Drug therapy in critically ill children

are you awake?

Nienke Vet

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Drug Therapy in Critically Ill Children
Are you awake?

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Ben je wakker?

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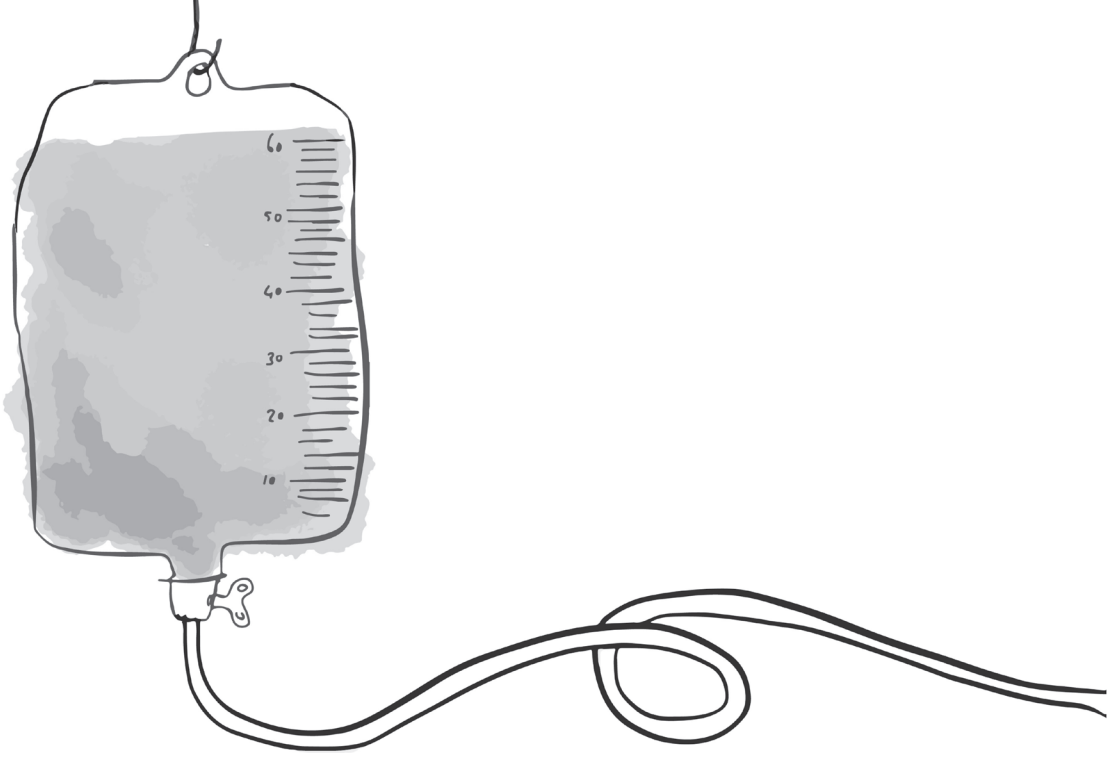
PART I

Introduction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Chapter 1

General introduction

Yearly, around 5,000 children between the ages of 1 day and 18 years are admitted to one of the eight pediatric intensive care units (PICU) in the Netherlands (1). They form a heterogeneous group, and 45-55% present with acute, severe pathology and are deemed critically ill. Critically ill children often require pharmacological intervention to support organ function, treat underlying diseases or reduce pain and agitation, which easily results in polypharmacy. A study from 2001 found that children admitted to our PICU on average received 10 different drugs (2).

Drug dose selection in children is often a normalization of the adult dose based on the child's body weight or age group (preterm, term newborns, infants, toddlers, children and adolescents). However, this approach does not take account of infants' developmental changes and physiological differences between adults and children. This may lead to unsafe or ineffective dosing in children. To date, pharmacokinetic data from studies in children are scarce, and the more so with regard to critically ill children data. This is an undesirable situation because particularly in this vulnerable population many other factors may influence drug disposition and response. Therefore, we are still a long way from evidence-based dosing in critically ill children.

Factors influencing drug disposition and response in critically ill children

The pharmacokinetic properties of a drug include the processes of absorption, distribution, metabolism and excretion of a drug, while the pharmacodynamic properties comprise the physiological and biological responses to the administered drug and therefore may represent both efficacy and safety measures. Variability in pharmacokinetic and pharmacodynamic processes in critically ill children can be explained by many factors, as shown in Figure 1.

Although children differ from each other with regard to age and weight, it is mainly the underlying physiological changes that explain this variability in pharmacokinetic and pharmacodynamic processes, or: drug disposition and response. First, the maturation of drug-metabolizing enzymes leads to age-related changes in clearance of drugs and most cytochrome P450 (CYP) enzymes show an enzyme-dependent increase in activity after birth (3, 4). Second, genetic differences may also result in different phenotypes, e.g. poor and extensive metabolizers. Relevant genetic polymorphisms have been identified for CYP2D6, CYP2C9, CYP2C19, CYP3A4 and CYP3A5 (5, 6). Third, the underlying disease state and organ failure may alter the pharmacokinetic properties of a drug and its clinical effect (7, 8). Hepatic and renal dysfunction are well-known to alter pharmacokinetic and pharmacodynamic processes, but also cardiac, respiratory and gastrointestinal dysfunction affect drug therapy (8). More specifically, animal and limited human adult studies suggest a profound effect of the inflammatory response, which occurs in many critically ill patients and patients with other inflammatory disease states, on drug metabolizing enzymes (9-11).

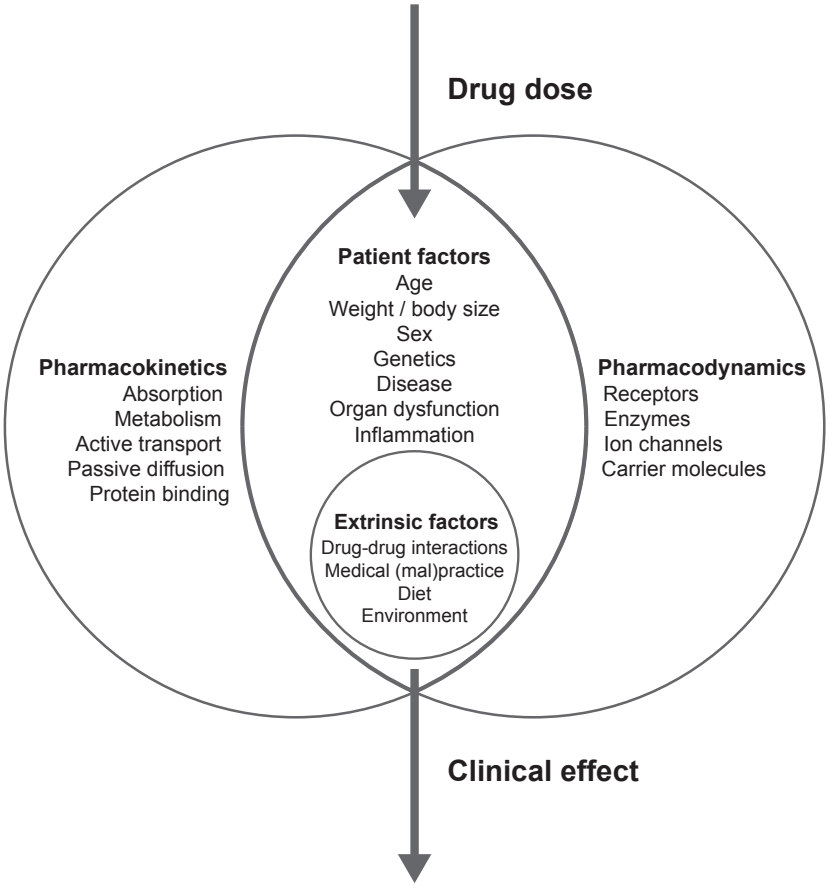

Figure 1. The pharmacokinetic-pharmacodynamic relationship in critically ill children
Theoretical framework of factors explaining inter- and intra-individual variability in pharmacokinetics and pharmacodynamics in a critically ill child.

Taken together, intrinsic factors only partially explain the pharmacokinetic and pharmacodynamic variation in critically ill children. Differences in diet, environmental factors and concomitant administration of other therapeutic drugs (drug-drug interactions) may also contribute to this variation. For example, ketoconazole is a potent inhibitor of CYP2C9, CYP2C19 and CYP3A and inhibition of these enzymes leads to a reduced drug clearance of drugs metabolized by these enzymes (12). Specifically, in critically ill patients, non-drug therapies such as dialysis, cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO) and cooling all potentially contribute to pharmacokinetic and pharmacodynamic variation (13). Hence, the disposition and effect of drugs in critically ill children is subject to many intrinsic and extrinsic factors, leaving these vulnerable patients at high risk of toxicity or therapy failure.

To disentangle the observed inter- and intra-individual variability, it is important to study specific factors, preferably in the context of age-related changes, taking a systems approach (14). A key element of the systems approach is the distinction between drug-specific and system-specific parameters in pharmacokinetic models. System-specific parameters are parameters describing physiological processes, such as organ perfusion and the expression/function of drug-metabolizing enzymes. Knowledge on the changes in the system-specific parameters characterizing the absorption, distribution, metabolism and excretion of drugs, is essential for individually tailored drug dosing that takes all these covariates into account.

