5 | 31 | 0.79 |
| 4 | 22 | 10 | 63 | **<0.001** |
| 3 | 17 | 10 | 63 | **<0.001** |
| 18 | 2 [2-3] | 16 | 4 [3-5] | **<0.001** |
| | | | | 0.239 |
| 6 | 33 | 5 | 31 | |
| 2 | 11 | 1 | 6 | |
| 6 | 33 | 5 | 31 | 0.79 |
| | | | | |
| 18 | 9 [5-12] | 16 | 1 [1-6] | **<0.001** |
| 18 | 15 [12-19] | 11 | 24 [4-44] | **0.01** |
| | | | | |
| 3 | 17 | 0 | 0 | 0.59 |
| 4 | 22 | 0 | 0 | 0.07 |
| 5 | 26,3 | 0 | 0 | **<0.001** |
| 2 | 11 | 5 | 33 | **0.04** |
| 3 | 17 | 0 | 0 | **0.003** |
| 18 | 12.0 [5.0 – 16.0] | 15 | 16.0 [5.0 -16.0] | **<0.001** |
| 18 | 4.0 [4.0 -5.0] | 16 | 5.0 [4.0-5.0] | **<0.001** |

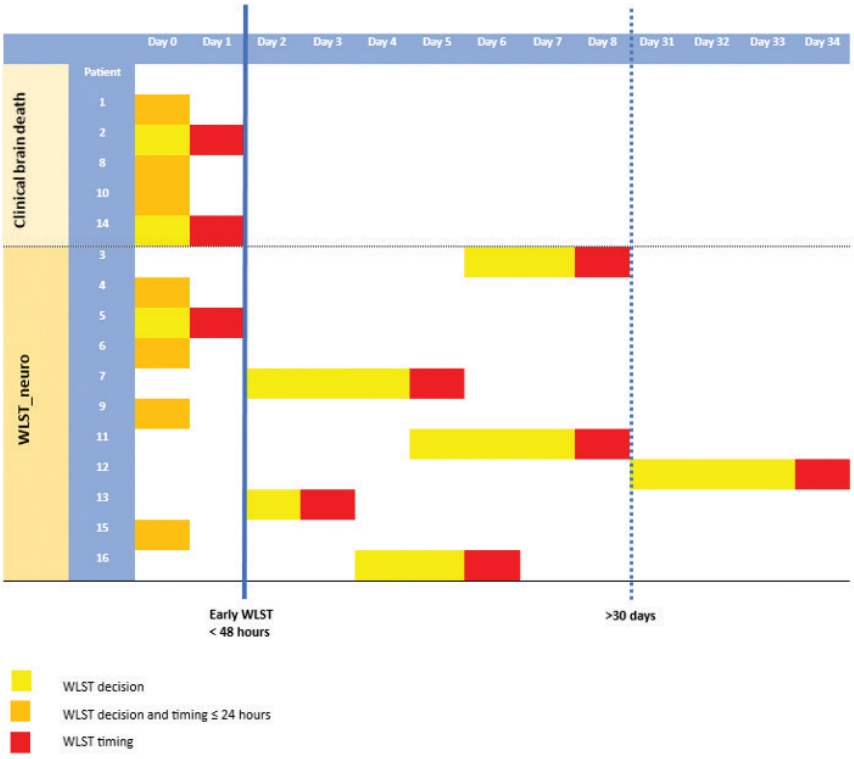
Subdivision survivor group (one year post injury): Good outcome defined as PCPC score 1 and 2, poor outcome defined as PCPC score 3, 4 and 5. Missing data: 2 patients did not want to participate in the follow-up program. Data are presented as median ([IQR] or frequencies (%). a.the presence of seizures on electroencephalogram was subdivided into early (< 1 week after TBI) or late (> 1 week after TBI). CNS: central nervous system, PCPC: Pediatric Cerebral Performance Category, GCS: Glasgow Coma Scale, M: motor, CT computed tomography, EDH: epidural hematoma, SDH: subdural hematoma, SAH: subarachnoid hemorrhage, ICP: intracranial pressure, PSH: paroxysmal sympathetic hyperactivity, DI: Diabetes Insipidus, PRISM_neuro: Pediatric Risk of Mortality Score_neurological score, AIS_head: abbreviated injury scale _ head score.

## Non-survivors

The modes of death for non-survivors (n = 16) were: clinical BD (n = 5, 31%) and WLST-neuro (n = 11, 69%). **Table 2** (Appendix) provides a detailed overview of the non-survivor cohort. The overall median time to WLST decision for non-survivors was 21.3 hours post-injury [IQR 2.8 - 84.0 hours]. WLST decision and timing occurred within 48 hours post-injury in the majority of patients (10/16, 63%), so-called 'early' WLST (< 48 hours post-injury). Differences in WLST decision and timing between cBD and WLST-neuro were: median time *to* decision 20.5 [IQR 8.8-23] versus 48 [1-120] hours respectively. The median time *between* WLST decision and timing was 7.5 [4.3-18.5] versus 32 [7-72] hours respectively. The timeline of WLST is depicted in **Figure 3**. The WLST decision was always in daytime after multidisciplinary review (treating pediatric intensivist, (pediatric) neurosurgeon, pediatric neurologist and PICU nursing staff). All cases had 100% agreement about the WLST decision within the multidisciplinary medical team. There was immediate WLST agreement between the medical team and caregivers in 13 cases (81%). In the other cases, caregivers indicated doubt about the projected poor neurological prognosis and requested more time to consider the WLST decision. This time was used for additional family counselling and repeated clinical examinations per family request. WLST consensus was eventually reached between the medical team and all caregivers and no external second opinion was required. WLST mode was: withdrawal of invasive mechanical ventilation (15/16), cessation of vasoactive/inotropic drugs (9/16), no escalation of current therapy (4/16), withdrawal of ECMO (1/16). The time between WLST and death was ≤ 1 hour for all patients.

Consent for organ donation was granted in 3 cases (patients 2, 3 and 5), declined in 9 and 2 patients were not a candidate due to fulminant multiorgan failure. In 2 cases it was not documented whether consent for organ donation had been requested.

**Figure 3.** Overview WLST decision and timing based on mode of death




WLST: withdrawal of life sustaining therapy. WLST_neuro: WLST based on poor neurological prognosis. For example, in patient 7 the WLST decision was made on day 2 and WLST was performed on day 5 after PICU admission.

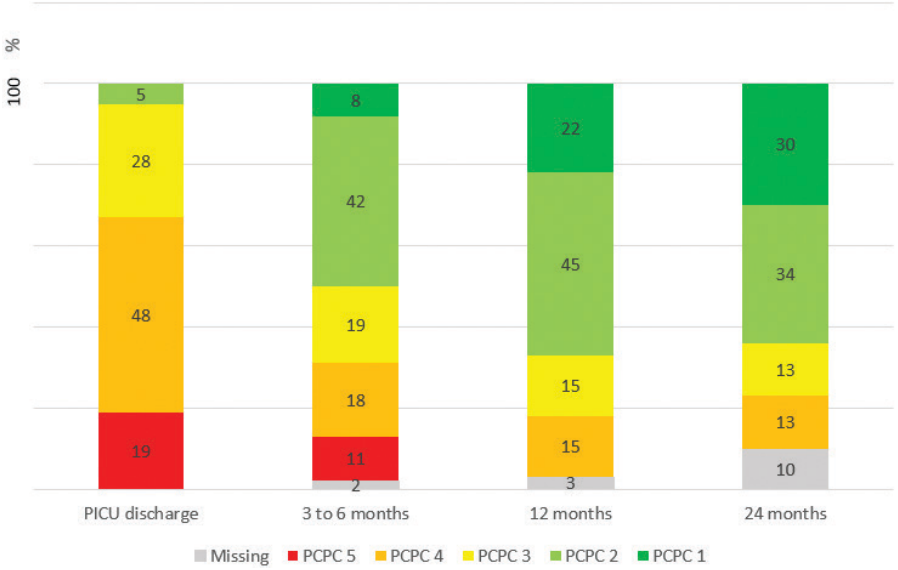
### WLST_neuro decision and timing

Reasons for not meeting clinical BD criteria in the WLST_neuro group (n=11) were: (high) cervical lesions or technical causes (ECMO cannula in jugular vein) (n = 3; patients 5, 7 and 9) preventing brain stem reflex testing, analgosedation ≤ 24 hours (n = 8) and/or CPR ≤ 12 hours (n = 1). All patients were normothermic at WLST decision. Neurological examination showed bilateral non-reactive pupils in 8 (73%) and M-score 1 in all WLST_neuro cases. Refractory ICH and signs of brain herniation/basal cisternal effacement were noted as important reasons in the WLST_neuro decision process (5/11, 45% and 8/11, 73% respectively). A subgroup of WLST_neuro patients (6/11), for whom the WLST decision and timing was longer than 48 hours, showed more time *between* the decision and actual WLST timing (mean 2.2 days, range 0.5 to 3 days) and included 5 patients (5/6, 83%) in whom a decompressive craniotomy was performed (patients 3, 11, 12, 13 and 16).

## Survivor outcome

No survivors had a PCPC score of ≥ 3 prior to sustaining sTBI which could have influenced post-injury PCPC score. The PCPC score evolution post-TBI is depicted in **Figure 4**. The median PCPC at PICU discharge evolved from 4 [IQR 3-5] to 2 [IQR 2-3] one year after sTBI. The median PCPC score at 2 years post-injury remained 2 [IQR 1-4]. No survivors had a PCPC score of 5 after one year. There was no mortality (PCPC 6) after PICU discharge.

**Figure 4.** Evolution of PCPC score post-injury




PICU: pediatric intensive care unit, PCPC: pediatric cerebral performance category. PCPC score ranges from 1 to 6 which respectively represents normal functioning, mild, moderate, severe disability, vegetative state, or death. No patients died after PICU discharge and missing patients were due to refusal to participate in the follow-up program or relocation overseas.

Review of survivor educational level demonstrated that 21% (13/61) were not able to attend school at one year post-injury. This amount remained consistent (20%; 12/60) at two years after sTBI. One year post-injury 25% (15/61) of survivors were able to recommence school at pre-injury educational level and maintained that educational level when assessed at 2-years post-injury. The amount of survivors who required an adjusted educational level increased from 36% (22/61) to 45% (27/60) at two years post-injury. Frequently cited chronic and debilitating complaints were headache (47%; 28/60), behavioral problems (27%; 16/60) and sleeping problems (15%; 9/60).

**Survivors in vegetative state at PICU discharge**

Twelve survivors (19%) were in a vegetative state (PCPC5) at PICU discharge of which one patient had a WLST discussion documented 60 hours after admission. Documented reasons were persistent raised ICP (20-30 mmHg) and progressive hemodynamic instability. Neurological examination showed absent brain stem reflexes after sedation interruption. The follow-up CT scan demonstrated loss of grey-white matter differentiation and slight uncal herniation. On day 4 all sedation was ceased for a final neurological re-examination whereby brain stem reflexes steadily returned and ICP's stabilized < 20 mmHg. This improvement resulted in continuation of supportive therapy. The PCPC score of this patient after one-year was 4.

When comparing the *WLST-neuro subgroup* to the PCPC5 group at PICU discharge the occurrence of CPR was not significant ($p = 0.155$) nor was first pupillary reaction ($p = 0.326$). Significant differences between WLST-neuro and PCPC5 at PICU discharge were first lactate ($p = 0.009$), PRISM3 ($p = 0.005$) and open versus obliterated basal cisterns as scored by the Rotterdam CT score ($p = 0.005$). The total Rotterdam CT score was not significant ($p = 0.075$). Four patients (4/12; 33%) received a tracheal cannula (TC) during PICU admission. All patients were discharged to an inpatient rehabilitation facility of which 3 still had a TC. One year post-injury no patients required a TC and had returned to an adapted home environment and/or with daytime out-patient facility programs. Two patients with spastic tetraplegia were able to communicate via eye computers and 3 participated in Robotics programs to improve their range of movement. These 3 patients demonstrated a cognitive level that allows interaction, communication and degrees of trainability. The mean PCPC score for survivors in a vegetative state at PICU discharge was 4 (range 2-4) one year post-injury and improved to a mean PCPC of 3 (range 1-4) two years post-injury.



## DISCUSSION

To our knowledge, this is the first study to describe the entire outcome spectrum of a pediatric sTBI cohort with a detailed analysis of WLST factors, mortality after PICU discharge and survivor outcome trajectory beyond 1 year post-injury. This study showed an overall mortality rate of 21% (1/3 clinical BD and 2/3 WLST_neuro). Significant differences between survivors and non-survivors were first GCS score, first pupillary reaction and first lactate, ISS, CPR at scene and Rotterdam CT score. The median time to WLST_neuro decision was 2 days [IQR 0-5]. Recurring items in WLST_neuro decisions were neurological examination features (pupils, M-score), presence of refractory ICH and specific CT-head findings (herniation/basal cistern effacement). Additional ancillary testing (EEG and MRI) varied per case. The WLST discussion was multidisciplinary at consultants level. Survivor outcome showed no mortality after PICU discharge. The median PCPC score had improved from 4 [IQR 3-5] at PICU

discharge to 2 [IQR 2-3] one-year post-injury with no more patients in a vegetative state (PCPC 5). Additional survivor outcome data showed 20% of patients were not able to attend school and 45% required adjusted schooling. Chronic complaints included headache and behavioral problems.

Our WLST_neuro rate was higher than the only other comparable study on this topic (69% versus 44% in non-survivors) although overall mortality rates were similar (28% versus 21%).[18] The WLST_neuro difference could be attributed to a higher rate of BD and death due to cardiac arrest in the pediatric sTBI cohort from the study by Baird et al. This may be secondary to their more variable cohort which included patients without ICP-monitoring due to a moribund state or primarily opting for clinical surveillance.[18] In our cohort, all patients received ICP-monitoring with full supportive therapy at onset of PICU admission thereby potentially representing a more homogenous cohort from a therapeutic intention viewpoint. This homogeneity, and thus possibly more clinically stable cohort, might be reflected by the fact that none of these patients admitted for invasive neuromonitoring died primarily due to hemodynamic failure or other reasons. Meeting our clinical BD criteria (as defined in the 'Methods' section, subsection 'outcome measures') proved difficult given the presence of cervical lesions in 3 patients. The difficulty of meeting BD criteria in (pediatric) sTBI is internationally recognized and includes the presence of traumatic cervical lesions hampering brainstem reflex testing, analgosedation as fundamental supportive measure which at the same time is a preclusion to fulfilling BD criteria and variation in BD criteria across countries.[18,25-28] It is thus conceivable that there is an underrepresentation of actual (clinical) BD in (pediatric) sTBI in general.