Pharmacokinetics in pediatric critical illness - midazolam as CYP3A probe

The cytochrome P450 (CYP) family is the most abundant enzyme family in the liver involved in the metabolism of drugs. CYP3A is the most prominent subfamily in terms of proportion of total CYP activity in the liver and number of substrates; it metabolizes more than half of all therapeutic drugs (12). Many of the drugs used in children are metabolized by this enzyme, such as analgesics (e.g. fentanyl and lidocaine), benzodiazepines (e.g. midazolam and diazepam), macrolide antibiotics, antiarrhythmics (e.g. verapamil and propanolol), prokinetics (e.g. domperidone) and anticancer drugs (12).
In critically ill children, the maturation of drug-metabolizing enzymes is probably the predominant factor accounting for variation in drug clearance (3, 4), followed by inflammation and organ failure. Cytokines, released during inflammation, downregulate drug-metabolizing enzymes by up to 70% (11). In adults, inflammation-related changes in drug disposition have been described for different disease states, such as infection and cancer (15, 16). In children with sepsis and organ failure a two- and fourfold lower antipyrine clearance, respectively, was found compared to children without sepsis (7). In addition, level of IL-6 was negatively correlated with antipyrine clearance, suggesting an important role of inflammation. Antipyrine is a global marker for CYP450; it is metabolized by several CYP isoforms, and individual CYPs appear to be differentially regulated by inflammation. To better understand the impact of inflammation on individual CYPs, and to be able to individualize drug therapy, individual enzymes need to be studied.

Midazolam as probe of CYP3A activity

Midazolam is a short-acting benzodiazepine routinely used in pediatric patients as a sedative agent. Midazolam is metabolized by CYP3A4 and CYP3A5 to hydroxylated metabolites (1-OH-midazolam, 4-OH-midazolam and 1,4-OH-midazolam), which exhibit equivalent pharmacological activity to midazolam (17). These metabolites are excreted in the urine as glucuronide conjugates (18). 1-OH-midazolam-glucuronide appears to have sedative properties when concentrations are high, as has been observed in adult patients with renal failure (17).

Midazolam is a validated probe for determining CYP3A activity *in vivo*. It has a low to intermediate extraction ratio implying a hepatic clearance predominantly dependent on CYP enzymes (19). As CYP3A is responsible for the metabolism of >50% of all clinically used drugs, including several important substrates used in the PICU, the study of midazolam pharmacokinetics gives a unique opportunity to study CYP3A metabolism in critically ill children.
We therefore hypothesize that studying the pharmacokinetics of midazolam in critically ill children can provide valuable information on the relation between critical illness (inflammation and disease state) and clearance of midazolam as a model for CYP3A mediated drug metabolism.

Pharmacodynamics in pediatric critical illness – midazolam as sedative

Like pharmacokinetic data and dosing recommendations, the effect of drugs cannot be extrapolated from adults to children. Apart from age-related maturation in the expression and function of proteins and receptors, children have other diseases and measurement of effect may be different. To illustrate this, many children are unable to express pain verbally, but express pain through changes in behavior.
Extrapolation from relatively healthy children to critically ill children is also not feasible, as pharmacokinetic processes are different in critical illness, as described above. In addition, pharmacodynamic processes may be different in critically ill children. For instance, a critically ill child who is less reactive due to its underlying illness will respond differently to a sedative drug from a relatively healthy and probably anxious child who receives a sedative drug as premedication before an elective procedure. Furthermore, the pharmacokinetic-pharmacodynamic relationship can be different in critically ill children. It may well be that exposure-response relationship is non-linear and changes in drug-receptor interactions may occur as a result of illness (20, 21). Therefore, increased drug concentrations owing to reduced clearance do not necessarily lead to higher efficacy or toxicity as the pharmacodynamic processes can change concomitantly. Regrettably, little pharmacodynamic data on drugs administered to critically ill children are available, and this is a field that should be urgently explored.

Midazolam for sedation

Critically ill children who are mechanically ventilated often require sedative and/or analgesic drugs to diminish anxiety or pain and ensure their comfort. Moreover, a state of sedation facilitates synchronization with mechanical ventilation and enables invasive procedures to be performed. The sedative of choice in pediatric intensive care is often midazolam. It is usually given continuously by the intravenous route. Midazolam is a central nervous system depressant that exerts its clinical effect by binding to a receptor complex, which facilitates the action of the inhibitory neurotransmitter gamma-amino

butyric acid (GABA) in the brain. Through this effect, midazolam possesses sedative, anxiolytic, anticonvulsant, muscle relaxant and amnesic properties (22).
Adequate sedation has been described as the level of sedation at which patients are asleep but easily arousable (23). In ICU practice this means that a child is conscious, breathes in synergy with the ventilator, and is tolerant or compliant with other therapeutic procedures. However, the optimal level of sedation varies for each patient, depending on the type of underlying disease, the severity of disease and the application of certain therapeutic, invasive procedures.
To achieve the optimal level of sedation in individual patients, doses of sedatives are titrated to effect on the guidance of observational sedation scales validated for the population in question, e.g. the COMFORT-behavior scale (24). It can be difficult to reach optimal sedation, because of variability in plasma drug levels and response. Both under- and oversedation are undesirable, as these conditions may adversely affect patient outcomes. Oversedation delays recovery, as greater sedatives consumption is associated with longer duration of ventilation as well as extubation failure (25). Oversedation also induces tolerance and withdrawal syndrome (26, 27). Undersedation, on the other hand, may cause distress and adverse events such as unintentional extubation or displacement of catheters. All this may lead to a longer PICU stay.
Despite the use of sedation algorithms to optimize dosing, oversedation is still common in the ICU setting. In adults, daily sedation interruption (DSI), has been proposed as a method of reducing the adverse effects of continuous sedation infusions, especially midazolam (28, 29). Clinical trials have shown that DSI can reduce the duration of mechanical ventilation, hospital stay and amount of sedatives administered, without compromising patient comfort or safety (28, 30). It is not known whether this holds for critically ill children as well. Obviously, results from adult DSI studies cannot be extrapolated to children for several reasons. First, adult patients receive other sedative agents, such as propofol, which is contra-indicated for the prolonged sedation of children, and fentanyl. Second, the elimination half-life of sedatives may differ between adults and children. The elimination half-life of midazolam is longer in critically ill children than in adults (6.5-12 hours vs. 1.8-6.4 hours) (31). Third, children often cannot fully comprehend the situation in which they are when they wake up, and consequently may show more distress than adults.
Still, we hypothesize that DSI in addition to protocolized sedation improves clinical outcome in critically ill children.

In **conclusion**, many intrinsic and extrinsic factors seem to contribute to the inter- and intra-individual variability seen in the disposition and effect of drugs. With regard to critically ill children, both pharmacokinetic and pharmacodynamic data that take into account age and underlying disease are scarce.

Studying the effects of critical illness on CYP3A activity, in the context of age-related changes and using midazolam as a surrogate marker, is an important first step to gain more knowledge. In addition, studying the effect of midazolam with the use of a more tailor-made sedation strategy can help to achieve more rational dosing in this vulnerable patient group. Studies of this kind serve as blueprints for an approach that considers pharmacotherapy in the critically ill child as a complex system which affects both drug disposition and effect.

Aims and outline of this thesis

The aims of this thesis are:

- To study the influence of critical illness (inflammation and disease state) on midazolam pharmacokinetics, as a surrogate measure of CYP3A activity in critically ill children.
- To study the safety and efficacy of a new sedation strategy of daily sedation interruption in critically ill children.

In **chapter 2** the current knowledge on the effect of inflammation on CYP450-mediated drug metabolism and drug effect in children is reviewed. **Chapters 3 and 4** present studies on the effect of inflammation and organ dysfunction on midazolam clearance in critically ill children. The pilot study in chapter 3 evaluates the effect of inflammation and severity of illness on midazolam pharmacokinetics and pharmacodynamics in 21 critically ill children. The prospective population pharmacokinetic study in chapter 4 addresses the relationship of inflammation and organ failure, with midazolam clearance in critically ill children. This study serves as a model for the impact of inflammation and critical illness on CYP3A-mediated drug metabolism.

Chapter 5 deals with the reported incidences of under-, optimal, and oversedation in pediatric intensive care patients and the question to what extent the goal of adequate sedation is met. **Chapter 6** describes the study protocol of a multicenter randomized controlled trial to compare the outcomes of daily sedation interruption plus protocolized sedation and protocolized sedation only in critically ill children. The results of this trial are presented in **chapter 7**. **Chapter 8** concerns children's short-term health-related quality of life following daily sedation interruption.

Lastly, in **chapter 9**, the main findings and conclusions of this thesis are discussed, and recommendations for future research are given.

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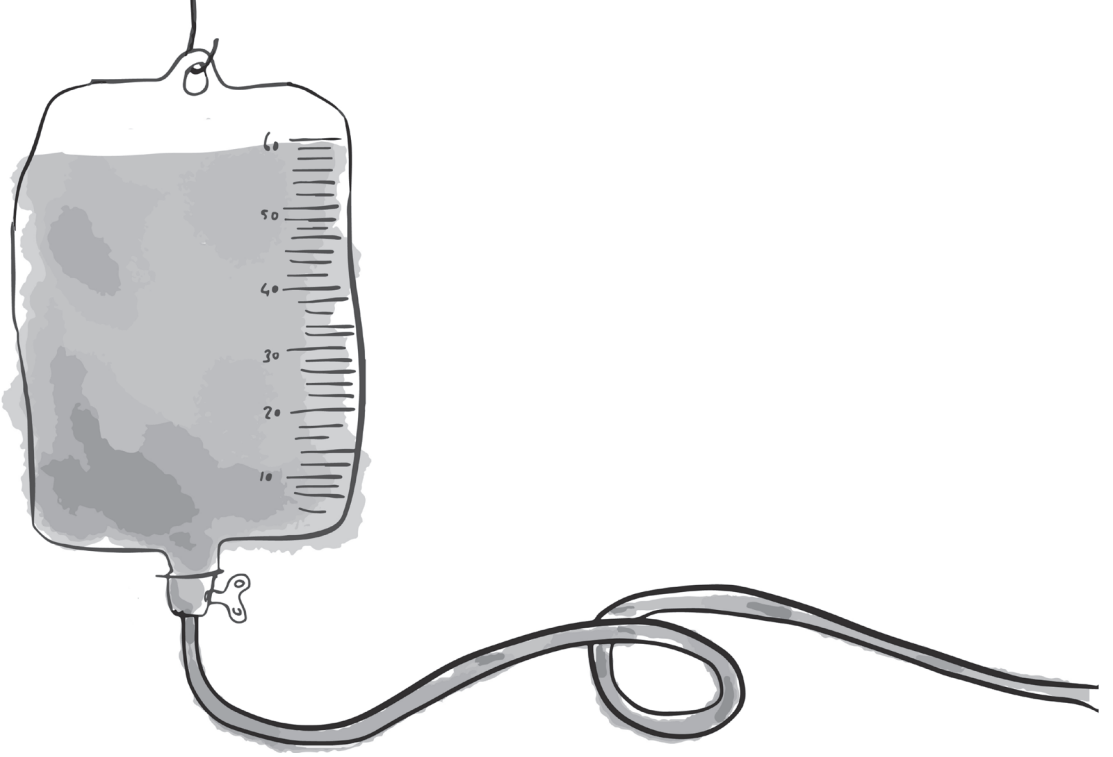
PART II