Our nonsurvivor group analysis affirmed clinical admission features associated with increased risk of mortality (so-called 'early predictors of mortality'): higher injury/severity scores, lower first GCS score, more frequent abnormal first pupillary reaction and higher Rotterdam CT score.[18,23,29] A frequent head CT finding in our non-survivor group, that mirrors others studies, was brain herniation and basal cistern effacement which is often cited as an important neuroprognostication item.[30,31] Nonsurvivors also had a significantly higher first lactate and incidence of CPR at scene. The latter has been associated with lower survival rate and unfavourable outcome in trauma survivors.[2,32,33] Regarding the clinical course in our WLST cohort, overall median ICP values were significantly different ($p$ = 0.01) and visualization of the daily median ICP trend showed potentially different patterns based on outcome category. However, caution is necessary not to over-interpret these ICP trends given missing data in the non-survivor group. Furthermore, early presentation of DI was also present in our study cohort and an indicator of poor prognosis in accordance with other studies.[18,34] Thus, similar presenting clinical features associated with unfavourable outcome (both mortality and poor neurological survivor outcome) were identified in accordance

with other studies on this topic.[2,18,31,33-35] These factors could be incorporated in future recommendations regarding neuroprognostication.

Similar to the study by Baird, the WLST timing was often ≤ 48-72 hours.[18] This encompassed all cBD patients (5/5) and a substantial portion of the WLST_neuro (5/11) patients in our study. Both studies showed that WLST_neuro patients demonstrated a longer time *to* WLST decision and timing than the cBD patients. This could indicate more time taken to evaluate clinical course and neuroprognostication. This may reflect how WLST_neuro patients are given 'the benefit of the doubt' despite other clinical features which are indicators of poor prognosis. In this regard, time should be viewed as a helpful instrument both for the clinician as well as the family in cases where either party may have feelings of doubt and to avoid so-called 'self-fulfilling' prophecies.[11,26,36] Time allows for cardiorespiratory stabilization and repeated assessments (neurological examination, ancillary tests). The defining role of time in the WLST decision process is reflected by the recommendation in adult TBI consensus statements of observing a pre-determined waiting period of > 48 hours (up to 72 hours post-injury).[26,36]

The role of organ donation in WLST timing could not be properly discerned due to the small number of organ donors (3/16) and limited documentation. However, WLST_neuro timing and subsequent organ donation could be associated as shown in a large, multicenter study whereby 25% of early WLST patients were followed by organ donation in contrast to 13% in the late WLST group.[37] Adult consensus statements stress the importance of considering organ donation in this patient category yet at the same time underline only discussing this after families understand and accept the BD diagnosis or WLST decision (based on poor neurological prognosis and/or due to other clinical conditions).[26]

Outcome is inherently associated with WLST_neuro timing. On the one hand, early WLST_neuro could mean mortality whereby acceptable recovery might have been attainable. Although it needs to be underlined that what is deemed 'acceptable' is multifactorial and subjective. Alternatively, WLST_neuro decision delay could result in less mortality at the cost of profound and lifelong morbidity. In general, the question often lingers whether other decisions should have been made in the acute phase for patients who are in a persistent vegetative state at PICU discharge? It is therefore imperative to improve our understanding of factors taken into account in the WLST_neuro decision and where differences lie with poor outcome survivors. To this end, we chose the PCPC5 group at PICU discharge as this outcome is deemed undesirable as consciousness is seen as a pre-requisite for any form of quality of life.[7] In the PCPC5 group, only one patient (1/12) had a WLST discussion documented. The clinical factors that triggered this discussion were comparable to the WLST-neuro group (no brain stem reflexes present and raised ICP) in contrast to the other PCPC5 patients. However it remains speculation whether the absence of WLST discussion

documentation in other patients represents no WLST discussion at all. Comparison of the WLST_neuro and PCPC5 groups demonstrate evident clinical and radiographic differences and a consistent appraisal of these factors in the WLST_neuro decision. The PCPC5 group outcome trajectory was encouraging as it demonstrated all patients regained consciousness ≤ 1 year as well as the ability to communicate. To a certain extent, it supports the WLST_neuro decisions in the overall cohort because no survivors remained in a persistent vegetative state. It does raise the question whether this may have been attainable for patients in the WLST_neuro group? First of all, it is conceivable that if more time to WLST was observed a cBD diagnosis could have been possible in a subset of WLST_neuro patients. Secondly, given the distinct radiographic findings and clinical course of WLST_neuro patients, possible survival would probably have been with considerable functional impairment.

Study limitations are first and foremost the retrospective design with a relatively small cohort whereby investigators relied on medical and nursing file documentation which not always reflects the nuance in the WLST decision process. Secondly, a single-center study is potentially subject to institutional customs and practice which cannot be extrapolated to WLST decision-making and practice in general. Notwithstanding, review of our data showed similar features in the WLST decision process with comparable studies.[9,18,29,31,37,38] Thirdly, we used PCPC score as a functional outcome measure whereby our subdivision (PCPC score 1-2 = good, PCPC score 3-5 = bad) possibly led to underreporting of 'good' outcome instead of overestimation. It is not uncommon to cluster a PCPC score of 3 with 'good' outcome however we chose not to because we wanted a critical appraisal of functional outcome. PCPC does not cover neuropsychological domains and potential deficits in higher executive functioning. We gained insight into the latter by evaluating school attendance and educational level. Our findings suggest obstacles in higher executive functioning based on the high percentage of survivors requiring adjusted schooling (45%). However, specific neuropsychological evaluation is required to determine the domains and extent of potential deficits. Therefore aspects such as 'growing into deficit' [9,39] as well as long term (>2 years post-injury) recovery potential[6,40] add extra challenges in pediatric sTBI neuroprognostication. This emphasizes the importance of long-term outcome data that also provide information on cognitive impairment and health-related quality of life, both for the patient and their family.[41] Hereby keeping in mind that 'years-lived' is much shorter than in adults and potential benefit and burden therefore longer.

## Future directions

More comprehensive and standardized documentation (in terms of content and repeated assessments) regarding WLST discussion and decisions would provide better understanding, transparency and the possibility to share data and serve as quality insurance by medical audits.[26] An example of such a standardized form for clinical use is presented in the **Appendix**. The development of an international consensus

statement on neuroprognostication in pediatric sTBI is long overdue and urgently needed. The potential of ancillary tests such as functional MRI, biomarkers and EEG need to be determined for this patient group. Also, alternative methods of determining ICP-related burden (eg. time-weighted vs cut-off), brain tissue oxygenation and targeting optimal cerebral perfusion pressure based on autoregulation indexes require further investigation into their role in neuroprognostication and outcome.[42-44] Analogous to adult consensus recommendations, it is conceivable that the process of neuroprognostication in pediatric sTBI is ultimately an individualized (repeated) assessment of the wide range of poor prognostic indicators in combination with ancillary tests by a multidisciplinary team over the course of days.[36] Furthermore, it is understandable that a uniform international WLST practice might not be attainable given subjective factors such as medical-professional, family and societal views on meaningful quality of life as well as variation in BD definition.[7,11,28] Nonetheless, the first step in improving our understanding of neuroprognostication and subsequent WLST practice in children with sTBI is a standardized manner of WLST discussion documentation with uniform core outcome data sets for long-term follow-up which include functional, neuropsychological and quality of life assessments.

## CONCLUSION

It is imperative to share clinical experience concerning WLST in pediatric sTBI in the absence of formal, international neuroprognostication guidelines. In this manner, the medical community gains insight into factors that are taken into account in this challenging decision process. Outcome data is crucial to this discussion as it reflects choices made in the acute phase when WLST is performed. Non-survival in our pediatric sTBI cohort was mostly due to WLST based on poor neurological prognosis (WLST_neuro; 69%). Reasons for WLST_neuro were the combination of distinct radiographic findings, refractory ICH and absent brain stem reflexes as well as the inability to comply with BD criteria. One year outcome data of survivors discharged in a vegetative state suggest major radiographic and clinical differences compared to WLST_neuro patients. Furthermore, these survivors all recovered from a vegetative state ≤ 1 year and the median PCPC score was 2 in all survivors 2 years post-injury. WLST_neuro in pediatric sTBI is in the frontline of individualized and shared-decision medicine yet in need of international neuroprognostication consensus recommendations to provide a framework for clinicians and families.

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**Appendix: Box 1.** Documentation WLST decision process:

**Date:**
**Pre-injury functioning:**
**Date of traumatic injury:**
**Pre-hospital:**
- First recorded GCS
- Pupils (both reactive, anisocoric, fixed):
- CPR (Yes/No):

**Injury characteristics:**
- Cerebral injury on first CT:
- Additional (traumatic) injury and Injury Severity Score (ISS):

**Clinical course:**
- Refractory intracranial hypertension (> 40 mmHG longer than 1 hour) (Yes/No):
- Decompressive craniotomy (Yes/No):
- Hypernatriemia (Na > 160 mmol/L)
- DI (polyuria necessitating DDAVP), (Yes/No):

**Ancillary tests (indication and results):**
- Follow-up CT scan brain (timing post-injury and result):
- Other (MRI, EEG, other):

**Neurological examination at WLST decision process** (note if analgosedation ≤ 24 hours or CPR ≤ 12 hours):

**Participants WLST decision process (note date, and whether daytime decision):**

**Family views on quality of life:**

**Conclusion multidisciplinary review (clinical brain death or poor neurological prognosis; note date):**

**Date and time WLST:**

**Date and time declaration of death:**

**Organ donation (yes/no including reason):**

**Appendix, Table 2.** Characteristics non-survivors pediatric severe TBI

| | Sex (M/F) | Age (years) | Event | GCS and pupils[a] | CPR | Neurological exam[b] | CT brain |
|---|---|---|---|---|---|---|---|
| **1** | M | 1 | Fall from height (15 m) | E1 V1M1 Dilated, non-reactive | No | No reactive pupils; No CR; No OCR; no caloric reflex, apnea test negative. No cough reflex. E1 Vt M1 | TAI, transtentorial herniation and supratentorial ischemia |
| **2** | M | 11 | Bicycle vs motor vehicle | E1 V1M1 Pupils not documented | Yes | No reactive pupils; No CR; No OCR; no caloric reflex, apnea test negative. No cough reflex. E1 Vt M1 | Uncal herniation and tonsil herniation through foramen magnum. Right sided SDH and contusions. |
| **3** | F | 16 | Bicycle vs motor vehicle | E1 V1M5 Isocoric, reactive | No | Reactive pupils; No CR; OCR ND; No triggering ventilation; E1 Vt M1 | Initial CT: multiple contusions. Serial follow-up CT show progressive evolution of contusions and uncal herniation. |
| **4** | F | 0.3 | Fall from height | E1 V2M1 Isocoric, reactive | No | Anisocoric, non-reactive pupils. E1 Vt M1 | Progressive global ischemia on follow-up scan. Diffuse cerebral and cerebellar swelling. Herniation cerebellar tonsils. |
| **5** | F | 12 | Crush injury | E1 V1M1 Dilated, non-reactive | Yes | No reactive pupils; No CR; OCR not tested due suspected central chord lesions; no caloric reflex tested due to CSF leakage from the ear; No triggering ventilation; E1 Vt M1 | CTA: brain perfusion present, diffuse ischemia cortex and basal ganglia |
| **6** | F | 10 | Pedestrian vs motor vehicle | E1 Vt M1 Dilated, non-reactive | Yes | Anisocoric (PR 8-/4+); No CR; no caloric reflex, OCR not tested No triggering ventilation; E1 Vt M1 | SDH and contusions. Diffuse ischemia. Herniation with hypodens brain stem. |
| **7** | F | 6 | Pedestrian vs motor vehicle | E1 Vt M1 Isocoric, reactive | Yes | Anisocoric, non-reactive pupils; No CR; OCR not tested due to ECMO; E1 Vt M1 | Diffuse swelling and compression basal cisterns. Progressive loss of grey-white matter differentiation |
| **8** | M | 11 | Bicycle vs motor vehicle | E1 V1M2 Dilated, non-reactive | No | No reactive pupils; No CR; No OCR; No cough reflex or trigger ventilation; E1 Vt M1 | Diffuse swelling, uncal herniation. SDH. |
| **9** | F | 5 | Passenger motor vehicle | E1 Vt M1 Dilated, non-reactive | Yes | No reactive pupils; E1 Vt M1, however severe myelum injury (radiological decapitation) | Diffuse swelling and herniation (mostly infratentorial). Severe traumatic cranio-cervical dislocation |
| **10** | F | 8 | Pedestrian vs motor vehicle | E1 Vt M1 Dilated non-reactive | No | No reactive pupils; No CR; No OCR; no cough reflex; no triggering ventilation; E1 Vt M1 | SAH and SDH. Diffuse swelling with effacement basal cisterns and peripheral liquor space |

| | Intervention | EEG | MRI brain | Analgosedation[c] | Decision WLST[d] | Timing WLST[d] | Decision WLST based on[e] | Clinical BD[f] |
|---|---|---|---|---|---|---|---|---|
| | Bifrontal EVD | - | - | No | 1 | 1 | Neurologic exam + CT imaging | Y |
| | None | Isoelectric | - | No | 1 | 1,5 | Neurologic exam + CT imaging + EEG | Y |
| | DC | Low voltage | Diffuse ischemia cortex, basal ganglia, brain stem | Yes | 6 | 8 | Neurologic exam + serial imaging (CT and MRI) + EEG | N |
| | None | - | Diffuse ischemia cortex, subcortical tissue and basal ganglia | Yes | < 1 | < 1 | Neurologic exam, refractory ICH (70-90) + serial imaging (CT and MRI) | N |
| | None | - | Diffuse ischemia supratentorial cortex, basal ganglia. Central chord lesion C1-C2. SDH Th1-Th7 (no myelum signal deficit) | Yes | < 1 | 1,5 | Neurologic exam + serial imaging (CT, MRI) | N |
| | None | - | - | No | < 1 | 1 | Neurologic exam + CT imaging | N |
| | None | Low voltage | - | Yes | 2 | 5 | Neurologic exam, refractory ICH (>70) + serial CT imaging + EEG | N |
| | None | - | - | No | < 1 | 1 | Neurologic exam + CT imaging | Y |
| | None | - | - | No | < 1 | < 1 | Neurologic exam + CT imaging | N |
| | None | - | - | No | < 1 | < 1 | Neurologic exam, refractory ICH (>100) + CT imaging | Y |

**Appendix, Table 2.** Characteristics non-survivors pediatric severe TBI (continued)

| | Sex (M/F) | Age (years) | Event | GCS and pupils[a] | CPR | Neurological exam[b] | CT brain |
|---|---|---|---|---|---|---|---|
| **11** | M | 15 | Passenger motor vehicle accident | E1 V1M1 Dilated, non-reactive | No | No reactive pupils; E1 Vt M1 | SDH with midline shift. Multiple thoracic and cervical fractures. Progressive frontoparietal ischemia on follow-up scan. |
| **12** | F | 16 | Pedestrian vs motor vehicle | E1 Vt M (ND), Anisocoric, non-reactive left pupil | No | E2 Vt M1, reactive pupils; CR ND; OCR ND; No triggering ventilation, no cough reflex. Areflexia all limbs; Best Motor score M1 | SDH left, diffuse brain swelling with diminished grey-white matter differentiation, TAI. |
| **13** | M | 12 | Bicycle vs motor vehicle | E1 V1 M2 Dilated, non-reactive | No | E1 Vt M1, irregular and non-reactive pupils. Areflexia limbs. Progressive clinical instability. | Bilateral SDH, diffuse brain swelling with transtentorial herniation. Diminished grey-white matter differentiation. |
| **14** | F | 0,8 | Fall from height (forensic investigation into NAI) | E1 V1 M1 Anisocoric | Yes | E1 Vt M1, pupils anisocoric and non-reactive; no CR, no OCR, no cough reflex. | Diffuse brain swelling with development of bilateral uncal herniation. Diminished grey-white matter differentiation |
| **15** | F | 1,3 | Passenger motor vehicle accident | E1 V1M1 Dilated, non-reactive | Yes | E1 Vt M1, anisocoric non-reactive pupils, no CR, no OCR, no cough reflex | Diffuse subarachnoidal and subdural bleeding with herniation. Disseminated skull fractures. |
| **16** | M | 14,5 | Pedestrian vs motor vehicle | E1 V1M1 Dilated, non-reactive | No | E1 Vt M1, non-reactive pupils, no CR, no triggering ventilation | Cerebellar and uncal herniation, supratentorial swelling with midline shift. SDH. |

[a] = first documented GCS and pupil reaction; [b] = at time of decision WLST, [c] = analgosedation < 24 hours from decision and timing of WLST, [d] = number of days after injury, [e] = characteristics the multidisciplinary clinical team decided to withdraw treatment for each individual patient, based on documentation in medical records.

BD = brain death (clinical definition), BS=burst suppression, CR= corneal reflex, CT = computer tomography, DC = Decompressive craniotomy, ECMO = extracorporeal membrane oxygenation, EEG = electroencephalogram, EVD = extraventricular drain, GCS = Glasgow Coma Scale, ICH = intracranial hypertension (in mmHg), MRI = magnetic resonance imaging, ND= not documented, OCR=oculocephalic reflex, OP = opening pressure, PR = pupil reaction, SAH = subarachnoidal hemorrhage, SDH = subdural hemorrhage, SIRPID = stimulus induced rhythmic, periodic, or ictal discharges, TAI = traumatic axonal injury, TBI = traumatic brain injury, WLST=withdrawal of life sustaining therapies

| | Intervention | EEG | MRI brain | Analgosedation[c] | Decision WLST[d] | Timing WLST[d] | Decision WLST based on[e] | Clinical BD[f] |
|---|---|---|---|---|---|---|---|---|
| | DC | - | - | Yes | 5 | 8 | Neurologic exam, refractory ICH (>80) + serial CT imaging | N |
| | DC | Low voltage. Right parietal SIRPIDs | Progressive swelling and effacement gyri and sulci with herniation brain tissue through bilateral craniotomy defects. Hydrocephalus. | Yes | 31 | 34 | Neurologic exam + multiorgan failure + serial imaging (CT and MRI) + EEG | N |
| | DC (bifrontal) | Low voltage frontal activity (artefact) | - | Yes | 2 | 2,5 | Neurological exam, refractory ICH (~30-40), EEG + serial CT imaging | N |
| | None | Isoelectric | Diffuse supra- and infratentorial swelling with diffuse ischemia. Heterogenous signal thalami, bilateral cerebellar tonsil herniation. | No | < 1 | 1,2 | Neurological exam, refractory ICH (> 80), EEG + MRI | Y |
| | None | - | - | No | <0,5 | < 0,5 | Neurological exam and imaging | N |
| | DC | Isoelectric | - | Yes | 4 | 5,5 | Neurological exam, refractory ICH (~45) + serial CT imaging | N |

# 8

# Biomarkers in pediatric traumatic brain injury

**Naomi Ketharanathan, Ursula Rohlwink, Dick Tibboel, Anthony Figaji**

***Lancet Child Adol Health*** *2019; 3: 516-518.*

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide with a significant health and socioeconomic impact (1, 2). The potential long term sequelae of mild TBI (mTBI) are becoming increasingly apparent (2-4). Tools to assess injury severity, monitor patients for early signs of clinical deterioration, and improve prognosis are being investigated. For these reasons, brain biomarkers have attracted increasing interest, with more than 90 different biomarkers studied in pediatric patients with TBI to date (5, 6). The ideal biomarker would indicate the site of injury, and its concentration would indicate severity. Despite major research efforts (3,6), the clinical association between biomarker concentrations and disease severity, clinical and radiological findings, and patient outcome is weak. Additional challenges of studying paediatric patients with TBI are their age-related anatomical and physiological differences, both systemic and in the developing brain, that might contribute to different normative and consequently disease-related biomarker concentrations across the paediatric age range (4, 6, 7).

The study by Sophie Stukas and colleagues,(8) published in *The Lancet Child & Adolescent Health*, measured serum total tau, which is indicative of axonal injury, in 416 healthy children. Blood samples from these control participants were obtained from the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) biobank. Quantification of serum total tau in the control group identified three significant age reference intervals (1-3 years [0.88-19.2 pg/ml], 4-15 years [0.93-5.31 pg/ml] and 16-19 years [0.79-4.20 pg/ml]), with the highest and broadest range of concentrations observed in the youngest age category. The identification of age-related reference intervals for total tau is the key finding of this study, showing that extrapolation of adult values to children is inappropriate and underlining the necessity for generating age-related normative values as a first step in biomarker research before investigating biomarker thresholds in the clinical context.

The investigators used these normative data to interpret serum total tau in 158 children with TBI. Nevertheless, caution is required when interpreting these data to avoid presumptions about a biomarker's value as a clinical tool. Important questions concerning biomarker the clinical usefulness of biomarkers are: is there a diagnostic threshold that allows sufficiently sensitive differentiation of disease severity and appropriate alterations in patient management (eg, requirement for a CT scan), and is there a temporal profile that can guide clinical decision-making and help with prognostication.

The study (8) found that, during day 1 of TBI, median serum concentrations of total tau were three times higher in children with scores on the Glasgow Coma Scale (GCS) for consciousness (GCS) of less than 15 points compared with controls. This finding supported total tau as a marker of injury and offers insight into TBI pathophysiology. However, it did not associate very well with injury severity and abnormalities on CT

scan images. Of note, total tau in the GCS 15 group was indistinguishable from that in control participants, implying that children in this injury group might not require a brain scan or follow-up. Still, these are averaged values and clinical experience suggests that the course of mTBI is variable: some patients with a normal initial GCS score can have abnormal scans and later deteriorate or have a serious disease course after concussion. The suggestions that total tau might differ within subgroups of patients with TBI or might be associated with secondary injury are possibly premature, given that the GCS 13-14 group comprised only nine patients, there was overlap between all grades of TBI severity, including severe TBI. Temporal analysis showed that total tau concentrations decreased from a peak on day 1 in patients with mild and moderate TBI, but remained elevated in patients with severe TBI, albeit following variable trajectories in this group. Thus, these data are preliminary, and the authors correctly state that larger cohorts are necessary to determine the role of total tau in the course and management of TBI.

To date, no biomarker with sufficient sensitivity and specificity has been validated as a clinical tool in pediatric patients with TBI, which poses the question why a bench-to-bedside transition for this condition in this population has not yet been possible. Overall, this study (8) highlights obstacles currently impeding the interpretation and generalisability of biomarker data. These obstacles include heterogeneity of the patient cohort and methodological aspects such as sample type (eg, plasma and serum might yield different biomarker concentrations), sample volume (children have lower absolute circulating volumes of serum than adults), method of sample collection, and type of biological fluid. Other limitations include variation in testing platforms, variability in biomarker-related clinical data elements, inconsistent terminology, and different outcome measures (3, 6). These substantial challenges do not diminish the potential, uniqueness, and necessity of biobanking in paediatric research, as shown by Stukas and colleagues (8). Their study highlighted the importance of determining age-related reference intervals and reiterated the need for an internationally uniform practice of sample and data collection. The need for common practices has already been emphasized by the formation of a working group within the Biospecimens and Biomarkers Workgroup (9) of the interagency TBI Common Data Elements initiative to specifically address paediatric issues to advance research by enabling multicenter collaborations and pooling of data (9, 10).

In conclusion, it is prudent not to prematurely extrapolate preclinical data to a clinical context. Important steps in biomarker translational research include the continued discovery of biomarkers; establishing validated normative data across the paediatric age span; generating standardized protocols for sample collection, processing and analysis; guaranteeing quality control of test assay performance before clinical application; and establishing a clear association between biomarkers and clinical end-points (4). Future directions in clinical application of biomarkers might include a

multi-analyte assay, which would probably better capture the heterogeneity of the TBI disease process (6) and would be advantageous in children in whom sample volume is a limiting factor (4). A solid research infrastructure, such as a biobank, for which best-practice guidelines exist, could prove instrumental in facilitating international collaborations to advance this field of paediatric TBI research.

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# PART IV

## Discussion Summary

# 9

# General Discussion

# DISCUSSION: *CROSSING* BARRIERS

**Barrier [bar-ee-er], *noun*, obstruction (to goal) - Thesaurus**

The brain is the most complex, intriguing and influential organ of the body. Shielded by the skull, floating in liquor and fenced off from direct contact with other substances, it governs the essence of our being. The word barrier means 'an obstruction to goal'. In the context of the brain, this can be seen as desirable when considering the blood-liquor-, and blood-brain-barrier and the protection it offers from harmful elements such as pathogens and toxins. However these barriers are not mere static obstructions. They are highly regulated passages which allow for 'crossing' of that barrier in various manners to maintain homeostasis for the brain tissue environment (1-3). Regarding pharmacotherapy, these barriers potentially pose a challenge as they might lead to a different drug time concentration profile in brain tissue compared to blood plasma as detailed in **chapter 3**, thereby yielding a different efficacy and safety profile depending on site of action. It is therefore of the utmost importance to understand whether and how drugs 'cross barriers' to reach the brain tissue as well as how disruption of such barriers leads to alterations in brain tissue drug disposition.

This thesis describes international analgosedation practices in pediatric severe traumatic brain injury (sTBI) as well as the methods used to investigate pharmacokinetic (PK) behavior and build PK models of frequently administered drugs in children. These methods are put into practice to study Morphine and Pentobarbital PK in pediatric sTBI. Finally, modes of outcome are explored and subsequent decisions about withdrawal of life-sustaining therapies based on projected outcome are described to improve understanding of neuroprognostication factors.

A conceptual framework was introduced in **chapter 1** (**Figure 1**) to describe the 3 main categories that influence the overall result of pharmacotherapy: disease, patient and pharmacotherapy. The following paragraphs will highlight findings and insights from the studies presented in this thesis in terms of the encountered barriers for each aforementioned category and the manners in which these could be crossed.

# DISEASE

## Severe traumatic brain injury

Traumatic brain injury (TBI) remains a leading cause of death and disability across the world (4). It is a heterogeneous disease on various levels. First, the primary injury can vary in degree (focal or diffuse, although this division is not as clear cut as it might seem) and localization (anatomical). Secondly, the extent and interrelation between pathophysiological cascades can vary per patient or within the patient over time; these include brain swelling and compromised cerebral blood flow, oxidative stress, neuroinflammation, blood brain barrier disruption or increased permeability and mitochondrial failure (4-6). In addition, this is further complicated by critical illness that develops due to other injuries (e.g. orthopedic fractures, soft tissue traumatic injuries), hemodynamics (shock states leading to hypoxia), alterations in renal function, organ specific enzyme functioning and generalized inflammation (4, 7). These all combine to create potential inter- and intra-patient differences in brain tissue drug distribution.

To better grasp the extent of this heterogeneity, as well as their dynamic interplay, it is necessary to improve our understanding of the disease process itself. To this end, multimodal neuromonitoring (MMN) can play a key role, whereby high frequency physiological data is gathered in real-time to develop patient-specific therapeutic targets (8-10). Appavu *et al.* reported the implementation of a MMN program in pediatric sTBI management which impacted clinical decisions such as adjustments in patient-specific CPP thresholds and $PaCO_2$ targets in 16.7% and 11.1% of cases respectively. Furthermore, they reported a significant reduction in overall ICP monitoring duration (median 7.0 versus 3.5 days; $p = 0.0017$) and ventilator days (median 9.0 versus 5.5 days, $p = 0.0018$ respectively) (11). These findings suggest an impact on clinical decision-making and a feasibility to tailor clinical care, although the full realm of possible MMN modalities was not used and careful investigation of the specific clinical decision process needs to be performed in larger cohorts and coupled to overall outcome. The plethora of brain-specific parameters that can currently be monitored include intracranial pressure, cerebral perfusion, oxygenation, electrophysiology, and markers of cerebral metabolism and tissue injury. All these opportunities give rise to new challenges in the form of data acquisition, analysis, display and interpretation that require specific expertise from bioinformatics to partner with clinicians to translate and present this data in a manner that is useful at the bedside (12).

Nonetheless, MMN provides the opportunity of correlating (pharmacological) interventions to patient-specific (patho-)physiology. Given the multitude of disease factors as mentioned earlier, the first step in this process is to attempt to discern disease subgroups and related clinical patterns. This requires large patient cohorts with uniform data acquisition to enable disease characterization and clinical course profiling. There are currently 3 large, prospective multi-centered TBI studies performed

as part of the International Initiative for TBI Research (InTBIR): ADAPT (Approaches and Decisions in Acute Pediatric TBI; international study on pediatric TBI), CENTER-TBI (Collaborative European NeuroTrauma Effectiveness Research in TBI; adult and pediatric patients in Europe and Israel) and TRACK-TBI (Transforming Research and Clinical Knowledge in TBI; adult and pediatric patients in U.S.) (13). Uniform data acquisition holds the potential for alternative study designs such as comparative effectiveness. Other trial approaches used in so-called implementation science include staggered approaches, which aim to assess the effect of an intervention in the absence of randomization (14-16). These strategies, amongst others, might specifically benefit pediatric research because the existing evidence is weak. Single centre studies are often hampered by small patient cohorts, from which it is difficult to draw any meaningful conclusions. To illustrate this, the international guidelines for severe pediatric TBI management include 22 recommendations of which *none* are Level I evidence, 3 are Level II and the remaining 19 (including analgosedation) are Level III evidence (17).

In light of the past two years, an observation must be made about the impact of *other* diseases on clinical care and research in general. The SARS-CoV2 pandemic that held the world in its grip for 2 years has proved to be a double-edged sword. On the one hand, lock-down measures reduced access to care for the patient and family/visitors with all its physical and psychological ramifications in the short and long term (18). As for sTBI (severe TBI) management, critical care was maintained but the subsequent rehabilitation programs and physical outpatient follow-up programs were adversely impacted by social restrictions (19). On the other hand, the lockdown period was associated with a significant drop in injuries: Keays et al reported that Emergency Department (ED) visits for motor vehicle collisions were almost non-existent compared to epidemiological data during the same period in previous years (20). A multicenter study from the Netherlands reported that pediatric ED visits and hospital admissions decreased by a third during lockdown (21). A multi-center study of accident- and injury-related Pediatric Intensive Care Unit (PICU) admissions in Germany observed a total decrease in admission secondary to accidents and injuries. Understandably trauma mechanisms were also altered – while outdoor mechanisms (e.g. traffic and school/kindergarten) decreased, household and leisure-related accidents became more prevalent. There was no evidence for increased child abuse cases requiring PICU admission (22).

There were also major implications for research. The pandemic led to unprecedented scientific breakthroughs in vaccine development because of swift collaborative efforts across all scientific lines. At the same time however, a shift in prioritizing resources resulted in a near halt to most (clinical) non-Covid related research projects and scientific output decreased (23). Awareness of this phenomenon and active reinvigoration of halted

projects need to be a priority now that Covid-restrictions are being lifted. Arguably, conditions with high pediatric mortality and morbidity, such as TBI, should be prioritized.