Pharmacokinetics in pediatric critical illness – midazolam as CYP3A probe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Chapter 2

The effect of inflammation on drug metabolism: a focus on pediatrics

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ABSTRACT

Inflammation is associated with downregulation of the expression and activity of cytochrome P450 enzymes (CYP450) involved in hepatic drug metabolism. Elevated plasma drug levels and increased toxicity might be the consequences of this downregulation. Few clinical studies have investigated these consequences of inflammation in children, who are prescribed many off-label or unlicensed drugs. This review describes the impact of inflammation on CYP450 drug metabolism and drug effect in children, with the consequent implications for drug studies and clinical therapy in this group.

INTRODUCTION

Pharmacokinetic and pharmacodynamic studies in children are scarce. Knowledge of the behavior of drugs in these patients is limited, and is based mainly on information derived from studies in adult healthy volunteers and patients. There are important differences in pathophysiology and disease spectrum between children and adults, as well as developmental changes that might affect the pharmacokinetics and pharmacodynamics of a drug. Therefore, adult data on the disposition and effect of drugs cannot generally be extrapolated to children, as reviewed by Kearns et al. (1).

In critically ill children, extrapolation is even more problematic, because drug disposition and effect might be influenced by a range of other factors. Pediatric intensive care patients are frequently exposed to polypharmacy, and more than 70% of drugs prescribed are either unlicensed or off-label (2). Both factors could impose an increased risk of drug therapy failure or adverse drug reactions on these patients. Critical illness is associated with renal failure, hepatic dysfunction and cardiac failure, all leading to altered drug clearance (3).

A relatively unrecognized factor that can greatly affect the disposition of drugs is the underlying inflammation. Inflammation is common in several disease states in children, such as critical illness, autoimmune diseases and cancer. Numerous animal and limited human studies have shown that inflammation is associated with the downregulation of several drug-metabolizing enzymes, especially the cytochrome P450 (CYP) enzymes, as reviewed by several authors (4-8). Given that CYP is the major enzyme system involved in drug metabolism, changes in the expression or activity of these enzymes could have a significant impact on the clearance and clinical effect of drugs (9). Although understanding the effect of inflammation on drug disposition and effect in critically ill children and children with other inflammatory disease states could be of considerable clinical relevance, data are scarce. The purpose of this review is to summarize the effect of inflammation on CYP450-mediated drug metabolism, and drug effect in children with inflammatory disease.

HEPATIC DRUG METABOLISM IN CHILDREN AND THE INFLAMMATORY RESPONSE

The CYP450 enzyme family consists of several subfamilies and these enzymes are the most abundant drug-metabolizing enzymes in humans. CYP3A is the most prominent subfamily in terms of number of substrates and proportion of total CYP in the liver, and it metabolizes more than half of all therapeutic drugs (10). Many of the drugs used in children are also metabolized by this enzyme, such as analgesics (e.g. fentanyl and

lidocaine), benzodiazepines (e.g. midazolam and diazepam), macrolide antibiotics, antiarrhythmics (e.g. nifedipine, verapamil and propanolol), prokinetics (e.g. domperidone and cisapride) and anticancer drugs (10).
Changes in CYP activity could have a significant impact on drug metabolism. In children, most CYP enzymes show an increase in activity after birth (1). Furthermore, CYP enzyme activity might change as a result of the concomitant administration of other drugs, genetic polymorphisms and concomitant diseases.
The inflammatory response, which occurs in many diseases, has also been associated with decreased CYP enzyme activity. The release of proinflammatory cytokines, especially interleukins (IL-1, IL-6 and IL-8), tumor necrosis factor (TNF-α) and interferon gamma (IFN-γ), induce the production of acute phase proteins by the liver (e.g. fibrinogen, α1-acid glycoprotein and C-reactive protein) and decrease the synthesis of normal export proteins (e.g. albumin and transferrin). The proinflammatory cytokines involved in the acute phase response can also alter drug-metabolizing enzyme capabilities.

THE EFFECT OF INFLAMMATION ON DRUG METABOLISM

Animal studies

The effect of inflammation on CYP expression and activity has been extensively studied in animals and has been described in several reviews (4-6, 11, 12). These studies showed a downregulation of expression and activity of CYP450 enzymes after the administration of endotoxins (lipopolysaccharide (LPS)) and cytokines (TNF-α, IL-1, IL-6 and IFN-γ) (13). The most affected CYPs belong to the CYP1A, 2A, 2C, 2E and 3A subfamilies. The inflammatory response to viruses, bacteria and parasites also negatively alters CYP expression and function (11). Similarly, the inflammatory response to infection, injury or autoimmune disease negatively impact drug biotransformation in animals (14).
Consequently, the downregulation of CYP activity by inflammation leads to decreased drug clearance and elevated plasma drug levels. In LPS-treated rats, a reduced clearance is observed for several drugs, such as midazolam, chlorzoxazone, telithromycin and antipyrine (12, 15). In addition, propranolol plasma concentrations are markedly elevated in inflammatory conditions in rats (16).
Given that a homology of proteins between human and rat CYP isoenzymes is reported, it could be expected that human drug metabolism is also affected by inflammation. However, the extrapolation of animal data to humans is hampered by interspecies differences in CYP450 enzymes and their regulation (13).

In vitro studies in human hepatocytes

In vitro studies with primary cultured human hepatocytes have served as a model for the *in vivo* effects of cytokines on CYP activity (13). Recently, Aitken et al. reported that expression of CYP3A4 and CYP2C8 was downregulated by all cytokines studied (IL-1, IL-6, TNF-α, IFN-γ and transforming growth factor-β (TGF-β)), whereas CYP2C18 expression was unaffected. Expression of CYP2C9 and CYP2C19 was affected by IL-6 and TGF-β, but not by TNF-α, IFN-γ and IL-1. CYP2B6 expression was only decreased after administration of IL-6 and IFN-γ (17). This study confirmed that inflammatory cytokines differentially regulate human CYP expression.

In addition to downregulation of expression, it was recently shown that IL-6 also mediates repression of CYP3A4 protein levels and enzymatic activity (18). Given that different diseases have different cytokine profiles and time courses, the influence of inflammation on human drug metabolism might be disease and drug specific.

THE EFFECT OF INFLAMMATION ON HUMAN PHARMACOKINETICS

Adults

During the past 40 years, several clinical studies in adults have reported alterations in drug metabolism and the pharmacokinetics of drugs in the presence of inflammation. These studies have been reviewed previously (4-8, 11). Table 1 provides a summary of all the clinical studies we identified as looking at the effect of inflammation on drug metabolism.

Reduced activity is reported for CYP3A, CYP1A2, CYP2C9, CYP2C19 and, recently, for CYP2D6 in patients with an acute infection or inflammatory disease. This cytokine-mediated decrease in drug metabolism can be up to 70%. Therefore, the clinical concern is that patients with an inflammatory disease will have an increased exposure to drugs because of a decreased clearance, and thereby an increased risk of adverse drug effects. Additionally, as inflammation can also affect the expression and activity of important drug transporters, the uptake and clearance of drugs can be further affected (19). For instance, a recent study in patients with HIV showed that not only overall CYP3A activity, but also P-glycoprotein activity was lower in these patients compared with healthy volunteers (20). Furthermore, other factors that are influenced by inflammation, such as protein binding, capillary permeability, cardiac output and liver blood flow, also have the potential to influence pharmacokinetics and pharmacodynamics (21). All together, these changes could have important consequences in terms of pharmacokinetic and pharmacodynamic disposition of drugs in adults.

Table 1. Studies on the effect of inflammation on drug metabolism in adults

Inflammation mechanism	CYP activity	Measurement	Effect	Correlated with	Refs
Healthy subjects					
LPS	Overall CYP	Antipyrine, theophylline and hexobarbital	↓ 22-35%	TNF-α, IL-6	(54, 55)
	CYP2E1	Chlorzoxazone	↔		(56)
IL-10	CYP3A	Midazolam	↓ 12%	IL-10	(57)
	CYP2C9	Tolbutamide	↔		
	CYP1A2	Caffeine	↔		
	CYP2D6	Dextromethorphan	↔		
Influenza vaccination	CYP3A4	Erythromycin breath test	↓ 4%	IFN-γ	(58)
Inflammatory diseases					
Elective surgery	CYP3A4	Erythromycin breath test	↓ 20-60%	IL-6	(59)
Allogeneic bone marrow transplantation	CYP3A4	Cyclosporine	↓	IL-6, CRP	(60)
HIV	CYP3A CYP2D6	Midazolam Dextromethorphan	↓ 18% ↓ 90%	TNF-α	(61)
	CYP3A CYP2D6	Midazolam Dextromethorphan	↓ 50% ↔	NA	(20)
Hepatitis C with Helicobacter pylori infection	CYP3A4	Lidocaine (MEGX test)	↓ 60-70%	NA	(62)
Rheumatoid arthritis	CYP3A4 and CYP1A2	Verapamil	↓	IL-6	(63)
Infection in schizophrenia patients	CYP1A2	Clozapine	↓	NA	(64)
Congestive heart failure	CYP1A2 CYP2C9 CYP2E1	Caffeine Mephenytoin Chlorzoxazone	↓ ↓ ↔	IL-6, TNF-α	(65)
Cancer					
Cancer with acute phase response	CYP3A	Erythromycin breath test	↓ 30%	CRP, IL-6	(66)
Advanced solid tumors	CYP3A	Erythromycin breath test	↓	α1-acid glycoprotein	(67)
Advanced cancer	CYP3A	Midazolam	↓	Ferritin	(68)
	CYP2C19	Omeprazole	↓	NA	(69)
	CYP2C19	Omeprazole	↓	-	(70)
Cancer	CYP2C9	Tolbutamide	↔	-	(71)

Critically ill adults

In 1987, it was reported that drug metabolism is altered in critically ill patients. In patients with septic shock, a reduced clearance of midazolam was found. This altered clearance was due to a reduced capability to form the 1-OH metabolite, but was reversible after improvement of the clinical condition (22). The reduced clearance of midazolam could

be the result of reduced liver perfusion, as suggested by the authors but, given that midazolam is a medium-clearance drug, it is likely that reduced CYP3A activity is also a factor of influence.

During the past few years, additional studies have suggested a reduced CYP activity in critically ill patients with sepsis. The clearance of theophylline (CYP1A2) is reduced in patients with sepsis and multiple organ failure (23). The formation of MEGX from lidocaine, formed by CYP3A4, is decreased in patients with sepsis and this was not influenced by acute changes in hepatosplanchnic blood flow after dopamine infusion (24). In addition, plasma levels of atorvastatin, metabolized by CYP3A4, are high in patients with sepsis (25). It is likely that cytokines have an important role in the suppression of CYP activity in these patients. This is further supported by the results of Novotny et al., who found a significant decrease in overall CYP450 activity, measured by the aminopyrine breath test, in patients with sepsis and this reduction was inversely correlated with TNF-α serum levels (26). In addition, mephenytoin and chlorzoxazone (CYP2C19 and CYP2E1, respectively) metabolism was depressed in severely injured patients, who also display an intense inflammatory response (27).

Children

In children, studies on the effect of inflammation on the pharmacokinetics of drugs are scarce. In 1978, a reduced clearance of theophylline was described in asthmatic children suffering from a viral upper respiratory tract infection caused by influenza A or adenovirus (28). Yamaguchi et al. showed that children who have raised serum concentrations of C-reactive protein (>0.5 mg/dl) and fever (>37.5 °C) had a reduced clearance of theophylline. Although cytokines were not determined in this study, this suggests that the *in vivo* activity of CYP1A2 was suppressed by cytokines released in the process of acute illness (29).

Critically ill children

To the best of our best knowledge, only two studies have specifically looked at the effect of inflammation on drug metabolism in children with an inflammatory response. In critically ill children, one study focused on CYP activity in the presence of critical illness and inflammation. Antipyrine metabolism, as global marker of CYP activity, was studied in 51 children with sepsis and six critically ill children without sepsis. Children with sepsis had a two-time reduction in antipyrine clearance compared with controls (0.38 ± 0.28 vs. 0.74 ± 0.31 ml/kg/min, $p<0.05$) and children with multiple organ failure had a four-time reduction in clearance compared with controls (0.22 ± 0.15 vs. 0.74 ± 0.31 ml/kg/min, $p<0.05$). The clearance of antipyrine was inversely correlated to circulating IL-6 concentration and to the number of failing organs (30). Recently, the pharmacokinetics of intravenous pantoprazole in pediatric intensive care patients was described. The

authors showed that the systemic inflammatory response was a significant covariate affecting the clearance of pantoprazole, a CYP2C19 and a CYP3A4 probe. The presence of the systemic inflammatory response in these children was associated with a 62.3% decrease in pantoprazole clearance (31). Both studies illustrate the potentially dramatic effects of inflammation on drug metabolism in critically ill children.

SUPPORTING EVIDENCE FROM PHARMACOKINETIC STUDIES IN CHILDREN

As presented above, only a few studies have specifically looked at the effect of inflammation on drug metabolism in children. Additional information can be inferred from individual pharmacokinetic and pharmacodynamic studies, comparing (relatively) healthy children with those with inflammatory disease.

Midazolam

Midazolam is one of the most widely used drugs in pediatric intensive care for sedation. It undergoes extensive metabolism by the CYP3A subfamily to form a major hydroxylated metabolite (1-OH midazolam) and is an acknowledged *in vivo* CYP3A probe.

In children, the pharmacokinetics of midazolam has been described in several studies (Table 2). Looking at these studies, there are remarkable differences in midazolam clearances between the different populations. In critically ill neonates, the clearance of midazolam appears to be low (1.2-2.0 ml/kg/min), presumably as a result of immature CYP3A4/5 enzyme activity (32-35). In relatively healthy non-ventilated children, aged 3 months to 17 years, midazolam clearance is higher and ranges from 10 to 16 ml/kg/min (36-42). By contrast, in critically ill ventilated children, aged 2 days to 17 years, the reported clearance of midazolam appears to be lower than in non-ventilated children (2.3 to 9.1 ml/kg/min) (43-46). The overall average clearance, from the studies reported, is approximately 12 ml/kg/min in healthy children and approximately 7 ml/kg/min in critically ill children. Hence, the clearance of midazolam appears to be considerably lower in critically ill children compared with healthy children of the same age.

Children in the reported studies had diagnoses associated with inflammation (post-cardiac surgery, airway infections and systemic infections). It is therefore reasonable to postulate inflammation as a factor contributing to the decreased midazolam clearance in critically ill children. This observation is supported by a study in critically ill children undergoing cardiac surgery. The authors showed a tendency to a reduced clearance in children who had undergone cardiopulmonary bypass compared with children with cardiac surgery without cardiopulmonary bypass (44). Given that cardiopulmonary bypass triggers an inflammatory response (47), it supports inflammation as a covariate in midazolam clearance in children.

Table 2. Pharmacokinetic studies of midazolam in children

Age (average)	Patients	n	Reason for administration	Dose/route	Clearance (ml/kg/min) (SD and/or range)	Refs
Neonates (gestational age)						
26-34 weeks	Moderately ill neonates	24	Before stressful procedure	Single dose iv; 0.1 mg/kg	1.8 (0.7-6.7)	(32)
26-42 weeks	Critically ill neonates	187	Sedation during mechanical ventilation	Continuous infusion; Mean 69 mcg/kg/h	1.17 (0.22)	(33)
34-41 weeks	Critically ill neonates	10	Sedative therapy	Single dose iv; 0.2 mg/kg	2.03 (1.24)	(34)
29-41 weeks	Critically ill neonates	15	Sedation during mechanical ventilation	Continuous infusion; 0.06 mg/kg/h	1.7 (1.8; 0.6-2.7)	(35)
Children						
3.2-24.7 months (median 11.1 m)	Nonventilated infants after craniofacial surgery	24	Sedative therapy	Continuous infusion; Start dose 0.05 mg/kg/h	16.7	(36)
1.75-4 years (mean 2.5 y)	Healthy children scheduled for minor genitourinary operations	6	Study, after induction of anaesthesia	Single dose iv; 0.2 mg/kg	13.3 (4.28)	(37)
7-39 months (mean 27 m)	Children with severe malaria and convulsions	12	Convulsions	Single dose iv; 0.3 mg/kg	14.4 (9.2-19.7)	(38)
6 months to 16 years	Children scheduled for minor procedures	21	Sedative premedication	Single dose iv; 0.15 mg/kg	11.33 ± 6.33 (6 m-2 y) 10.0 ± 3.83 (2-12 y) 9.33 ± 3.83 (12-16 y)	(39)
3-10 years (mean 5.5 y)	Children with minor inguinal area surgery	8	Study, after induction of anesthesia	Single dose iv; 0.15 mg/kg	9.11 (1.21)	(40)
5-9 years (mean 6.5 y)	Healthy children undergoing circumcision	12	During induction of anesthesia	Single dose iv; 0.5 mg/kg	15.4 (3.2)	(41)
8-17 years (median 13.5 y)	Children undergoing endoscopy	20	Sedation during endoscopy	Single dose iv; 0.1 mg/kg	10.0 (5.0)	(42)

Table 2. Pharmacokinetic studies of midazolam in children (continued)

Age (average)	Patients	n	Reason for administration	Dose/route	Clearance (ml/kg/min) (SD and/or range)	Refs
Critically ill children						
26 days to 5 years (17 infants ≤ 1 y)	Critically ill children	24	Sedation during mechanical ventilation	Continuous infusion; 0.05-0.5 mg/kg/h	5.8 (3.8)	(43)
3 months-8 years	Children undergoing cardiac surgery	17	During (group A) or after (group B and C) surgery for study	Single dose iv; 0.3 mg/kg		(44)
Group A: 5.2 (2.5 y)	Closed heart surgery				11.98 (6.68)	
Group B: 4.7 (2.6 y)	Cardio-pulmonary bypass				8.53 (1.82)	
Group C: 1.3 (0.4 y)	Cardio-pulmonary bypass with circulatory arrest				9.07 (3.35)	
1 month to 13 years	Critically ill children	38	Sedation during mechanical ventilation	Continuous infusion	3.1 (≤12 months) 2.3 (1-2 years) 13.0 (>3 years)	(45)
2 days to 17 years	Critically ill children	21	Conscious sedation	Continuous infusion; 0.05-0.4 mg/kg/h	5.0 (3.9)	(46)

Unfortunately, although a logical next step, none of these studies evaluated the pharmacodynamic consequences of the altered midazolam clearance in critically ill children compared with healthy children.