**Table 1.** Disease specific barriers in pediatric neuropharmacology and manners in which these can be crossed.

| Barrier | Crossing |
|---|---|
| Disease heterogeneity and dynamic nature | • Collaboration (between disciplines, between centres)<br>• Multimodal neuromonitoring<br>• Uniform data acquisition and data sharing<br>• Alternative study designs (comparative effectiveness, staggered approach) |

## PATIENT

### A developing individual

The pediatric patient poses unique challenges in clinical and research pharmacology due to the astounding developmental changes up until adulthood (24, 25). Physical changes, such as weight and overall body composition, influence drug distribution. Less evident, but equally important, are age-related changes in drug enzyme maturation, plasma protein binding capacity, total body water %, renal and hepatic maturation influencing drug metabolisation and elimination (26). Each of these are crucial features of PK (ie. *'what the body does to the drug'*) which encompass the processes of absorption, distribution metabolism and excretion (27, 28). In terms of pharmacodynamics (PD; i.e. *'what the drug does to the body'*), drug transporter and receptor maturation influence drug effect (24). In addition, the disease itself can influence drug enzyme functionality thereby influencing drug PKPD. For example, Midazolam clearance is mediated by cytochrome P450 (CYP) 3A, which can be reduced secondary to inflammation and organ failure (29). Furthermore, pharmacogenomics adds an additional layer of heterogeneity to the aforementioned age- and disease-related developmental changes because inter-individual variability of expression of metabolizing enzymes (e.g. CYP2D6) and transporters (e.g. P-gp) can influence drug efficacy and toxicity (30-33). Anatomical and physiological changes of the brain are also relevant. First, there is an impressive postnatal growth spurt of the brain: at birth it is 25% of the adult size, tripling in size to 70% at 18 months, 90% at 5 to 8 years of age and reaching 95% of adult size by 10 years of age (25, 34). This affects brain tissue volume of distribution for drugs. Second, how the blood-brain barrier continues to develop after birth into early childhood needs better understanding. It seems the blood-brain barrier is not as immature as thought at birth regarding permeability, but drug transporter functionality (e.g. P-gp) is perhaps important in the postnatal phase and during infancy (35, 36).

Although the need for better understanding of pediatric sTBI pathophysiology as well as evidence-based therapies is clear, achieving this is difficult given how highly regulated pharmacological studies are in children. Although it is important that research be closely monitored, developing these studies from clinical imperatives is difficult. Very often it is the pharmaceutical industry that direct the studies because they have both the infrastructure and financial means to meet current regulatory demands. Understandably, questions arise about the research outcome of industry sponsorship (37-39). This may not always be in the best interests of the patient. Furthermore, pediatric pharmacological drug data is often derived from patients with a medical condition as, again, legislature practically inhibits research on healthy pediatric volunteers. Therefore, the question is how representative these data are for the general population as it is studied in a population with concurrent factors that possibly influence drug PK as detailed earlier (30, 31)? Paradoxically, efforts to protect vulnerable children with increased clinical trial regulations often lead to the opposite effect: little evidence is developed to guide clinical care. Children become so-called 'therapeutic orphans', in whom drugs are now administered without sufficient safety and efficacy data (40). Therefore, pharmacology study sponsorship from other sources need to be improved, and regulatory agencies reassessed. The essence of regulatory measures in the interest of patient welfare must remain intact but the administrative burdens must be relieved and the necessity for certain interventions must be recognized. A promising initiative in this direction is the establishment of a large collaborative European network called 'Conect4Children' (C4C) that encompasses both academic and private sectors (including industry) to facilitate drug therapy development for the entire pediatric population (41). Recent history has shown that collaborative efforts between commercial and non-commercial institutes can accelerate drug development thereby reaping rich rewards together (42).

Other well-established obstacles in pediatric pharmacology research are restrictions concerning sample volumes (≤ 3% of circulating volume) and sample numbers from the individual patient. Furthermore, studies that involve invasive procedures (e.g. cerebral microdialysis to obtain extracellular fluid from the brain, $brain_{ECF}$, the most representative of brain tissue itself) are reviewed with high scrutiny and frequently not deemed appropriate by medical review boards as they are primarily explorative instead of therapeutic (31). Therefore, when the opportunity arises that samples from highly sought-after target sites (such as brain tissue) are available, alternative study approaches need to be used to generate maximal and meaningful output. To this end, preclinical animal models (physiologically based PK models; PBPK) can be used to *generate* fundamental data to explore PK characteristics of a drug, *build* a PK template which is then scaled to human proportions depending on age and *validated* with human drug concentrations by comparing predicted and actual concentrations (43-47). Another valuable approach to developing a drug PK template for dosing is population-based modelling whereby scarce samples from single individuals are pooled

to explore potential significant covariates (e.g. weight, renal function) of importance (48-50). Other technical advancements, such as liquid chromatography tandem mass spectrometry (LS/MS-MS), that have been implemented to tackle the challenge of small sample volumes are addressed in the following section.

**Table 2.** Patient specific barriers in pediatric neuropharmacology and manners in which these can be crossed.

| Barriers | Crossing |
|---|---|
| Patient specific developmental changes | Translational research (ontogeny) |
| Sparse samples per patient (both size and number) | • Population based statistical analysis<br>• Technical advancements (LC-MS/MS) |
| Pediatric pharmacology research regulations | Alternative study designs (population based statistical analysis and pre-clinical animal models, PBPK) |
| Variation in privacy laws obstruct data sharing | Dialog with policy makers and regulatory agencies |

# PHARMACOTHERAPY

## Analgesics and sedatives

Analgesics and sedatives are among the most frequently prescribed drugs in the PICU and are fundamental in the supportive management of sTBI (51). As described in **chapter 1**, the failure rate of CNS candidate drugs is high (>90%) and the incidence of off-label and unlicensed medication use in PICUs astounding (80-90%) (42, 52). A major factor responsible for this unfavorable track record in neuropharmacology research is insufficient attention to the importance of unbound drug concentrations in plasma as this is what drives transportation into the brain and determines drug concentrations in brain tissue (53). Even impressive research consortia (Operation Brain Trauma Therapy; OBTT) that recognize the importance of pre-clinical drug candidate selection and use an array of animal injury models incorporating focal, generalized and repetitive injuries, fail to apply basic fundamental PK CNS research into unbound drug distribution. Instead, *serum* biomarkers are used as one of their outcome measures (54). Due to lack of evidence the choice of analgosedation is ultimately left to the treating physician (17):

> *'....the specific indications, choice and dosing of analgesics, sedatives and neuromuscular blocking agents should be left to the treating physician'.*
>
> Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, 3rd Ed, 2019.

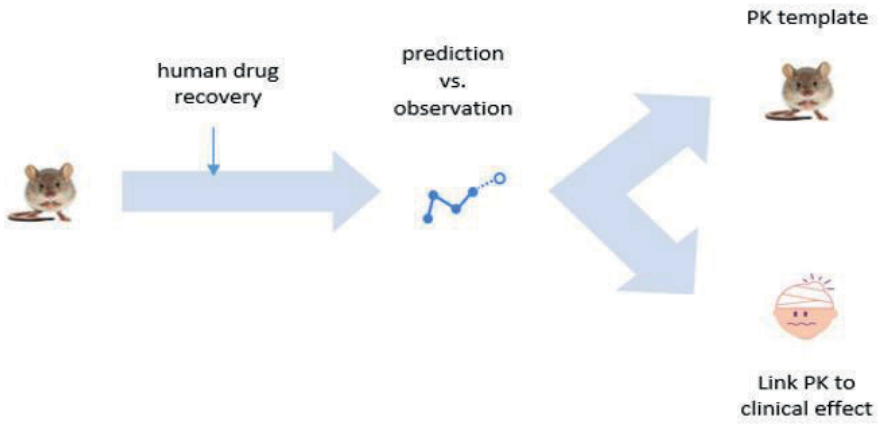
Notwithstanding, the high failure rate in CNS drug trials is not surprising given the fact that study designs are often similar to those of non-CNS target site drug candidates. This demonstrates an under-appreciation of the complexity of the brain barriers that unbound CNS drug has to cross and the many factors (patient, drug, disease-related) that influence this ability (55, 56). This is a key part of the failure to recognize the limited understanding of drug PK in sTBI. **Part 2** in this thesis focusses on the PK aspect of analgosedation with the aim of characterizing their time concentration profile dependent on patient- and disease-specific co-variates both in blood plasma and the CNS in the pediatric injured brain.

Alternative trial designs to elucidate CNS PK could entail collaborative efforts between pre-clinical and clinical institutions adopting the combination of technical advancements such as cerebral microdialysis, statistical and mathematical approaches to PK modelling, and the use of animal models in fundamental data acquisition on PK processes. The study presented in **chapter 4** is an example of the feasibility of this approach. We demonstrated it was possible to successfully develop a CNS PK template for Morphine in children with sTBI based on pre-clinically acquired data from rats which was scaled to human proportions, the so-called humanized PBPK model. Real-time patient samples from blood and $brain_{ECF}$ were obtained and low-volume concentrations successfully determined with LC/MS-MS techniques after transporting samples across two continents. In total, 4 centres, each with their specific expertise, were collaborators in this study. As for CNS-specific PK observations, the influence of injury characteristics (focal vs generalized injury) on BBB integrity and subsequent drug time concentration profiles where possibly reflected by this humanized CNS PBPK model whereby its predictive ability was less in patients with diffuse injury. This observation could be explained by the fact the animal PBPK model was built on healthy rodent data. It would be informative to investigate PBPK models with injury rat models (54, 57) instead of healthy rats as used in this study to possibly better capture the influence of injury characteristics on temporal profiles of CNS drug distribution. This study also reinforced the key role for cerebral microdialysis in obtaining samples most representative of the CNS target site (i.e. the brain): it was the $brain_{ECF}$ samples that suggested differences in drug distribution based on brain injury characteristics whereas the temporal drug distribution profile of morphine in blood did not (46, 55, 58). As such, this once again seems to reinforce the concept that extrapolating drug PK data from blood to the brain is inappropriate. Another technical advancement crucial for this study is the development of LC/MS-MS that is pivotal to detect small molecular drug levels in low volume samples and in alternative matrices to blood (59). The hourly samples of cerebral microdialysis (MD) from $brain_{ECF}$ are approximately 10 microLitres.

Despite the enormous potential of cerebral MD in CNS drug studies, 2 important aspects must be addressed. First of all, the cerebral MD catheter membrane has

a diameter of 0.6 mm and therefore reflects a small area of brain tissue (60). This requires consideration about where to place the MD catheter in brain tissue at the onset of monitoring as well as generalizability of MD data to the rest of the brain. It is important to acknowledge whether the acquired data reflect the pharmacological status of sick or relatively healthy brain tissue and whether this fits the study aims. Secondly, the MD catheter membrane is less apt to dialyze lipophilic substances (e.g. Midazolam) in contrast to hydrophilic components (e.g. Morphine and its metabolites). This influences MD drug component yield and how reflective it is of the actual CNS PK status of that specific drug. Improved MD membrane characteristics could solve this matter and enable better quantification of lipophilic CNS drug PK. Overall, the value of pediatric samples is enormous, especially from sites such as $brain_{ECF}$, which emphasize the importance of biobanking and datasharing platforms to maximize potential scientific output. The next step after this successful pilot study is to validate the current Morphine PBPK model with additional patient samples and then design a PD study using this PBPK Morphine model.

**Figure 1.** Overview stepwise approach to developing a humanized physiologically-based pharmacokinetic model. An animal-based pharmacokinetic (PK) model is developed and re-scaled to human proportions for the individual patient. The predicted versus observed drug concentrations (from human drug recovery by cerebral microdialysis) are compared and if there is good prognostic accuracy then a PK template has been validated for that specific drug. This PK template can be used to study pharmacodynamic (PD) properties of that specific drug.




Another valuable approach in pediatric pharmacology is population-based PK (popPK) modelling because it only requires a few samples per patient which can even be extracted from remnant clinical material and performed retrospectively thus minimizing burden to the child (48-50). This study design was applied in **chapter 5** to develop a population-based PK for Pentobarbital in Status Epilepticus (SE) and sTBI to facilitate therapeutic drug monitoring (TDM). TDM has rapidly become indispensable in clinical pharmacology to measure drug concentrations and assess whether dosing

adjustments are warranted (e.g. the amount of drug per time or interval time between doses) (61). By means of TDM, patient efficacy and safety is monitored. Despite the notable differences in underlying pathology requiring Pentobarbital infusion, the study described in **chapter 5** was able to develop a popPK model with good fit using a one-compartment model and allometric scaling. This popPK model then was used to identify potential significant covariates. Serum creatinine and CRP > 70 mg/L significantly correlated with Pentobarbital clearance leading to potentially important dosing adjustments in patients with elevated serum Creatinine and/or CRP. This could be of great importance as timely dose adjustments could be made and impending Pentobarbital intoxication deterred. The exact interpretation of serum creatinine in this context remains elusive as it could either represent renal impairment or be a measure of overall illness severity. The latter seems most applicable given the significant correlation with CRP. Furthermore, it was surprising that a renal marker would prove a significant covariate for a drug that is mostly hepatically metabolized. Therefore, the interpretation of serum Creatinine must be made with caution. As a marker of illness severity, it could reflect overall disease state and hemodynamic failure correlating with hepatic dysfunction on the microlevel of enzymatic function. Either way, the observations made during this study reflect Pentobarbital PK in terms of safety only and not efficacy. The latter could be incorporated by including EEG data to correlate Pentobarbital levels to EEG readings. The popPK model developed in this study could form a basis to build on for CNS PK models. Finally, regarding the choice of PK compartments in a PK model, it was interesting that a one-compartment model fit performed as well as a two-compartment model in this Pentobarbital popPK study, despite the lipophilic nature of Pentobarbital and its propensity for storage in adipose tissue. Despite this knowledge, the aim in developing a PK model is to describe PK adequately as well as keep it manageable for the modeler and clinical pharmacist in daily use. Further investigative studies based on our findings in **chapter 5**, would involve further refining the popPK model with additional covariates indicative of disease factors and severity, with special attention to various markers of inflammation which is known to influence drug PK (29, 62). In addition, application of the current Pentobarbital popPK model for simulation studies to the ADAPT study cohort, which consists of only sTBI patients, could further improve the model for undetermined disease-specific factors. Furthermore, it would be of interest to explore a manner in which the dynamic nature of certain (disease-) covariates used in the popPK model are better represented. MMN fulfills herein an important role in capturing changes incremental to drug effect and toxicity during drug administration (eg. hemodynamic changes and EEG patterns) (8, 63). In the meantime, steps that could already be taken involve the international multi center studies ADAPT and CENTER-TBI that contain a plethora of observational data on drug dosing and clinical variables. The development of drug specific CNS PK templates could be a valuable way of linking patient-specific PK to PD and provide the next step in determining the road forward in evidence-based pharmacotherapy in sTBI.

It needs to be reiterated that the choice of study design in PK research should fit the purpose (26); i.e. are we attempting to further our understanding about fundamental PK behavior of a drug and if so, are the samples we collect representative for the target site? Is the objective to couple PK to PD and if so, how do we measure and define the clinical targets? This is a multidisciplinary discussion that must be held with representatives between disciplines and centers to create an infrastructure that supports and facilitates such an approach.

All the aforementioned steps reinforce the concept that including a critical care pharmacist in the daily decision-making of the ICU team improves outcome as this could lead to valuable recommendations about dosing and timely dose adjustments (64).

**Table 3.** Pharmacotherapy specific barriers in pediatric neuropharmacology and manners in which these can be crossed.

| Barrier | Crossing |
|---|---|
| Lack of PK data in the pediatric population | • Translational research at target sites<br>• Biobanking<br>• Datasharing<br>• Statistical and mathematic methods (PopPK, PBPK) |
| Samples (from target site, sufficient volume) | Technical advancements (microdialysis, LC/MS-MS) |
| Age- and weight-based dosing insufficient | • Individualized dosing with PK templates<br>• Pharmacogenetic screening<br>• MMN to incorporate dynamic disease factors |
| Multifaceted, complex studies | Interdisciplinary and inter-center collaboration (national, international, preclinical and clinical, bioinformatics, technical) |

In summary, neuropharmacology is an incremental part of sTBI management, for which many factors in terms of disease, patient and pharmacotherapy characteristics need further investigation. The need is urgent, given the paucity of evidence-based data on (pediatric) neuropharmacology, the potential safety issues, and the risk of suboptimal therapies. Current infrastructure in both the pharmaceutical industry and academia need re-assessment on how best to cross the barriers encountered in providing evidence-based therapeutic recommendations. To this end, increased awareness and appreciation for neuropharmacovigilance is required (65, 66). Only with joint efforts, steps can be taken to improve therapies and ultimately improve overall outcome in severe traumatic brain injury. This concept is summarized in **Figure 2**.

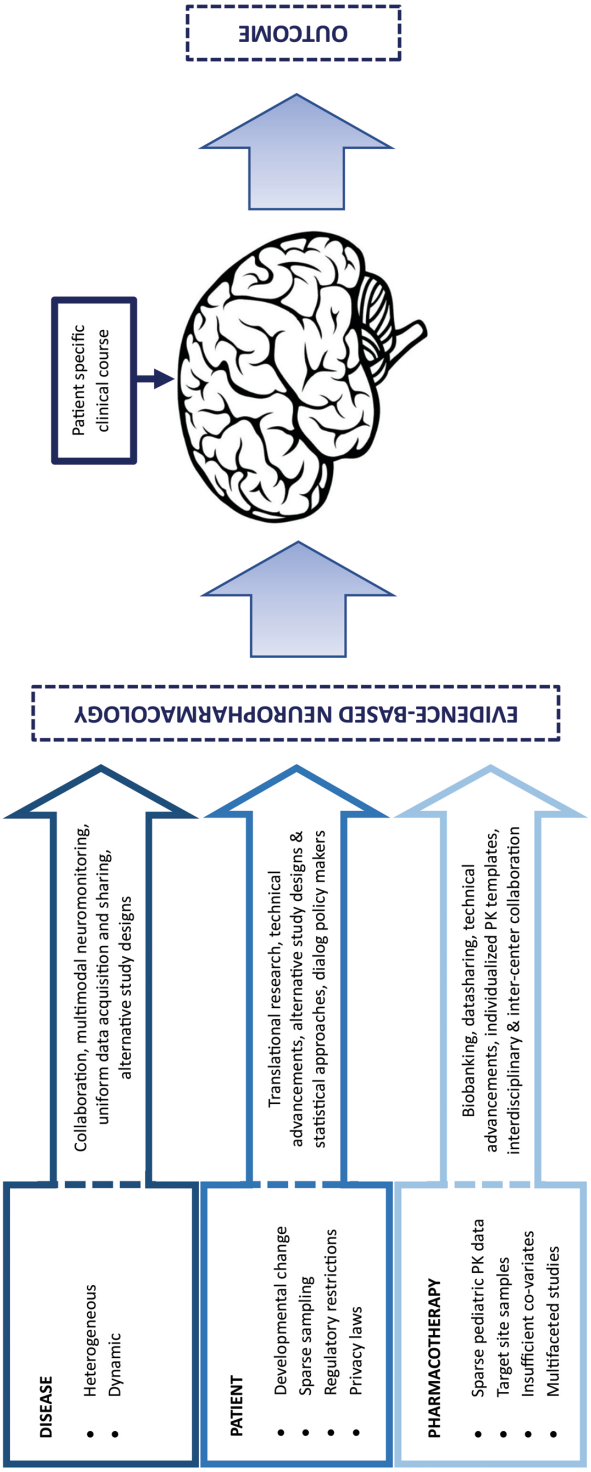



**Figure 2.** Overview of disease, patient and pharmacotherapy specific barriers and how to cross these barriers towards evidence-based neuropharmacology.

# OUTCOME

## Disability, death and decisions

TBI poses a global health problem of significant proportions. Annually, over 50 million people sustain TBI worldwide and it has been estimated that approximately half of the world's population will have one or more TBI's during the course of their life. Besides the impact to the individual and their direct environment, society as a whole is burdened by this disease: costs to the global economy are estimated at around $US 400 billion each year (4). The worldwide incidence of pediatric TBI shows geographical variations, ranging from 47 to 280 per 100.000 children. The age distribution is a bimodal pattern: infants (< 2 years) and adolescents (15 to 18 years) are most commonly affected. Although attention is mostly focused on sTBI, this is a relatively small group within the TBI spectrum. Mild TBI (GCS ≥ 13) constitutes the vast majority (80%) (67). Therefore, the reality of TBI disease burden to society is probably even greater than anticipated. In recent years the potential long-term impact of mild to moderate TBI is garnering increased interest due to concerns about chronic traumatic encephalopathy and increased risk of neurodegenerative diseases over time (4, 43, 68, 69).

The outcome studies in this thesis first investigated how target definition influences patient categorization, this is fundamental to outcome studies. In **chapter 6** oxygen exposure was used as an example of one of the most commonly prescribed 'drugs' in critical care settings that have potential for toxicity (70). Analogies were drawn from pharmacotherapeutic principles whereby one could consider how to perform optimal TDM for this specific 'drug': cut-off versus cumulative exposure? Our findings demonstrated a difference in patient categorization in what could be considered hyperoxia and risk for adverse outcome. Such findings should challenge our paradigm of thinking and the choices we make regarding therapeutic or safety targets and their association with outcome. In this study we advocated further prospective studies regarding cumulative oxygen exposure because this may best represent the time- and dose-dependent manner of supplemental oxygen therapy. Applications to other (patho-)physiological parameters should also be considered, especially those we target in sTBI management, such as ICP, CPP, $PbO_2$. The spectrum of these parameters could be further expanded from focal data (such MD measures of glutamate exposure/ burden, lactate/pyruvate ratio, glucose) to systemic factors (such as blood sodium as a marker of hyperosmolar therapies). In recent years there has been increased interest in the concept of cumulative burden, for example ICP in relation to autoregulation indexes (e.g. PRx), whereby MMN and advanced mathematical techniques, such as machine learning, seem promising for quantifying patient-specific disease courses and ultimately formulating individualized physiological targets and outcome prediction (7, 10, 71-73).

Secondly, **chapter 7** explored outcome modes in pediatric sTBI in a single-centre PICU cohort: the functional outcome trajectory of survivors 1-year post-injury, brain death (BD) or withdrawal of life-sustaining therapies based on poor neurological prognosis (WLST-neuro). The latter is potentially one of the most difficult considerations in pediatric neurocritical care as there are no guidelines to assist in this decision-making process. Special attention was given to the comparison between WLST-neuro patients and patients who were discharged from the PICU in a vegetative state (PCPC score 5) regarding injury and disease characteristics to identify where potential differences lay in the decision to withdraw or continue life sustaining therapies. This study showed 2 distinct differentiation points in the decision-making process. First, the *determination of brain death* was often difficult because analgosedation had been administered in the context of supportive management. Other factors included additional injuries (mostly cervical) which impeded brainstem reflex testing. These observations are in line with other reports on the difficulty of BD determination in TBI and subsequent variation in BD practice (74, 75). As a consequence, a subset of patients were categorized as WLST-neuro who might have actually been BD. This could suggest an underrepresentation of BD incidence in our study and also globally. Increased time to discontinue analgosedation and eliminate this factor in neurological examination is an option. Conversely, it is debatable whether this is in the best interest of the patient in the acute phase as analgosedation is an integral part of supportive therapy and implemented to observe the clinical course of (refractory) ICP which is also used as a variable in neuroprognostication. Importantly, the role of analgosedation in sTBI is different from other PICU disease categories, such as patients after cardiac arrest. Thus, withholding analgosedation would not be applying current best-practice and therefore influence outcome. An alternative approach would be adopting analgosedative practices with (ultra-)short acting agents, such as Propofol and Remifentanil which allow for clinical examination within a short time frame after discontinuation. However, this remains speculative, especially for Propofol, given the risk of potentially fatal Propofol Infusion Syndrome (76). It deserves consideration also whether adhering to a time frame of 72 hours prior to drawing any definitive conclusions about outcome and subsequent WLST, as advised in adult sTBI neuroprognostication consensus statements, should also be adopted for pediatric sTBI (77). The second definitive decision-making point is *neuroprognostication practice*, specifically the conclusion that neurological prognosis is so poor as to be incompatible with a meaningful quality of life (QoL). This is a much more complex evaluation as it also incorporates personal, professional and societal concepts about QoL. The process leading up to such a conclusion involved evaluation of pre-hospital and clinical course characteristics, injury characteristics and diagnostic findings. A similar pattern of features leading to a WLST-neuro decision was found in other studies and included: pupil reactions and GCS, refractory intracranial hypertension, diabetes insipidus, brain herniation or signs of basal cistern effacement (78-81). An additional finding consistent with the few pediatric sTBI WLST studies available was absent or sparse documentation of WLST-neuro deliberation. Also,

documentation regarding patients in whom WLST-neuro might have been considered but not performed was virtually non-existent although this is of equal importance in understanding the decision-making process and overall outcome patterns. This is concerning at multiple levels. First and foremost in the context of transparency in clinical practice and for benchmarking or clinical audit purposes. As for scientific studies, LeBlanc et al reported that approx. 20% of adult RCT's reported WLST whereby 63% of deaths was secondary to WLST. An analysis whereby a hypothetical 4% differential rate was imputed between study groups regarding WLST practice led to different results and conclusions in a third of the RCTs (82). Thus, the first step in better understanding the decision-making process surrounding WLST practice is a standardized and consistent documentation of WLST-neuro deliberations. A proposal for such a document is presented in **chapter 7**. Better documentation will improve reporting of WLST in relation to death in scientific studies.

Thirdly, in the context of neuroprognostication, the question remains how to correlate acute phase physiological data to outcome both in the short- and long term. There are many factors to account for, including the drugs used and the plethora of possible physiological markers, their interrelated dynamic course during the disease process, and developmental influences. Teasing out a specific relationship is challenging. Furthermore, there needs to be a framework of normative data to enable interpretation of these parameters. The importance of this step, especially in children in whom age-related developmental changes can contribute to variations in normative values, is underlined in **chapter 8**. It is necessary to compile normative data about both patient and disease characteristics. These include CNS biomarkers of which normal values can change with age due to physiological development. The key messages highlighted in this editorial are how preclinical data could successfully be translated to clinical practice and include a pivotal role for standardized sample collection and analysis, data sharing and biobanking of materials (83). For children in particular, development of multi-analyte assays could prove the best way forward to capture both heterogeneity of the disease process as well as solve the issue of limited sample volume.

Finally, we need better quantification of outcome; current follow-up infrastructure varies in duration, frequency, type and quality of testing. Mostly, robust outcome measures of (physical) functionality are used, such as the Functional Status Score (FSS), Pediatric Cerebral Performance Category Scale (PCPC) or GOS-E-Peds (84-86). It is increasingly recognized, however, that these are crude outcome measures that fail to detect more subtle deficits in cognitive, higher executive functioning and psychosocial welfare. The concept of Post-Intensive Care Syndrome in Pediatrics (PICS-p) addresses physical, cognitive, emotional and social health domains and how novel or pre-existing disabilities in PICU survivors can fall within these domains. It also encompasses how health status prior to PICU admission, PICU disease course and management, as well as developmental state all influence ongoing disabilities. Finally, it takes the family

unit into account and how all members of this unit might be affected after a PICU admission. PICS-p comprehensively provides a holistic picture of the patient and their environment (87). This framework can be used for a holistic follow-up infrastructure that actively screens for deficits in these domains and provides support or therapies for potentially modifiable items for the individual and the family system it affects. The use of core outcome sets (COS) in such follow-up programs would allow multicenter evaluation of data for patient care and research purposes (88). However, the variation in diseases requiring PICU admission is great and a specified pediatric COS for TBI, analogous to the recently developed COS for pediatric survivors of cardiac arrest (p-COSCA) (89), would be of great added value for patient-specific care and TBI outcome research in general.

**Table 4.** Outcome specific barriers in pediatric TBI management and manners in which these can be crossed.

| Barrier | Crossing |
|---|---|
| Disability:<br>• Insufficient recognition scope of TBI disability<br>• Follow-up infrastructure (robust outcome measures, short follow-up duration) | • Follow-up program over range of TBI spectrum into adulthood<br>• Multi domain outcome measurements (physical, cognitive, emotional and social)<br>• Follow-up program into adulthood (and beyond?)<br>• Multidisciplinary (intensivist, neurologist, psychologist)<br>• Core outcome sets and data sharing |
| Death:<br>• Lack of pediatric sTBI neuroprognostication guidelines<br>• Brain death definition (variation, applicability in TBI) | • Consistent and standardized documentation of neuroprognostication process<br>• Datasharing platforms<br>• Formulate (inter-)national recommendations |
| Decisions:<br>• Linking acute injury and disease data to long term outcome | • Multimodality neuromonitoring (machine learning)<br>• Compile normative data<br>• Common Data Elements (CDE), datasharing platforms<br>• Comparative effectiveness (ADAPT study) |

# FUTURE DIRECTIONS

## How to continue crossing barriers

The field of neuropharmacology is challenging, exciting and at times overwhelming. It calls for creative solutions, collaborations across disciplines and borders and re-evaluation of paradigms. Essentially, it requires a holistic approach to problem-solving that takes into account disease, patient and pharmacotherapy factors against the background of the ever-changing developmental physiology of the child at different ages. The foundation for how future research in this field could take shape and advance fundamental PK understanding of CNS drugs, as well as how to correlate compartmental drug concentrations to drug effect, is presented in this thesis.

The various methods detailed in this thesis can be applied to different areas within and beyond neurocritical care. First, regarding the **disease** of TBI, there seems to be progress to be gained with better understanding of fundamental pathophysiological processes that could identify mechanistic routes for neuroprotective therapies. Also, pre-clinical selection of drug candidates by means of data on unbound drugs concentrations in CNS compartments for current supportive and potential neuroprotective therapies could vastly improve clinical trial success rates which have been dismal so far (43, 90). An interesting route with promising results from pre-clinical studies is the regulation of neuroinflammation (90). It also illustrates the importance of proper understanding of disease processes, because inflammatory responses post-TBI can have a dual function (protective and destructive) depending on the time point and natural history after onset of injury. In addition, age-dependent variations can exist that influence the degree of (neuro-) inflammatory response which also needs to be taken into account (91). In general, different approaches might be adopted depending on the time point within the disease trajectory (5, 92). To illustrate the potential for therapies targeting excitotoxicity and neuronal death: in the critical phase potent NMDAR antagonists could be used that are switched to more refined anti-excitotoxic therapies, such as Levetiracetam, during the recovery phase (5). In TBI more broadly, perhaps the therapeutic indication needs to be expanded to include neuroprotective therapies for moderate (and maybe even mild) TBI given increasing reports about long-term neurodegenerative sequelae and the potentially larger burden this entails in comparison to the relatively small number of sTBI patients (4, 43). To this end, improved disease classification is required to adequately identify potential subjects (4).