Omeprazole

Omeprazole, an acid pump inhibitor, is frequently used to treat gastroesophageal reflux in children and infants. Omeprazole is primarily metabolized in humans by CYP2C19 and, to a minor extent, by CYP3A.

In children, only a few data are available on the clearance of omeprazole (Table 3). Two studies have examined the pharmacokinetic parameters of intravenous omeprazole. Faure et al. found a median omeprazole clearance of 0.53 L/kg/h in children requiring intravenous omeprazole for esophagitis or an ulcer (48). Jacqz-Agrain et al. studied the pharmacokinetics of omeprazole in a heterogeneous group of children who needed omeprazole for an acute gastrointestinal disease. They found a median omeprazole clearance of 0.23 L/kg/h (49). In this study, systemic clearance was variable between individuals. When looking at the individual clearances, the lowest clearances were reported for patients with a disease that is most likely to be accompanied by an inflammatory response (e.g. Crohn's disease, leukemia, renal and liver transplantation). Inflammation could therefore also have a role in the reduced clearance. However, with only two studies available, one can only speculate on the role of inflammation as a reason for the observed difference in omeprazole clearance. If omeprazole clearance is reduced in critically ill children, it would be expected that low doses are needed to reach adequate acid-suppression. By contrast, in a large proportion of critically ill pediatric patients, acid suppression was inadequate with 'therapeutic' doses of oral omeprazole (up to 1.6 mg/kg/d). An important limitation of this study is the lack of omeprazol plasma concentrations to link exposure with (lack of) effect (50).

Antipyrine

Antipyrine has served as a good probe drug for overall CYP activity. Antipyrine clearance is a useful method for evaluating drug-metabolizing capacity. In children, a few studies using antipyrine as a probe have been performed (Table 3). Average antipyrine clearance reported in these studies was 0.9 ml/kg/min.

Interestingly, Relling et al. have demonstrated that there is an improvement in antipyrine clearance in children with acute lymphocytic leukemia (ALL) from before to after remission (0.65 to 0.95 ml/kg/min, p=0.007) (51). The authors hypothesize that eradication of hepatic leukemic infiltration by ALL remission therapy resulted in an improvement in the microsomal metabolism of antipyrine. Interestingly, α1-acid glycoprotein concentrations significantly decreased after induction therapy (211 vs. 128 mg/dl, p<0.0001). Given that α1-acid glycoprotein is an acute phase protein, this indicates that an inflam-

matory response is present in patients with ALL. This is also reported by other authors (52). This observation suggests a relationship between inflammation and reduced drug metabolism in children with cancer, as also reported in adult cancer patients (4). We speculate that, after therapy, when the inflammatory response diminishes, α1-acid glycoprotein concentrations decrease and antipyrine clearance increases.

Table 3. Pharmacokinetic studies of omeprazole and antipyrine in children

Age (mean)	Patients	n	Dose/route	Clearance (L/kg/h) (SD)	Reference
Omeprazole					
4.5-27 months	Children with esophagitis or an ulcer	9	Once a day (iv)	0.53 (0.29)	(48)
0.3-19 years	Heterogeneous group of children with an acute gastrointestinal disease	13	Twice a day (iv)	0.23 (0.32)	(49)
Antipyrine					
2-16 years (5.3 years)	Children with acute lymphocytic leukemia before and after remission-induction therapy	14	Single dose (iv)	Before remission: 0.65 (0.30) After remission: 0.95 (0.29)	(51)
2.3-17.8 years (7.8 years)	Children with acute lymphocytic leukemia in complete remission	50	Single dose (iv)	0.91	(72)
14.6-20.2 years (cystic fibrosis)	Patients with cystic fibrosis and patients with cancer treated only with surgery and radiation	14	Single dose (iv)	0.9 (0.1)	(73)
7.2-19.4 years (cancer)		12		0.7 (0.09)	

THE EFFECT OF INFLAMMATION ON PHARMACODYNAMICS

Both clinical and preclinical studies suggest that the inflammatory response alters the pharmacokinetics of CYP450-metabolized drugs. Reduced clearance with consequent increased drug concentrations might expose the patient to increased effect and toxicity. However, data supporting these pharmacodynamic consequences of inflammation-mediated reduced clearance are currently limited.

For some drugs, it is shown that an increased exposure consequent to inflammation leads to increased toxicity (e.g. docetaxel) (4), However, for other drugs, this pharmacokinetic-pharmacodynamic relationship is less clear. Inflammation might also downregulate receptors (e.g. cardiovascular receptors), leading to a reduced drug effect despite increased plasma drug concentrations as reviewed elsewhere (4, 21).

Little is known about the clinical implications of these changes in the exposure-response relationship during inflammation. Clinical studies are lacking, and data from children relating to the pharmacokinetic-pharmacodynamic relationship in inflammation are absent.

INFLAMMATION AND THE IMPACT ON DRUG DEVELOPMENT AND THERAPY

In vitro and *in vivo* adult studies have so far shown that CYP enzymes, which catalyze the metabolism of most drugs currently in use, are differentially downregulated by proinflammatory cytokines. By contrast, consequent high drug concentrations might not necessarily lead to higher efficacy or toxicity, as pharmacodynamics can change concomitantly. Preliminary studies described here have demonstrated that the inflammatory response in children with inflammatory diseases also appears to be associated with marked reduced hepatic drug metabolism, although pharmacodynamic data are lacking. Therefore, extrapolation of data from healthy adults and children to a pediatric population with inflammatory disease cannot be done automatically. The differential effect of inflammation on pharmacokinetics and pharmacodynamics could further complicate extrapolation. Increased drug concentrations, owing to reduced clearance, could result in toxic levels (Figure 1b), but could also result in therapeutic, subtherapeutic or toxic levels owing to changed pharmacodynamics (Figure 1c-e).

Consequently, the design of pharmacokinetic and pharmacodynamic studies and, ultimately, of dose regimens for CYP-metabolized drugs must capture inflammation as a covariate to ensure adequate characterization of the disposition of drugs and the translation of this information into the provision of safe drug therapy for children.

Until the relationship between exposure and response is better characterized, we need to dose carefully for safe and effective drug therapy in children. Nevertheless, a standard dose decrease in children with inflammatory disease could be considered for drugs that are easily titrated to effect (i.e. sedative drugs). Close monitoring of the effect of drugs and adequate dose adjustments are needed, also when the inflammatory response resolves because it is unclear whether, and in what time period, the activity of drug-metabolizing enzymes will normalize when inflammation diminishes (21).

FUTURE DIRECTIONS

There are therefore several crucial information gaps with regard to the overall impact of inflammation on drug metabolism and drug effect, not only in children but also in adults. First, more pharmacokinetic studies are needed to understand how drug disposition is regulated in inflammatory diseases. In children, clinical drug studies must be designed,

using minimal sample strategies and population pharmacokinetic modeling, to increase knowledge on drug disposition in this population (53). Pharmacokinetic studies alone will not suffice. It is imperative that the pharmacodynamic consequences of inflammation are also studied. These studies in children will be challenging, as they need