Secondly, other neurological diseases could benefit from better PK understanding and enhanced CNS drug delivery, including neurodegenerative disease (e.g. Parkinson and Alzheimer's disease), epilepsy, neuro-oncology and CNS infections. For example, cerebral MD studies in experimental meningitis have shown an altered exposure to medication secondary to decreased active efflux and increased passive diffusion (93).

The topic of neuro-oncology and CNS infections raises the issue of the topography of **pharmacotherapy** delivery and whether generalized drug distribution is as important as focal administration in certain circumstances. Cerebral MD could be useful for the latter as so-called 'retro-dialysis' enables CNS drug delivery to specific lesions (94, 95). Another important issue concerning drug delivery is not only the mode of delivery but also the drug vehicle, as certain drug characteristics influence unbound drug CNS distribution. As such, MD studies have been performed with liposomal formulations, small molecules and nanodelivery to investigate how these affect temporal profiles of drug distribution (96, 97). Other investigations into novel modes of drug delivery include receptor-mediated transcytosis, neurotropic viruses and exosomes (98). The application of neural stem cells coupled with specific drug therapy is garnering increased interest as a mode of delivery to migrate to areas of injury (99). In this regard, the mode of application is also of interest, as demonstrated by a recent study of *intranasally* administered mesenchymal stromal cells in neonatal patients who suffered a perinatal arterial stroke (the PASSIon trial) (100). Because of the non-invasive nature of administration, such developments open avenues for future applications of neuroregenerative therapies to other less severe patient groups (e.g. mild to moderate TBI).

Further investigation into **patient** specific factors is required, not only regarding influence of disease state on variable patient physiology (such as renal and hepatic function), but also other factors such as the influence of circadian rhythm on P-gb activity (which is an efflux mechanism at the BBB) (96). In terms of pharmacological targets, this could be of influence if a continuous minimal inhibitory concentration (MIC) of drug in CNS infections is needed. In addition, given the heterogeneity of patient and disease factors in general, combination therapies could potentiate each other, analogous to cancer therapies (5). Finally, ongoing investigations into the merit of additional (non-invasive) technical methods to investigate CNS drug delivery should continue, especially for the purpose of pediatric neuropharmacology, where regulatory constraints are so high. An example is the application of positron emission tomography (PET), although an important disadvantage of this method is that it cannot distinguish between bound and unbound molecules (97, 101).



Ultimately, the key role for prevention in TBI needs to be re-emphasized with ongoing strategies to increase public and political awareness for this global health problem. There is room for improvement in protective head gear practice, car seat safety and civic road infrastructure (4, 67). The power of concerted efforts regarding prevention programs, and the disturbing lack in other public health areas, were presented recently by Lee *et al*, who showed that after four decades firearm-related injuries had surpassed motor vehicle accidents as the leading cause of death among children, adolescents and young adults in the U.S. (102).

Envisioning how neuropharmacology 'at the bedside' might take shape, the following represents the potential course of a pediatric sTBI patient admitted to the PICU:

> *Patient baseline data collection at admission allows for patient-specific validated PBPK templates to be drawn up for protocol-based analgosedative drugs based on covariates such as age, weight, renal function, and pharmaco-/genetic phenotyping (e.g. P-gp functionality and Cyp-enzyme activity). During the disease course multimodality neuromonitoring detects dynamic (patho-)physiological changes by machine learning (disease-related items such as ICP, CPP, autoregulation indexes and patient-related items such as renal function, inflammation) which lead to potential drug dose adjustments based on desired drug effect as defined by the combination of various PD targets (e.g. EEG pattern, sedation and pain scores, therapeutic drug monitoring levels). The PD targets are displayed on a digital dashboard in real-time with visual graphics of thresholds, time-weighted exposure and trends as appropriate. Algorithms provide additional early-warning signs based on impeding undesirable values so pre-emptive action is possible. Standardized documentation of common data elements allows for datasharing and further evaluation for research purposes to improve patient care. This scene does not only apply to sTBI but could be adapted to any critical illness in the PICU. Furthermore, the disease process does not stop after discharge from the PICU. Ongoing patient-specific care with multidimensional outcome measures should continue with a multidisciplinary team.*

A limiting step in current TDM is the lag time in sampling and receiving actual drug level data. Current research efforts are underway to develop a continuous intravenous biosensing system that monitors drug concentrations in real-time which could significantly improve the reaction time to potentially noxious stimuli.

Therefore, taking all of the above into consideration in the quest for evidence-based medicine in pediatric pharmacotherapy and the injured brain, the question remains whether it is feasible to identify a specific, optimal drug in supportive management of pediatric sTBI. Or are we starting to realize that, given the multitude of dynamic variables inherent to the disease and patient, the way forward is patient-tailored therapies whereby the optimal drug for that specific patient at that specific moment in time is determined (5)? So perhaps the recommendation from the brain injury guidelines is not so much reflective of the lack of high-level evidence but instead ahead of its time with the addition of the following phrase:

> *'....the specific indications, choice and dosing of analgesics, sedatives and neuromuscular blocking agents should be left to the treating physician* ***and PICU pharmacist with the aid of PKPD models and multimodality neuromonitoring to enable model informed precision dosing****'*
>
> Thesis *'Crossing Barriers'* – pharmacotherapy and the pediatric injured brain

## CONCLUSIONS AND RECOMMENDATIONS

In conclusion, to advance our understanding of neuropharmacology ***collaboration*** and ***innovation*** is imperative. Collaboration at various levels, pre-clinical and clinical initiatives, joining forces with technical and bioinformatics groups as well as multi- and interdisciplinary collaboration on the work floor. Innovation to break-away from the mainstream approaches to pharmacology studies. This involves adopting alternative designs, such as mathematical and statistical methods, and applying technical advances to derive samples from CNS targets to provide fundamental PK knowledge. Such an approach will improve drug efficacy and safety which is further ameliorated with the application of multimodality neuromonitoring. This thesis provides a framework how steps can be made to improve CNS PK knowledge and how to apply this to future studies, including the translation to PKPD studies, and ultimately from bench to bedside. Outcome after PICU admission is the net result of a multitude of factors of which neuropharmacology plays an important role. The disease process after PICU discharge is ongoing and demands a solid and interdisciplinary follow-up infrastructure. Future directions in pediatric pharmacology and the injured brain include expansion of translational CNS PK studies, and application to other disease severities and categories beyond sTBI. Recommendations regarding how to cross disease, patient and drug-specific barriers are detailed in the tables of this chapter and summarized in **Figure 2**. Given the heterogeneity of the disease, the (developing) patient and analgosedation practice, it is inevitable that the aforementioned steps will ultimately lead to patient specific, ***tailored (neuro-) pharmacotherapy***.

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# 10

## Summary

# SUMMARY

Severe traumatic brain injury (sTBI) remains one of the leading causes of morbidity and mortality worldwide. Children are an especially vulnerable group given the significant developmental changes the brain undergoes throughout childhood. Analgesia and sedation are a cornerstone of supportive management in sTBI. Nonetheless, only low-level evidence exists for analgosedation therapies and overall choices on type of medication and subsequent dosing are left to the discretion of the treating physician or institution. This practice is undesirable given serious concerns about safe and effective pharmacotherapy. Also, this practice is potentially unnecessary. Despite the challenges of deriving evidence-based pharmacotherapy of central nervous system (CNS) drugs in the pediatric population, there are techniques and methods to overcome these.

This thesis describes the current field of analgosedation practice in pediatric sTBI and investigates different methods by which we can reach a better understanding of pharmacokinetic (PK) properties of commonly used drugs. The ultimate aim of improving pharmacotherapeutic strategies in sTBI is to minimize or prevent secondary cerebral injury and thereby improve outcome. Outcome is explored in terms of the specific patient in relation to pharmacotherapeutic interventions and in general regarding end-of-life decisions.

The data presented in this thesis are the result of international collaborative efforts from preclinical and clinical institutions (Erasmus MC, Rotterdam, The Netherlands; Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa; Leiden Academic Center for Drug Research, Leiden, The Netherlands, Amsterdam University medical Center, Amsterdam, The Netherlands).

**Part 1** gives an overview of pharmacotherapeutic practice in pediatric sTBI.

**Chapter 1** gives a general introduction to the three factors that influence pharmacotherapy: the patient, the disease and the medication. The disease investigated in this thesis is sTBI requiring invasive neuromonitoring and admission to a pediatric intensive care unit (PICU). The patient is a child which means significant developmental changes that need to be accounted for. The medication investigated is analgosedation, a cornerstone of sTBI management, and focusses on the aspect of PK ('what the body does to the drug'). **Chapter 2** provides a narrative review of international analgosedation practices in pediatric sTBI and summarizes key PK and pharmacodynamic (PD) features. Potential short and long-term adverse effects are addressed which need to be considered when choosing medication type and dose. Finally, a framework of how to advance our understanding of (pediatric) CNS pharmacotherapy is provided and includes preclinical initiatives such as physiologically-based PK models (PBPK), mathematical methods such as population-based PK models

and clinical technical advances like cerebral microdialysis (MD) which enable sampling from CNS target sites. Part 1 is concluded by **chapter 3** regarding the application of cerebral MD in sTBI drug therapy as detailed in a neuroscience book chapter. The spectrum of steps involved with CNS drug investigation are covered ranging from the technical aspects of MD to mathematical and statistical techniques in PK modelling as well as suggestions how to link PK data to PD markers.

**Part 2** describes the results of two PK studies of commonly used drugs in the management of pediatric sTBI.

A pilot study is presented in **chapter 4** whereby a physiologically (animal-)based PK (PBPK) model for morphine was translated for pediatric human use to predict morphine concentrations in the extracellular fluid of the brain ($brain_{ECF}$). The aim of this prospective study was to evaluate the predictive value of this PBPK morphine model for concentration time profiles of morphine in $brain_{ECF}$ by comparing predicted values to samples from pediatric sTBI patients as retrieved by cerebral MD (n = 6). Overall the PBPK morphine model showed good predictive value both for morphine concentrations in blood plasma and $brain_{ECF}$. It was of interest to observe that the predictive power was more accurate if patient samples were sampled from MC catheters located in relatively 'un-injured' brain compared to samples from 'injured' brain. This alludes to the role of the blood-brain barrier in medication disposition. The successful development of this PBPK morphine model demonstrates the feasibility of such an approach in designing predictive PK models. The next step is to validate this PBPK morphine model to enable its use in further pharmacological studies, such as linking target site concentrations to PD end points and thereby improve patient specific dosing strategies. **Chapter 5** describes the development and validation (both internal and external) of a population-based PK model for pentobarbital. In addition, pentobarbital dosing simulations were performed with this population-based PK model to improve our PK understanding of different dosing regimens. Retrospective data were retrieved from 36 pediatric patients who received pentobarbital for either status epilepticus (SE) or sTBI. A one-compartment pentobarbital PK model with allometrically scaled weight on clearance and volume of distribution best described the observed pentobarbital concentrations. Serum creatinine and CRP >70 mg/L were significant covariates incorporated in the final model. It was undetermined whether elevated creatinine reflected actual renal failure or overall degree of critical illness. Dosing simulations showed that patients with an elevated serum creatinine and CRP failed to achieve a steady state of pentobarbital concentration but progressed to toxic levels. Adjusted pentobarbital dosing recommendations were formulated based on simulations with varying creatinine or CRP values. This high PK variability underlines the importance of therapeutic drug monitoring and PK model development to facilitate and adjust individual dosing.

**Part 3** focusses on different aspects of outcome in sTBI as the ultimate goal of all management and research efforts is to improve outcome of this potentially devastating disease.

Oxygen is the most commonly used drug in the PICU and hyperoxia has been associated with worse outcome. The study presented in **chapter 6** compares hyperoxia classification of pediatric sTBI patients during the first 24 hours in the PICU by using conventional $PaO_2$ cutoff analysis and area-under-the-curve (AUC) $PaO_2$ cumulative analysis. The rationale being that patient classification is crucial to how we subsequently associate hyperoxia to outcome. Seventy-one patients were included in this retrospective analysis and showed a high variability in hyperoxia classification: 52% in the $PaO_2$ cutoff group were classified in the highest hyperoxia category versus 26% in the AUC group. Classification variability was reflected by a Pearson correlation coefficient of 0.40 (*p* 0.001). We consider classification by cumulative oxygen exposure better approximates (patho-)physiological circumstances due to its time and dose dependent approach. Further prospective studies are necessary to explore the association between cumulative oxygen exposure, physiological parameters and outcome.

End-of-life decisions and subsequent withdrawal of life sustaining therapy occur frequently in children with sTBI. However there are currently no formal guidelines on this topic to assist the medical team and families. The process by which such decisions are reached and the clinical factors taken into account are described in **chapter 7** for a retrospective cohort of 78 patients at our PICU. Challenges in this specific patient group include meeting clinical brain death definitions in conjunction with standardized supportive management strategies (such as administering sedation) that hamper neurological examination. Prospective one-year follow-up data was also evaluated to further understand the trajectory of survivors from this cohort.

**Chapter 8** outlines the potential of biomarkers for neuroprognostication in pediatric TBI in an editorial regarding a study that investigated serum levels of total tau (t-tau), a marker of axonal injury, in both healthy children and pediatric TBI patients. The study generated age-related normative data to assist in biomarker level interpretation. Awareness that there are age-related differences in biomarker thresholds is crucial and emphasizes the differences between children and adults. The multitude of other items that need to be taken into account before a transition from preclinical to clinical application can be made are detailed against the background of current international initiatives.

In **part 4** the general discussion **(chapter 9)** reflects on the findings of the studies presented in this thesis. It places them in the broader scope of patient, disease and

pharmacotherapy to discuss barriers in current pediatric CNS pharmacology and provides suggestions on how these barriers can be crossed.

The conclusion of this thesis is that efforts towards crossing current barriers in the development of evidence-based neuropharmacology recommendations in (pediatric) sTBI incorporate collaboration between centres and disciplines as well as innovative approaches towards studies. The latter involves alternative study designs and statistical approaches as well as technical advances such as cerebral MD to obtain target site samples. Ultimately, the heterogenic character of the underlying disease against the backdrop of a developing individual, suggest the way forward is tailored (neuro-)pharmacology by means of individualized drug PKPD templates. Such patient-specific approaches to neuropharmacology will enable more safe and effective drug therapy which should ultimately contribute to improved outcome.