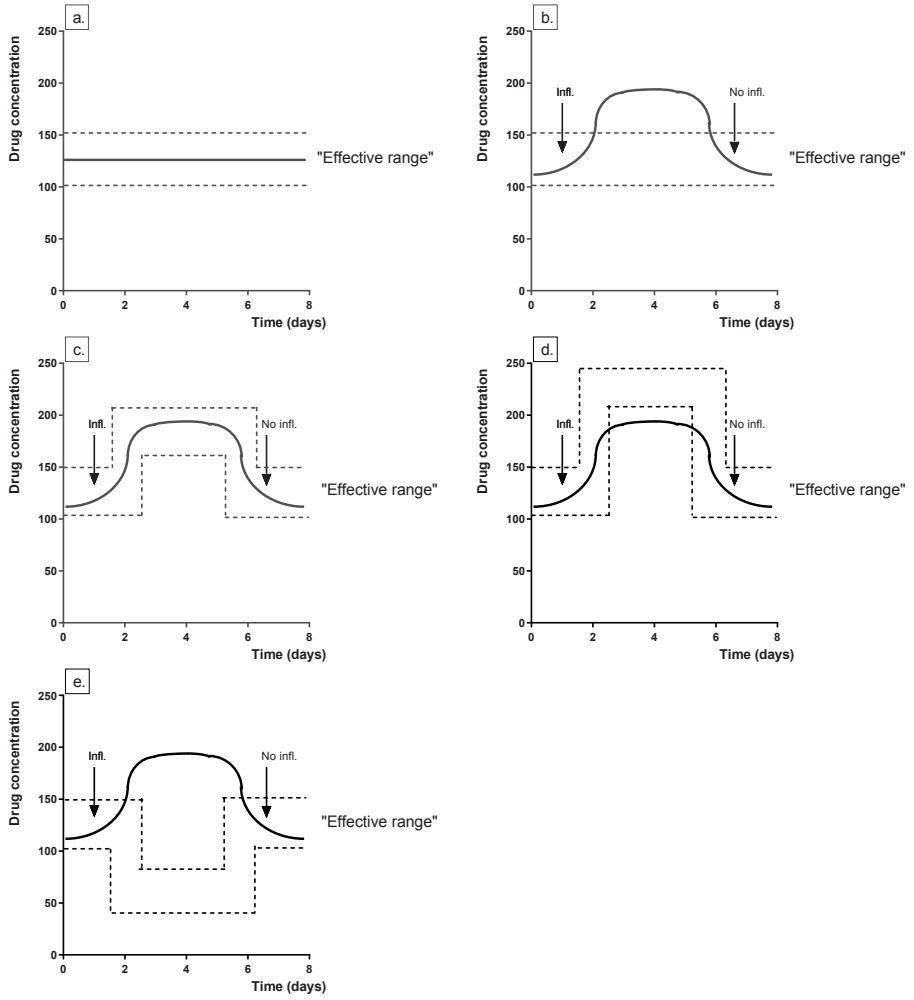

Figure 1. Possible pharmacokinetic-pharmacodynamic relationships during inflammatory diseases
The solid black line represents the estimated plasma drug concentration, whereas the dotted lines represent the effective range of the drug (pharmacodynamic window). **(a)** Patient without inflammation on a stable drug regimen with a therapeutic drug concentration. **(b)** Patient with acute inflammatory disease only affecting pharmacokinetics, resulting in toxic plasma drug concentrations. **(c)-(e)** Patient with acute inflammatory disease affecting both pharmacokinetics and pharmacodynamics, resulting in **(c)** altered effect concentration with therapeutic drug concentrations; **(d)** altered effect concentration with sub-therapeutic drug concentrations; and **(e)** altered effect concentration with toxic drug concentrations.
Infl.=inflammation; No infl.=no inflammation

to incorporate not only inflammation as covariate, but also disease- and age-related changes. Important age-related changes in pharmacokinetics and pharmacodynamics occur during childhood. It is of paramount importance that children over the whole age range are studied, as the interplay of developmental changes and inflammation-related variation has yet to be determined.

In addition, there is a need to identify the most appropriate way to assess inflammatory status in children. During the inflammatory response, multiple cytokines are increased and the exact cytokine pattern responsible for the downregulation in CYP activity is still not known (5). Given that a correlation between loss of drug clearance and IL-6 is described *in vitro*, in animals and in humans, IL-6 appears to have an important role in this loss. Although the time course of changes in IL-6 levels during different diseases in humans is poorly known, IL-6 might be a good biomarker to use to assess inflammation. Alternatively, measurement of acute-phase proteins, such as C-reactive protein or α1-acid glycoprotein, or a combination of several markers, could be useful in predicting the net effect of inflammation on drug pharmacokinetics (4). If a reliable biomarker of inflammation is available, with a time course fast enough to correlate with increase or reduction of inflammation, yet slow enough to be measured once daily, this biomarker could be measured along with drug concentrations and drug effect to characterize the pharmacokinetic-pharmacodynamic relationship in inflammatory diseases (9).

Finally, in addition to well-designed pharmacokinetic-pharmacodynamic studies, individual cases of increased toxicity, adverse effects or lack of efficacy of drug therapy in children with inflammation should be reported in the peer-reviewed literature. Given that many pediatric patient groups are small and/or heterogeneous, large well-controlled studies on the effect of individual drugs are a logistical challenge or even impossible. Hence, reporting of individual or combined cases could aid in improving understanding of inflammation in relation to pediatric drug therapy.

CONCLUSION

The inflammatory response downregulates CYP expression and activity and contributes to pharmacokinetic and probably pharmacodynamic variability in children with inflammation. These changes might be of clinical significance for drug studies and drug therapy. Investigators and clinicians must consider the impact of inflammation in the context of developmental changes on drug disposition and effect in both the design of drug studies and the provision of safe therapy to pediatric patients.

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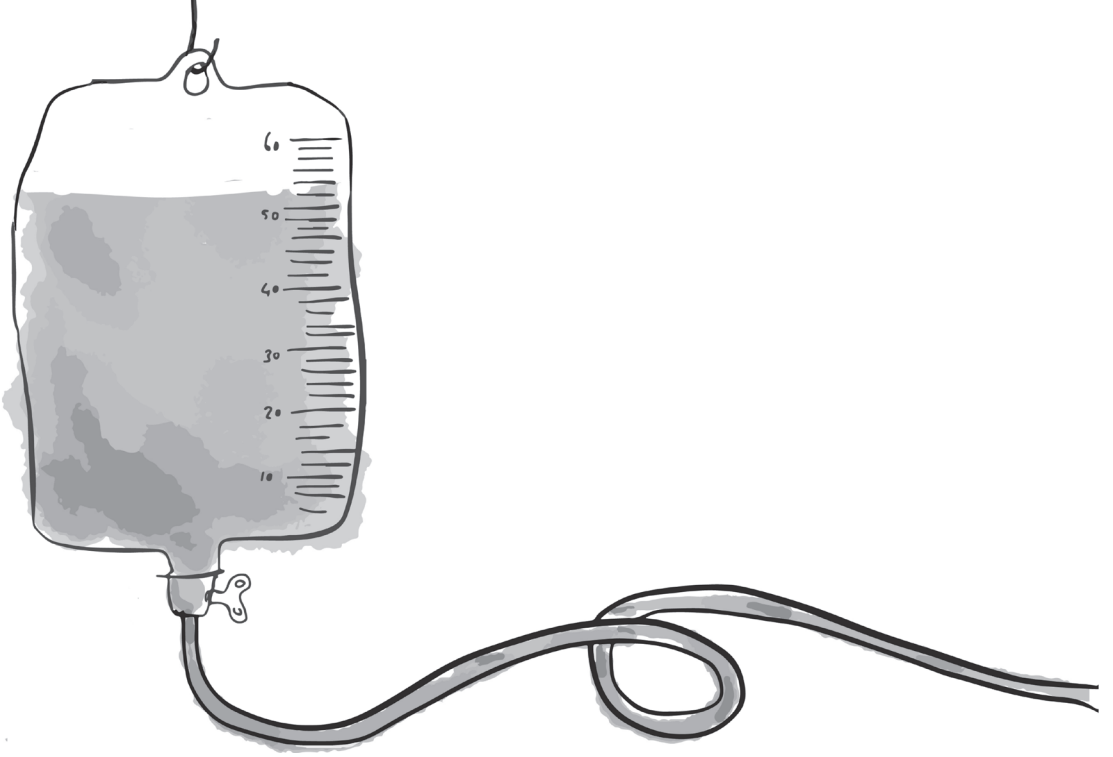
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Chapter 3

The effect of critical illness and inflammation on midazolam therapy in children

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ABSTRACT

Objective: To determine the effect of inflammation and disease severity on midazolam pharmacokinetics (as surrogate marker of cytochrome 3A activity) and pharmacodynamics in critically ill children.

Design: Analysis of prospectively collected pharmacokinetic and pharmacodynamic data from a midazolam study in critically ill children.

Setting: Pediatric intensive care unit of a university hospital.

Patients: Twenty-one critically ill children who needed midazolam for sedation.

Interventions: None.

Measurements and main results: We determined the relationship between inflammation (using C-reactive protein and leucocyte count as surrogate markers) and disease severity (Pediatric Logistic Organ Dysfunction and Pediatric Risk of Mortality scores) vs. the pharmacokinetics (clearance) and pharmacodynamics (COMFORT score, dose requirement) of midazolam. We found a significant negative correlation between disease severity and midazolam clearance corrected for body weight (r=-0.49, p=0.02). Midazolam clearance was significantly lower in children with multiple organ failure (defined as Pediatric Logistic Organ Dysfunction≥10, n=11) compared with children without multiple organ failure (Pediatric Logistic Organ Dysfunction<10, n=10) (median 0.14 (IQR 0.11-0.23) vs. 0.28 (IQR 0.14-0.43) L/kg/h, p=0.035). No other significant correlations were found.

Conclusions: Results from this pilot study suggest that increased disease severity is associated with reduced midazolam clearance in critically ill children, most likely as a result of reduced cytochrome 3A activity. In contrast, reduced midazolam clearance does not seem to result in decreased midazolam dose requirements.

INTRODUCTION

Inflammation greatly contributes to the inter-individual variability in response to drug therapy. In that, the acute inflammatory response strongly affects the hepatic cytochrome P450 (CYP450) enzyme system (1). *In vitro*, animal and limited human studies have demonstrated that proinflammatory cytokines, especially interleukin-6 and tumor necrosis factor-α, downregulate catalytic activity of CYP enzymes up to 70% (1). This may lead to an increase in drug exposure and increased clinical toxicity, especially for drugs with a narrow therapeutic window.

Inflammation resulting from infectious diseases, tissue injury, or trauma is quite common in critically ill children. Its effect on drug metabolism potentially exposes them to toxicity and adverse drug reactions. If we should be able to predict the impact of inflammation and disease state on disposition and effect of drugs, we could design more rational drug dosing guidelines for this vulnerable patient group. However, pediatric data looking at the effect of inflammation and disease severity on systemic exposure (pharmacokinetic) and response (pharmacodynamic) are scarce. We identified only one such study. Using a nonspecific surrogate marker for drug metabolism, the researchers showed reduced drug metabolism in pediatric intensive care patients with sepsis (2).

The aim of the pilot study reported here is to determine the effect of inflammation and disease severity on midazolam pharmacokinetics (as a marker of CYP3A activity) and pharmacodynamics in critically ill children.