## SAMENVATTING

Wereldwijd is ernstig traumatisch schedelhersenletsel is een van de meest voorkomende oorzaken van blijvende schade en mortaliteit. Kinderen zijn met name een kwetsbare groep vanwege de significante veranderingen die zij doormaken in hun ontwikkeling. Pijnstilling en sedatie zijn de pijlers van de ondersteunende therapie in ernstig traumatisch schedelhersenletsel. Desondanks bestaat er slechts matig bewijs voor de huidige therapieën en over het algemeen worden keuzes omtrent type medicatie en bijbehorende dosering overgelaten aan de behandelde arts of instelling. Deze aanpak is zeer onwenselijk aangezien er grote zorgen bestaan of er momenteel veilige en effectieve farmacotherapie wordt gegeven. Er zijn echter technieken en methoden beschikbaar om de uitdagingen op te lossen die rondom het ontwikkelen van zogenaamde 'evidence-based' neurofarmacologie bij kinderen bestaan.

Deze thesis beschrijft de huidige praktijk met betrekking tot analgosedatie in pediatrisch ernstig traumatisch schedelhersenletsel en onderzoekt verschillende methoden waarmee we een beter begrip krijgen van de farmacokinetische eigenschappen van frequent voorgeschreven medicatie. Het uiteindelijke doel van het verbeteren van farmacotherapeutische strategieën in pediatrisch ernstig traumatisch schedelhersenletsel is om secundair hersenletsel te verminderen (of voorkomen) en daarbij uitkomst te verbeteren. Uitkomst wordt onderzocht met betrekking tot de specifieke patient in relatie tot farmacotherapeutische interventies en in het algemeen aangaande besluitvorming over het levenseinde.

De resultaten weergegeven in deze thesis zijn het gevolg van een internationale samenwerking tussen preklinische en klinische instituten (Erasmus MC, Rotterdam, Nederland; Red Cross War Memorial Children's Hospital, Universiteit van Kaapstad, Kaapstad, Zuid-Afrika; Leiden Academic Center for Drug Research, Leiden, Nederland; Amsterdam Universiteit Medisch Centrum, Amsterdam, Nederland).

**Deel 1** geeft een overzicht van de huidige farmacotherapie praktijk in pediatrisch ernstig traumatisch schedelhersenletsel.



**Hoofdstuk 1** is een algemene introductie over de drie factoren die farmacotherapie beïnvloeden: de patiënt, de ziekte en de medicatie. De ziekte die wordt onderzocht in deze thesis is ernstig traumatisch schedelhersenletsel die invasieve neuromonitoring en opname op de kinder intensive care vereist. De patiënt is een kind wat betekent dat er significante veranderingen zijn, afhankelijk van ontwikkelingsstadium, waar rekening mee moet worden gehouden. De medicatie die wordt onderzocht is pijnstilling en sedatie, een hoeksteen van ernstig traumatisch schedelhersenletsel behandeling, en focust op het aspect van farmacokinetiek ('wat het lichaam doet met de medicatie'). **Hoofdstuk 2** geeft een overzicht van internationale analgosedatie

praktijken in pediatrisch ernstig traumatisch schedelhersenletsel en een samenvatting van belangrijke farmacokinetische (PK) en farmacodynamische (PD) eigenschappen van deze middelen. Potentiële korte en lange termijn bijwerkingen worden aangestipt waarmee rekening dient te worden gehouden bij keuzes omtrent medicatie type en dosering. Tot slot wordt een raamwerk geschetst hoe de kennis over (pediatrisch) neurofarmacologie kan worden verbeterd door middel van preklinische initiatieven zoals fysiologische PK modellen (PBPK), mathematische methoden zoals populatie-gebaseerde PK modellen (popPK) en klinisch technologische vooruitgangen zoals cerebrale microdialyse welke het verkrijgen van centraal zenuwstelsel (CZS) samples mogelijk maakt. Deel 1 wordt afgesloten met **hoofdstuk 3** waarin het toepassen van cerebrale microdialyse in ernstig traumatisch schedel hersenletsel voor farmacologisch onderzoek uiteen wordt gezet. In dit hoofdstuk wordt het spectrum van stappen belicht die zijn vereist in CZS farmacologie studies variërend van technische microdialyse aspecten tot mathematische en statische methoden in PK modeling alsook suggesties hoe PK kan worden gecorreleerd and PD markers.

**Deel 2** beschrijft de resultaten van twee PK studies van frequent gebruikte middelen in de behandeling van pediatrisch ernstig traumatisch schedelhersenletsel.

Een pilot studie wordt gepresenteerd in **hoofdstuk 4** waarbij een fysiologisch (dier-) PK (PBPK) model voor morfine is aangepast voor pediatrisch humaan gebruik om morfine concentraties te voorspellen in het extracellulair hersenvocht (hersen$_{ECF}$). Het doel van deze prospectieve studie was om de voorspellende waarde van dit PBPK model voor concentratie-tijd profielen van morfine in hersen$_{ECF}$ te evalueren. Dit werd uitgevoerd door de voorspelde waarden te vergelijken met samples verkregen van kinderen met ernstig traumatisch schedelhersenletsel middels cerebral microdialyse (n=6). Over het algemeen toonde het PBPK morfine model een goede voorspellende waarde voor zowel morfine concentraties in bloed en hersen$_{ECF}$. Het was opvallend dat de voorspellende waarde meer accuraat leek wanneer monsters uit relatief 'onbeschadigd' hersenweefsel afkomstig waren in plaats van 'beschadigd' hersen$_{ECF}$. Deze observatie zinspeelt op de rol van de bloed-hersen-barrière in medicatie dispositie. De succesvolle ontwikkeling van dit PBPK morfine model bevestigt de haalbaarheid van een dergelijke aanpak in het ontwerpen van voorspellende PK modellen. De volgende stap is het valideren van dit PBPK morfine model om het te kunnen toepassen in aanvullende farmacologische studies, zoals het koppelen van doel orgaan (het brein) concentraties met farmacodynamische eindpunten en daarmee patient-specifieke doseer strategieën te verbeteren. **Hoofdstuk 5** beschrijft de ontwikkeling en validatie (zowel intern als extern) van een populatie-gebaseerde PK model (popPK) voor Pentobarbital. Er werden met dit Pentobarbital popPK model eveneens doseersimulaties uitgevoerd om het PK begrip bij verschillende doseer schema's meer inzichtelijk te maken. Retrospectieve data werden verzameld van 36 pediatrische patiënten die pentobarbital hadden gekregen voor status epilepticus of ernstig traumatisch schedelhersenletsel. Een

1-compartiment pentobarbital PK model met allometrisch geschaald gewicht op klaring en distributievolume beschreef de geobserveerde pentobarbital concentraties het meest optimaal. Serum creatinine en C-reactive protein (CRP) waren significante covariaten die in het eind model werden toegevoegd. Het was niet evident of creatinine specifiek acuut nierfalen of algeheel mate van ziek-zijn weergaf. Doseersimulaties toonden aan dat patiënten met een verhoogd serum creatinine geen pentobarbital steady-state spiegel bereikten binnen 72 uur, maar progressie toonden naar toxische spiegels. Deze hoge mate van PK variabiliteit benadrukt het belang van therapeutische medicatie spiegel monitoring en het ontwikkelen van PK modellen om individuele doseer schema's mogelijk te maken.

**Deel 3** focust op verschillende aspecten van uitkomsten van ernstig traumatisch schedelhersenletsel aangezien het uiteindelijke doel van alle behandel- en onderzoeksinspanningen het verbeteren van dit destructieve ziektebeeld is.

Zuurstof is de meest voorkomende medicatie op de (kinder-) intensive care (IC) en hyperoxie is in verband gebracht met slechtere uitkomsten. De studie gepresenteerd in **hoofdstuk 6** vergelijkt verschillende typen van hyperoxie classificatie bij kinderen met ernstig traumatisch schedelhersenletsel in de eerste 24 uur van IC opname middels conventionele $PaO_2$ afkap analyse en oppervlakte-onder-de-curve $PaO_2$ cumulatieve analyse. De rationale van deze studie is dat hoe wij patiënten classificeren cruciaal is voor hoe we vervolgens hyperoxie in verband brengen met uitkomst. Er werden 71 patiënten geïncludeerd in deze retrospectieve analyse en er waren grote verschillen in hyperoxie classificatie afhankelijk van type analyse: bij de $PaO_2$ afkap methode werd 52% van de patiënten geclassificeerd in de hoogste hyperoxie groep versus 26% van patiënten middels de cumulatieve methode. Classificatie variabiliteit werd weergegeven door een Pearson correlatie coëfficiënt van 0.40 (*p*-waarde 0.001). Wij beschouwen de cumulatieve methode en classificatie als een betere weergave van (patho-)fysiologische omstandigheden vanwege de tijds- en dosisafhankelijke benadering. Aanvullende prospectieve studies zijn vereist om de associatie tussen cumulatieve zuurstof blootstelling, fysiologische parameters en outcome verder te exploreren.



Besluitvorming rondom het levenseinde en staken van behandeling gebeurt vaak in kinderen met ernstig traumatisch schedelhersenletsel. Echter, er zijn geen formele richtlijnen over dit onderwerp om het medisch team en familie hierbij te ondersteunen. Het proces van besluitvorming en de klinische factoren die hierin worden meegenomen zijn beschreven in **hoofdstuk 7** in een retrospectief cohort van 78 patiënten op onze kinder IC. De beschreven uitdagingen in deze specifieke patiëntengroep omvatten het voldoen aan hersendood definities in combinatie met de geldende ondersteunende behandelingen (zoals het toediening van sedatie) aangezien dit neurologisch onderzoek kan beïnvloeden. Prospectieve 2-jaars follow-up data werden geanalyseerd om het

beloop van overlevenden van dit cohort in kaart te brengen en zo het algeheel begrip over uitkomst te verbeteren.

**Hoofdstuk 8** is een weergave van het potentieel van biomarkers in neuroprognosticatie van ernstig traumatisch schedelhersenletsel bij kinderen middels een editorial over een studie die serum total tau (t-tau) spiegels, een marker van axonale schade, beschreef in zowel gezonde kinderen als kinderen met traumatisch schedelhersenletsel. De studie genereerde leeftijd-specifieke normatieve data om de biomarker spiegel interpretatie te verbeteren bij kinderen. Bewustwording dat er leeftijd-specifieke verschillen zijn in biomarker grenzen is cruciaal en benadrukt de verschillen tussen kinderen en volwassenen. Het veelvoud aan factoren die in overweging moeten worden genomen voordat een transitie van preklinische naar klinische toepassing van biomarkers kan worden gemaakt, wordt uiteengezet tegen de achtergrond van huidige internationale initiatieven.

In **deel 4** volgt in de algemene discussie (**hoofdstuk 9**) een uiteenzetting van de studiebevindingen die in deze thesis worden gepresenteerd. De bevindingen worden in een bredere context geplaatst van patiënt, ziekte en farmacologie waarbij barrières in de huidige neurofarmacologie worden besproken alsook suggesties worden gedaan hoe deze barrières kunnen worden doorkruist.

De conclusie van deze thesis is dat samenwerking, tussen centra en disciplines, en een innovatieve aanpak wat betreft type studies is vereist voor het doorkruisen van de huidige barrières in de ontwikkeling van 'evidence-based' neurofarmacologie in kinderen met ernstig traumatisch schedelhersenletsel. Dit omvat alternatieve studievormen en statistische methoden in combinatie met technische ontwikkelingen zoals cerebrale microdialyse om doel orgaan samples te verkrijgen. Uiteindelijk lijkt de weg voorwaarts patiënt-specifieke (neuro-)farmacologie middels geïndividualiseerde medicatie PKPD templates vanwege het heterogene karakter van de onderliggende ziekte tegen de achtergrond van het zich ontwikkelde individu. Dergelijke patiënt-specifieke aanpak in de neurofarmacologie zal veilige en meer effectieve medicamenteuze therapieën mogelijk maken die uiteindelijk bijdragen aan een betere algehele uitkomst.

# PART V

# Appendices

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ABG | arterial blood gas |
| ADAPT | Approaches and Decisions in Acute Pediatric Traumatic Brain Injury |
| AED | anti-epileptic drug |
| AIS | abbreviated injury scale |
| ALAT | alanine transaminase |
| ALP | alkaline phosphatase |
| ASAT | aspartate transaminase |
| AUC | area-under-the-curve |
| BBB | blood brain barrier |
| BCSFB | blood cerebrospinal fluid barrier |
| BD | brain death |
| CALIPER | Canadian Laboratory Initiative on Pediatric Reference Intervals |
| CBD | clinical brain death |
| CBF | cerebral blood flow |
| CENTER-TBI | Collaborative European NeuroTrauma Effectiveness Research in TBI |
| CI | confidence interval |
| CL | clearance |
| CNS | central nervous system |
| COX | cyclooxygenase |
| CPP | cerebral perfusion pressure |
| CPR | cardiopulmonary resuscitation |
| Cr | creatinine |
| CRP | C-Reactive Protein |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| CWRES | conditional weighted residuals |
| CYP450 | cytochrome P450 |
| DAI | diffuse axonal injury |
| DDAVP | desmopressin acetate |
| DI | diabetes insipidus |
| ECF | extracellular fluid |
| ECMO | extracorporeal membrane oxygenation |
| EDH | epidural hematoma |
| EEG | electroencephalogram |

| | |
|---|---|
| EMA | European Medicines Agency |
| $FiO_2$ | fraction of inspired oxygen |
| GABA | gamma-aminobutyric acid |
| GCS | Glasgow Coma Scale |
| GFAP | glial fibrillary acidic protein |
| GFR | glomerular filtration rate |
| γ –GT | gamma-glutamyl transferase |
| HLS | hospital length of stay |
| HREC | human research and ethics committee |
| ICH | intracranial hypertension |
| ICP | intracranial pressure |
| ICS | intracellular space |
| IIV | inter-individual variability |
| InTBIR | International Initiative for TBI Research |
| IPRED | individual predicted |
| IQR | interquartile range |
| IRB | institutional review board |
| ISS | injury severity score |
| I.V. | intravenous |
| KDIGO | kidney disease improving global outcomes |
| LC-MS | liquid chromatography mass spectrometry |
| LLOQ | lower limit of quantification |
| MAP | mean airway pressure |
| MD | microdialysis |
| MIC | minimum inhibitory concentration |
| MRI | magnetic resonance imaging |
| MRP | multidrug resistance-associated protein |
| MRS | magnetic resonance spectroscopy |
| MVA | motor vehicle accident |
| MWCO | molecular weight cut-off |
| M6G | morphine-6-glucunoride |
| NA | not applicable |
| NMDA | *N*-methyl-D-aspartate |
| NONMEM | non-linear mixed-effects modeling |

| | |
|---|---|
| NS | not significant |
| NSE | neuron-specific enolase |
| OI | oxygenation index |
| OFV | objective function value |
| OR | odds ratio |
| $PaO_2$ | partial pressure of arterial oxygen |
| $Pb(t)O_2$ | partial pressure of brain (tissue) oxygen |
| PBPK | physiology-based pharmacokinetic |
| PCPC | pediatric cerebral performance category |
| PD | pharmacodynamics |
| PEG | percutaneous gastrostomy |
| PET | positron emission tomography |
| PIM | pediatric index of mortality |
| P-gp | P-glycoprotein |
| PICU | Pediatric Intensive Care Unit |
| PICU-LS | Pediatric Intensive Care Unit length of stay |
| PK | pharmacokinetic |
| PLS | Pediatric Intensive Care Unit length of stay |
| PRED | predicted |
| PRIS | propofol infusion syndrome |
| PRISM | pediatric risk of mortality score |
| PSH | paroxysmal sympathetic hyperactivity |
| pTBI | pediatric traumatic brain injury |
| Q | inter-compartmental clearance |
| QoL | quality of life |
| RCWMCH | Red Cross War Memorial Children's Hospital |
| SAH | subarachnoid hemorrhage |
| SD | standard deviation |
| SDH | subdural hemorrhage |
| SE | status epilepticus |
| sTBI | severe traumatic brain injury |
| TAI | traumatic axonal injury |
| TBI | traumatic brain injury |
| TC | tracheal canula |
| TDM | therapeutic drug monitoring |
| t-tau | total-tau |
| t½ | half life |

| | |
|---|---|
| ULOQ | upper limit of quantification |
| VAP | ventilator associated pneumonia |
| Vd | volume of distribution |
| VPC | visual predictive check |
| WLST | withdrawal of life sustaining therapy |