MATERIALS AND METHODS

This study is an analysis of prospectively collected pharmacokinetic and pharmacodynamic data from a midazolam study in critically ill children (3). The study was approved by the local ethics review board. Subjects were critically ill children admitted to the intensive care unit of the Erasmus MC-Sophia Children's Hospital who needed midazolam for sedation. Midazolam was given as an intravenous bolus (0.1 mg/kg), after which an intravenous midazolam infusion was started at a rate of 0.1 mg/kg/h. Subsequently, the infusion rate was adjusted in a protocolized way based on predefined COMFORT scale cutoff points (3). The COMFORT score is a validated pediatric sedation score and consists of six behavioral items and two physiological dimensions of distress scored during a 2-minutes period of observation. The total COMFORT score is the total of all item scores with a maximum score of 40. COMFORT scores between 17 and 26 were considered reflective of optimal sedation, COMFORT scores of <17 as oversedation, and scores of >26 as distressed, undersedated and in need for further intervention. In all patients, blood samples, for midazolam concentrations, were taken once daily, before and after

each dose change, and as washout curve after discontinuation of the drug. With these midazolam concentration data, a population model was developed using the nonparametric expectation maximization algorithm and MW/Pharm and individual clearances were calculated. A detailed description of the study can be found in the original paper (3).

As a pharmacokinetic outcome measure, we used midazolam clearance as a surrogate marker for CYP3A activity (4). As a pharmacodynamic outcome measure, we used median midazolam dose (mg/kg/h) as a primary outcome measure, because midazolam infusion was adjusted based on the COMFORT score and thus reflects average need for sedation. We also used median COMFORT score as a pharmacodynamic endpoint.

In addition, we estimated disease severity using the Pediatric Risk of Mortality score (PRISM II) assessed at admission and the Paediatric Logistic Organ Dysfunction score (PELOD) assessed daily (5, 6). The PRISM score was developed to predict mortality risk and quantifies severity of illness. The PELOD score is an outcome measure of the severity of multiple organ dysfunction in pediatric intensive care patients. C-reactive protein (CRP) and leukocyte count served as surrogate markers for inflammation. The pharmacodynamic, disease severity, and inflammatory parameters were all collected during the course of the study. The study ended when the full pharmacokinetic washout curve was obtained after discontinuation of midazolam.

Data were analyzed with nonparametric tests (Spearman, Mann Whitney U) because data were distributed nonlinearly. We used median values of each daily parameter (PELOD, CRP, leukocyte count, COMFORT scores), as length of stay and numbers of daily measurements differed between patients. Statistical analyses were done using SPSS (version 15.0, Chicago, IL).

RESULTS

Subjects

We included 21 critically ill children ranging in age from 2 days to 17 years. The clinical and pharmacokinetic characteristics of the subjects included in the analysis are listed in Table 1.

Disease severity/inflammation - pharmacokinetics

We found significant negative relationships between PELOD score and both total midazolam clearance and for body weight-corrected clearance (r=-0.44, p=0.045 and r=-0.49, p=0.02, respectively) (Figure 1). The relationship between PRISM score and total clearance was significant as well (r=-0.50, p=0.02), but that between PRISM score and clearance corrected for body weight was not (r=-0.15, p=0.53).

Table 1. Clinical and pharmacokinetic characteristics (n=21)

Female/male (n)	9/12	
PICU admission reason (n)		
Congenital heart disease	4	
Upper airway infection	4	
Pneumonia	2	
Postcardiac surgery	2	
Pulmonary hypertension	2	
Other	7	
	Median	*IQR*
Age (years)	2.5	0.1-9.0
Weight (kg)	13.0	3.8-24.5
PELOD	10.0	1.0-11.0
PRISM	14	8-20
Length of stay PICU (days)	3	2-5
COMFORT score	18	15-20
	Median	*Range*
Total midazolam dose (mg/kg)	2.9	0.40-46.0
Midazolam dose (mg/kg/h)	0.09	0.05-0.27
	Mean	*SD*
Clearance (ml/kg/min)	5.0	3.9

PICU=pediatric intensive care unit; IQR=interquartile range; PELOD=Pediatric Logistic Organ Dysfunction; PRISM=Pediatric Risk of Mortality

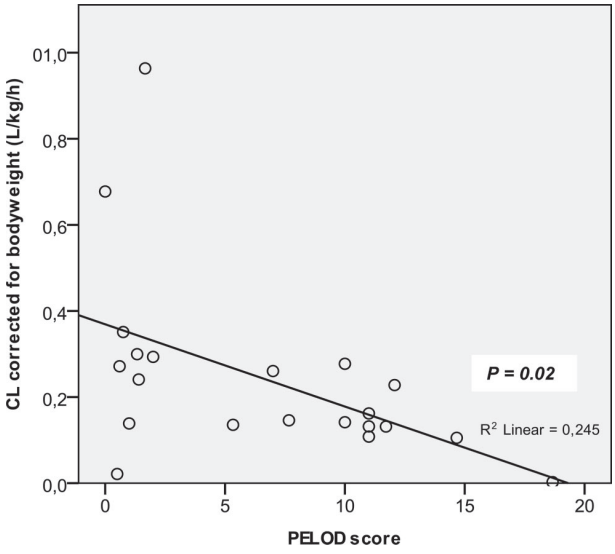

Figure 1. Correlation between Pediatric Logistic Organ Dysfunction (PELOD) score and midazolam clearance corrected for body weight (L/kg/h)

Midazolam clearance was significantly lower in children with multiple organ failure (defined as PELOD≥10, n=11) compared with children without multiple organ failure (PELOD<10, n=10) (median 0.14 (IQR 0.11-0.23) vs. 0.28 (IQR 0.14-0.43) L/kg/h, p=0.035). CRP (n=17) or leukocyte count (n=21) did not correlate with total clearance or clearance corrected for body weight (r=-0.27, p=0.30 and r=-0.29, p=0.90, respectively). Because there was no significant correlation between disease severity and inflammation, we consider them as independent parameters.

Disease severity/inflammation - pharmacodynamics

Relationships between disease severity (PELOD and PRISM score) and the mean administered dose of midazolam (mg/kg/h) or mean COMFORT score were not significant and neither were those between inflammation (CRP, leukocyte count) and pharmacodynamic parameters (Table 2). There was a small but not significant correlation between clearance corrected for body weight and the administered midazolam dose (mg/kg/h) (r=-0.41, p=0.06).

Table 2. Correlations disease severity/inflammation-pharmacodynamics

	COMFORT score		Administered midazolam, mg/kg/h	
Spearman's Rho	*r*	*p* value	*r*	*p* value
PELOD	0.04	0.87	0.07	0.77
PRISM	-0.25	0.27	0.11	0.64
CRP	-0.35	0.17	0.33	0.20
Leukocyte count	-0.03	0.91	-0.35	0.12

r =correlation coefficient; PELOD=Pediatric Logistic Organ Dysfunction; PRISM=Pediatric Risk of Mortality; CRP=C-reactive protein

DISCUSSION

This pilot study suggests that severity of organ failure, as reflected by the PELOD score, significantly correlates with midazolam clearance in critically ill children. Children with multiple organ failure have a significant reduced clearance compared with children without. This is most likely the result of reduced activity of CYP3A. Alternative explanations could be altered protein binding, because midazolam is highly bound to plasma proteins or, less likely, reduced blood flow, because midazolam has an intermediate extraction ratio (7). However, decreased clearance, with expected higher drug exposure, is seemingly unrelated to decreased dose requirements of midazolam as a surrogate pharmacodynamic marker in our population.

Our results are supported by the study of Carcillo and colleagues (2). They studied antipyrine metabolism as a global marker for CYP450 activity in 51 consecutive children with sepsis and six critically ill children without sepsis. There was a twofold lower overall estimated CYP450 activity in children with sepsis and a fourfold lower overall estimated CYP450 activity in children with multiple organ failure.

A decrease in hepatic CYP450 activity may result in lower clearance of substrate drugs. The resulting higher drug exposure may raise drug efficacy and give rise to risk of toxicity. However, the therapeutic consequences of increased drug exposure during inflammatory states are mainly unknown (8). The present study suggests that reduced clearance, with likely higher midazolam exposure, does not necessarily reduce dose requirements in critically ill children. We can only speculate on the reason for this observation. Saturation of midazolam pharmacokinetics, as was observed in adult patients, may explain why patients with higher midazolam doses could have lower clearance rates (9).
In addition, a change in the pharmacokinetic-pharmacodynamic relation may occur as a result of illness. For example, gamma aminobutyric acid receptors may be downregulated resulting in a reduced sedative effect; hence, sicker patients may need more drugs to reach the same sedation level. This speculation is in line with findings from a study in adult patients with rheumatoid arthritis. In this population, more severe disease (as reflected by increased interleukin-6 levels) was associated with decreased verapamil plasma clearance and higher verapamil plasma levels. However, despite higher plasma levels, patients with more severe inflammation showed significantly weaker dromotropic response. This observation may be explained by a direct effect of proinflammatory cytokines on the receptor level, resulting in its downregulation (10). This observation as well as our own suggest that inflammation may alter drug pharmacokinetics and pharmacodynamics differently.

Another reason for reduced clearance without lower dosing requirements may relate to one of the limitations of our study. Midazolam infusions were not always tapered off as dictated by the sedation protocol. Clinicians sometimes opted for maintaining a deeper level of sedation, e.g. in patients with pulmonary and systemic therapy resistant hypertension. Hence, one could speculate that sicker patients, with associated lower midazolam clearance, may have received higher midazolam doses to reach a relatively deeper level of sedation. A second limitation of our study is the small sample size for which CRP levels were available (n=17) coupled with the possibility that CRP might not be the best biomarker for inflammation in critically ill children. The exact inflammatory mediator responsible for the changes in CYP activity is still not known (1). Evidence exists that especially interleukin-6 is correlated with downregulation of CYP450; the value of CRP in this context is less studied (1). However, hepatic drug metabolism may be down-

regulated also in viral infections, which are generally not associated with significantly increased CRP levels (11, 12). Interleukin-6 may have been a better marker to support our hypothesis, but because inflammation was not the primary goal of the initial studies, this marker was not available for this study.