## LIST OF CO-AUTHORS (IN ALPHABETICAL ORDER)

Prof. dr. A.C. Argent
Dr. C.M.P. Buysse
Prof. dr. A.A. Figaji
Dr. I.K. Haitsma
Prof. dr. M. de Hoog
Dr. M.A.W. Hunfeld
Dr. Ir. M.C. de Jong
Dr. R.C.J. de Jonge
Drs. I. Klouwen
Prof. B.C.P. Koch
Prof. R.A.A. Mathôt
Prof. E.C.M. de Lange
Drs. A. Lili
Drs. J.M. Penning-de Vries
Prof. dr. I.K.M. Reiss
Dr. U.K. Rohlwink
Dr. J.K.H. Spoor
Prof. dr. D. Tibboel
Dr. E. D. Wildschut
Prof. dr. S.N. de Wildt
Dr. B.C.M. de Winter
Dr. Y. Yamamoto
Drs. E.J. van der Zanden

## ABOUT THE AUTHOR

Naomi Ketharanathan was born in **Melbourne**, Australia, on the 11th of May, 1980 and moved to The Netherlands at the age of 7. In 1998 she received her VWO degree (cum laude) at the Oostvaarders College in Almere. She started her university training at the Vrije Universiteit in Amsterdam with a year of Biomedical Sciences (foundation course cum laude) before commencing her medical training in 1999 at the same university. Her interest in pediatrics and international health care resulted in various internships abroad (Australia, United States of America and Kenya) and participation in the student health organization IFMSA (International Federation of Medical Student Associations). She graduated from medical school in 2006. Her first residency was in general pediatrics at the Albert Schweitzer Hospital in Dordrecht. This reinforced her ambition to pursue a career in pediatrics and she started her residency program in 2008 at Erasmus Medical Center, Sophia Children's Hospital, **Rotterdam**, The Netherlands. Extra-curricular activities during her residency included active roles in various medical residency councils, one of which she co-founded, and participation in medical outreach programs abroad. During her residency, her interest in pediatric intensive care grew due to its broad scala of medical challenges in a developing patient group, the combination of theoretical and practical aspects and research possibilities. This resulted in a senior residency at Red Cross War Memorial Children's Hospital in **Cape Town**, South Africa (supervisor: Prof. dr. A.C. Argent). Her interest in pediatric neurocritical care was sparked here due to their unique neuromonitoring infrastructure and it would mark the start of her research collaboration with their department of pediatric neurosurgery (supervisor: Prof. dr. A.A. Figaji). After finishing her pediatric residency training in 2013, she worked as a pediatrician in Maasstad hospital, Rotterdam, before commencing her PICU (Pediatric Intensive Care Unit) fellowship. This fellowship started with a 6 month research project on cerebral drug recovery with microdialysis in Cape Town. The result was a successful pilot study on cerebral morphine pharmacokinetics in traumatic brain injury which led to a two-year research grant from Sophia Stichting Wetenschappelijk Onderzoek in 2016. Subsequently this evolved into a PhD project on pharmacotherapy and the injured brain under the supervision of Prof. dr. D. Tibboel (Erasmus Medical Center) and Prof. dr. A.A. Figaji (University of Cape Town). In the meantime, she completed her PICU fellowship in 2017 and works as a pediatric intensivist with an area of interest in pediatric neurocritical care at Erasmus MC – Sophia Children's Hospital.

Naomi lives with her husband and two children in Rotterdam, The Netherlands.

# LIST OF PUBLICATIONS

## Thesis publications

**Ketharanathan N** et al. Brain microdialysis and applications to drug therapy in severe traumatic brain injury. In: Rajendram R, Preedy V and Martin C (Ed), Cellular, Molecular, Physiological, and Behavioral Aspects of Traumatic Brain Injury: ***The Neuroscience of traumatic brain injury***. Chapter 19, pp231-243. London, United Kingdom: Academic Press (Elsevier Inc). ISBN 9780323991971.

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**Ketharanathan N**, Rohlwink U, Tibboel D, Figaji AA. Biomarkers in pediatric traumatic brain injury. ***Lancet Child Adol Health*** 2019; 3: 516-518.

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**Ketharanathan N**/Lili A, Penning-de Vries J. Wildschut E, de Hoog M, de Winter B/ Koch B. A Population Pharmacokinetic Model of Pentobarbital for Children with Status Epilepticus and Sever Traumatic Brain Injury. ***Submitted***

## Other publications

Otten MH, Buysse CMP, Buddingh EP, Terheggen-Lagro SWJ, von Asmuth EGJ, de Sonnaville ESV, **Ketharanathan N**, Bunker-Wiersma HE, Haverman L, Hogenbirk K, de Hoog M, Humblet M, Joosten K, Kneyber M, Krabben G, Lemson J, Maas NM, Maebe S, Releveld P, van Schooneveld M, Timmers-Raaijmaakers B, van Waardenburg, Walker JC, Wassenberg R, van Wonesel J, de Wit E, Wolthuis DW, van Zwol A, Oostrom KJ, Knoester H, Dulfer K. Physical, Neurocognitive and Psychosocial Outcomes after Multisystem Inflammatory Syndrome in Children admitted to the Pediatric Intensive Care Unit. ***Pediatr Crit Care Med*** *2022; Accepted*

Biesbroek G, Kapitein B, Kuipers IM, Joosten SA, Gruppen MP, van Stijn D, Peros TE, van Veenendaal M, Jansen MH, van der Zee C, van der Kuip M, von Asmuth EGJ, Mooij MG, den Boer MEJ, Jandman GW, van Houten MA, Schonenberg-Meinema D, Tutu van Furth AM, Boele van Hensbroek M, Scherpbier H, van Meijgaarden KE, Ottenhoff THM, Joosten SA, **Ketharanathan N**, Blink M, Brackel CLH, Zaaijer H, Hombrink P. van den Berg JM, Buddingh EP, Kuijpers TW. Inflammatory responses in SARS-CoV-2 associated Multisystem Inflammatory Syndrome and Kawasaki Disease in children: an observational study. ***PLoS One*** 2022; *Accepted*

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**Ketharanathan N**, Herder C, Veenstra J, de Vries N. Isolated laryngeal sarcoidosis: a case report. ***Ned Tijdschr KNO*** 2006: 12: 23-25.

# PHD PORTFOLIO

| | |
|---|---|
| **Name of PhD student** | Naomi Ketharanathan |
| **Erasmus MC Department** | Intensive Care (Erasmus MC-Sophia) |
| **PhD period** | February 2017 – January 2023 |
| **Promotors** | Prof. Dr. D. Tibboel<br>Prof. Dr. A.A. Figaji |
| **Co-promotor** | Dr. E.D. Wildschut<br>Dr. U.K. Rohlwink |

| | Year | Workload (ECTS) |
|---|---|---|
| 1. **PhD training** | | |
| **General courses** | | |
| BROK (Basiscursus Regelgeving en organisatie voor Klinisch Onderzoekers- Good Clinical Practice for clinical research) | 2014 | 1.5 |
| Renewal BROK registration | 2019 | 0.5 |
| Integrity in scientific research | 2018 | 0.3 |
| Basic introduction course SPSS | 2018 | 1.0 |
| Open Clinica | 2017 | 0.2 |
| EndNote | 2017 | 0.2 |
| Biomedical English writing course | 2019 | 1.5 |
| **Specific courses** | | |
| 7th Annual course on the blood brain barrier in drug development, Leiden | 2016 | 1.0 |
| Dutch pediatric pharmacology course, Nijmegen | 2014 | 0.3 |
| Summer Neonatal Pharmacology Guest Lecture Series | 2020 | 0.1 |
| **Symposia, workshops and meetings** | | |
| SICK symposium, Haarzuilens | 2016, 2017 | 0.4 |
| PICU research meeting, Rotterdam | 2018 – present | 0.3 |
| Pediatric pharmacology meeting, Rotterdam | 2014 – present | 0.3 |

| | Year | Workload (ECTS) |
|---|---|---|
| **Presentations** | | |
| Pediatric Pharmacology meeting (3x), Rotterdam | 2014, 2021 | 0.3 |
| Grand Round Pediatrics (2x), Rotterdam | 2015, 2021 | 0.2 |
| International Neurotrauma Society (2x), Cape Town, SA | 2016 | 0.2 |
| 'Meet the professor' symposium, Rotterdam | 2018 | 0.1 |
| Neuroscience research meeting, Cape Town | 2019, 2022 | 0.2 |
| PICU research meeting (2x), Rotterdam | 2019 | 0.2 |
| PICU research symposium 'meten is weten', Rotterdam | 2019 | 0.1 |
| Pediatric trauma symposium 'impact after the impact', Rotterdam | 2022 | 0.1 |
| **(Inter)national conferences** | | |
| Neurocritical Care Society, Seattle, USA | 2014 | 1.0 |
| Neurocritical Care Society, Scottsdale, USA | 2015 | 1.0 |
| International Paediatric Brain Injury Society, Liverpool, UK | 2015 | 0.6 |
| International Neurotrauma Society, Cape Town, SA | 2016 | 1.0 |
| ISICEM, Brussels, Belgium | 2016, 2018 | 0.6 |
| 2. **Teaching** | | |
| Pediatric neurology minor | 2015 – 2017 | 0.5 |
| Supervisor PICU nurse-practitioner in training | 2015-2017 | 3.0 |
| Basic qualification in higher education teaching course (BKO certification) | 2016 - 2019 | 4.0 |
| Coordinator nurse practitioner symposia (4x/year) | 2018 - 2020 | 1.0 |
| PICU teaching (registrars, consultants, nursing staff) | 2014 – present | 2.0 |
| Supervisor master student (3x) and medical technical student (2x) | 2016 – present | 5.0 |
| 3. **Other** | | |
| Challenge and support coaching | 2016 - 2017 | 1.0 |
| Coaching medical bachelor students (5x) | 2017-2019 | 1.5 |
| Board member SICK (Dutch Pediatric Intensive Care Committee) | 2015 - 2018 | 2.0 |
| ADAPT study site coordinator | 2015 – 2018 | 2.0 |
| **Grants** | | |
| SSWO S16-26 (2 year young researcher grant) | 2016 | 1.0 |

ECTS = European Credit Transfer and Accumulation System; 1 ECTS credit represents 28 hours

## ACKNOWLEDGEMENTS

Cape Town, Coronaries and Covid, what a ride it has been! Not necessarily because of the thesis itself, but the circumstances surrounding it. As such, the title ***'Crossing barriers'*** has special meaning. It signifies travelling down pathways obstructed by barriers that seem impenetrable and overwhelming. Yet, in time, we marvel at the journey it has been and where and what it has brought us. The completion of this thesis proves barriers can be crossed both literally and figuratively.

From this personal experience, I profoundly thank the patients and families without whom this thesis would not have been possible and for whom we hope to provide better therapies, counselling and outcome. Their strength and courage in a time filled with uncertainty, as well as a future that needs to be reshaped, are both inspiring and humbling.

There are so many people who contributed to this thesis in all kinds of ways. A lot has been said, not enough can be said. Please know, my gratitude is immense.

Naomi


# TRAUMATIC BRAIN INJURY:

## integrated approaches to improve prevention, clinical care and research

Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, Bragge P, Brazinova A, Buki A, Chesnut RM, Citerio G, Coburn M, Cooper DJ, Crowder AT, Czeiter E, Czosnyka M, Diaz-Arrastia R, Dreier JP, Duhaime AC, Ercole A, van Essen TA, Feigin VL, Gao G, Giacino J, Gonzalez-Lara LE, Gruen RL, Gupta D, Hartings JA, Hill S, Jiang JY, **Ketharanathan N**, Kompanje EJO, Lanyon L, Laureys S, Lecky F, Levin H, Lingsma HF, Maegele M, Majdan M, Manley G, Marsteller J, Mascia L, McFadyen C, Mondello S, Newcombe V, Palotie A, Parizal PM, Peul W, Piercy J, Polinder S, Puybasset L, Rasmussen TE, Rossaint R, Smielewski P, Soderberg J, Stanworth SJ, Stein MB, van Steinbuchel N, Stewart W, Steyerberg EW, Stocchetti N, Synnot A, Te Ao B, Tenovuo O, Theadom A, Tibboel D, Videtta W, Wang KKW, Williams WH, Wilson L, Yaffe K for the InTBIR Participants and Investigators.

***Lancet Neurol*** 2017; 16: 987-1048.

# TRAUMATIC BRAIN INJURY:

## progress and challenges in prevention, clinical care, and research

Maas AIR, Menon DK, Manley GT, Abrams M, Akerlund C, Andelic N, Aries M, Bashford T, Bell MJ, Bodien YG, Brett BL, Buki A, Chesnut RM, Citerio G, Clark D, Clasby B, Cooper DJ, Czeiter E, Czosnyka M, Dams-O'Connor K, de Keyser V, Diaz-Arrastia R, Ercole A, van Essen TA, Falvey E, Ferguson AR, Figaji A, Fitgerald M, Foreman B, Gantner D, Gao G, Giacino J, Gravesteijn B, Guiza F, Gupta D, Gurnell M, Haagsma JA, Hammond FM, Hawryluk G, Hutchinson P, van der Jagt M, Jain S, Jain S, Jiang J, Kent H, Kolias A, Kompanje EJO, Lecky F, Lingsma HF, Maegele M, Majdan M, Markowitz A, McCrea M, Meyfroidt G, Mikolic A, Mondello S, Mukherjee P, Nelson D, Nelson LD, Newcombe V, Okonkwo D, Oresic M, Peul W, Pisica D, Polinder S, Ponsford J, Puybasset L, Raj R, Robba C, Roe C, Rosand J, Schueler P, Sharp DJ, Smielewski P, Stein MB, von Steinbuchel N, Stewart W, Steyerberg EW, Stocchetti N, Temkin N, Tenovuo O, Theadom A, Thomas I, Torres Espin A, Turgeon AF, Unterberg A, van Praag D, van Veen E, Verheyden J, vande Vyvere T, Wang KKW, Wiegers EJA, Williams WH, Wilson L, Wisniewski SR, Younsi A, Yue JK, Yuh EL, Zeiler FA, Zeldovich M, Zemek R, for the InTBIR Participants and Investigators.

***Lancet Neurol*** published online September 29th 2022
(https://doi.org/10.1016/S1474-4422(22)00309-X)