CONCLUSIONS

This pilot study suggests that severity of organ failure affects the clearance of midazolam in critically ill children, most likely as a result of reduced activity of CYP3A. This is not related, however, to decreased dose requirements of midazolam as a surrogate pharmacodynamic marker. The clinical magnitude of the impact of inflammation and disease state on disposition and effect may have therapeutic consequences. A prospective study in a larger group of patients, collecting pharmacokinetic and pharmacodynamics data in addition to cytokine and CRP levels, is needed to answer the questions raised in this pilot study.

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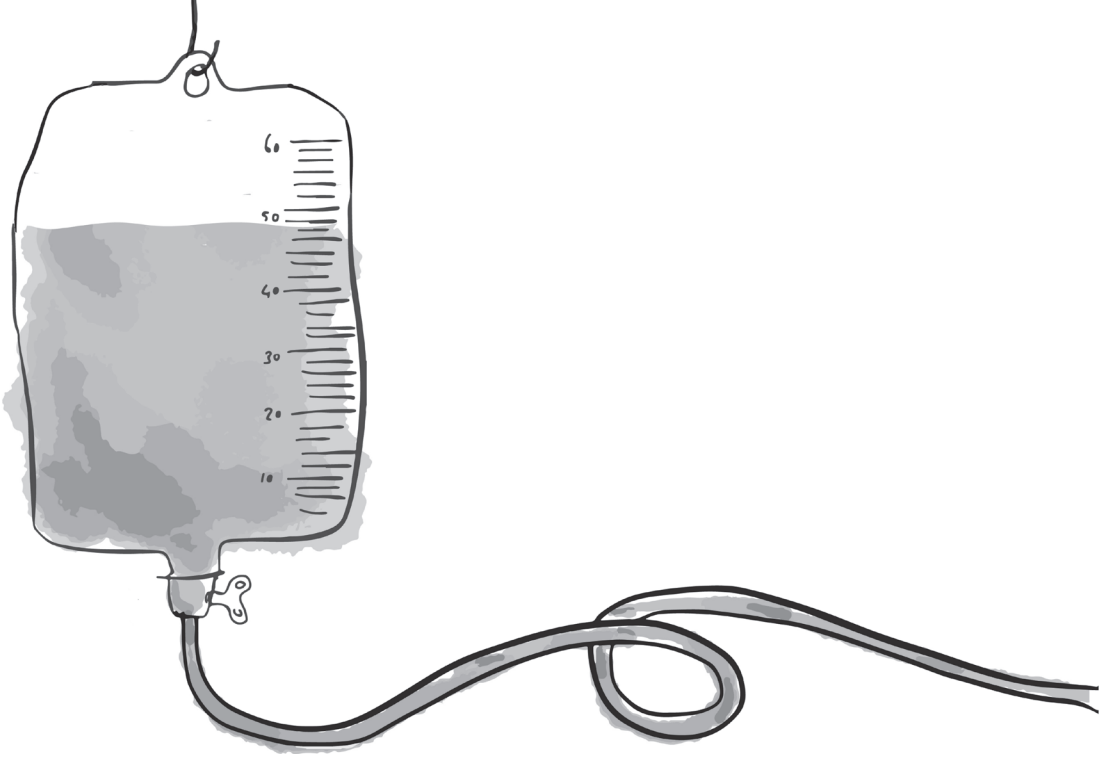
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Chapter 4

Inflammation and organ failure severely affect midazolam clearance in critically ill children

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ABSTRACT

Rationale: Various *in vitro*, animal and limited human adult studies suggest a profound inhibitory effect of inflammation and disease on cytochrome P450 3A (CYP3A)-mediated drug metabolism. Studies showing this relationship in critically ill patients are lacking, while clearance of many CYP3A drug substrates may be decreased, potentially leading to toxicity.

Objectives: To prospectively study the relationship between inflammation, organ failure and midazolam clearance, as validated marker of CYP3A mediated drug metabolism, in critically ill children.

Methods: From 83 critically ill children (median age 5.1 months (range 0.02-202 months)), midazolam plasma levels (n=523), cytokines (e.g. IL-6, TNF-α), C-reactive protein (CRP) and organ dysfunction scores (PRISM II, PIM 2, PELOD), as well as number of failing organs were prospectively collected. A population pharmacokinetic model to study the impact of inflammation and organ failure on midazolam pharmacokinetics was developed using NONMEM 7.3.

Main results: In a two-compartmental pharmacokinetic model, body weight was the most significant covariate for clearance and volume of distribution. Both CRP and organ failure were significantly associated with clearance (p<0.01), explaining both inter-individual and inter-occasional variability. In simulations a CRP of 300 mg/L was associated with a 65% lower clearance compared to 10 mg/L and three failing organs were associated with a 35% lower clearance compared to one failing organ.

Conclusions: Inflammation and organ failure strongly reduce midazolam clearance, a surrogate marker of CYP3A-mediated drug metabolism, in critically ill children. Hence, critically ill patients receiving CYP3A substrate drugs may be at risk of increased drug levels and associated toxicity.

INTRODUCTION

Critically ill patients often require life-saving polypharmacy including cardiotonics, antimicrobials and analgo-sedatives. Dependent on the underlying disease state, these patients show large variation in drug disposition and response (1). Understanding the underlying mechanisms contributing to this variation is of importance to ensure the safe and effective use of drugs in this vulnerable population.

Various *in vitro*, animal and limited human adult studies suggest a profound inhibitory effect of inflammation on drug metabolism by cytochrome P450 (CYP) enzymes. Drug-metabolizing enzymes are downregulated by cytokines released during inflammation (2). Inflammation-related changes in drug disposition have been described for disease states such as autoimmune disease and cancer (3). In addition, hepatic drug metabolism may be affected through a heavy loss of hepatocytes in liver failure or through a still unknown mechanism in renal failure (1, 4).

In children with sepsis and organ failure a two- and fourfold lower antipyrine clearance, respectively, was found compared to non-septic ICU children. In addition, IL-6 was negatively correlated with antipyrine clearance, suggesting inflammation as regulatory mechanism (5). Antipyrine is a global marker of CYP450 metabolism, and individual CYPs appear differentially regulated by inflammation (6). Individual enzymes need to be studied to better understand the substantial impact of drug metabolism on individual CYPs and to individualize drug therapy for individual drugs.

The most abundant CYP, CYP3A4/5, is involved in the metabolism of >50% of therapeutic drugs, of which many are prescribed daily to critically ill patients. Studies showing the relationship between inflammation and CYP3A mediated drug metabolism in critically ill patients are lacking, while clearance of many CYP3A drug substrates may be decreased, potentially leading to toxicity. The benzodiazepine midazolam is metabolized by CYP3A4/5 to a major hydroxylated active metabolite (1-OH midazolam), and subsequently metabolized to 1-OH-midazolam-glucuronide by UGTs and renally excreted (7). The clearance of midazolam to 1-OH-midazolam has been validated as surrogate measure of *in vivo* CYP3A4/5 activity (8). We therefore hypothesized that inflammation is inversely related to midazolam clearance in critically ill pediatric patients. A previous pilot study from our group, in 21 children (not included in this study) supports this hypothesis (9). The aim of this study was to prospectively study the relationship between inflammation, organ failure and midazolam clearance in critically ill children, as a model for CYP3A-mediated drug metabolism. Some of the results of this study have been previously reported in the form of an abstract (10).

METHODS

Subjects and setting

Patients were recruited in the context of a multicenter randomized controlled trial comparing daily sedation interruption plus protocolized sedation to protocolized sedation alone in critically ill children (11). For this pharmacokinetic study, patients from only two of the three participating PICUs in the Netherlands were enrolled: Erasmus MC-Sophia Children's Hospital and Radboud University Nijmegen Medical Center. Approval from each institutional review board and written informed consent from parents or legal representatives was obtained. Details on this study can be found elsewhere (11). The sample size of the original randomized controlled trial (n=200) was calculated from the study's primary outcome, the number of ventilator-free days (11). Of these 200 patients, we estimated to include 100 patients for this pharmacokinetic study. With variability in sampling and dosing times and 2 samples per subject, study power would be >80% with a total population of n=100 to show a 30% difference in clearance with a subpopulation of n=20.

Patients were eligible for the study if they were between 0 and 18 years of age, born at least at 37 weeks of postconceptual age, required mechanical ventilation with an expected duration of at least 48 hours and received sedative drugs. The following exclusion criteria were applied: anticipated death or withdrawal of life support within 48 hours; impossibility of assessing level of sedation due to an underlying neurologic condition; neurological, respiratory or cardiac instability that may not tolerate inadequate sedation; therapeutic hypothermia after cardiopulmonary resuscitation; difficult airway; fixed duration of mechanical ventilation, admission for ECMO; already having been ventilated/sedated for >2 days in a transferring PICU. Midazolam was administered as an intravenous bolus (100 µg/kg) followed by intravenous infusion at a rate of 100 µg/kg/h. Sedation was titrated based on COMFORT-B scores. In the sedation interruption group sedative infusions were interrupted daily.

Measurements

Blood for midazolam concentrations was sampled using an optimized sampling strategy for pharmacokinetic (PK) analysis, with 4 samples per day during the first 72 hours and 1 sample per day thereafter at different time points, for up to one week. Inflammatory markers (C-reactive protein (CRP), cytokines (IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, MCP-1, MIP1a, MIP1b, RANTES, IL-8, FGF-b, G-CSF, GM-CSF)), liver and kidney function were determined once daily, CYP3A4*1G, *22 and CYP3A5*3 single nucleotide polymorphisms were also determined. Detailed description of the analytical methods can be found in the Supplemental Methods.

Disease severity was scored using validated organ dysfunction scores: the Pediatric Risk of Mortality II (PRISM II) (range 0-100%) (12) and the Paediatric Index of Mortality (PIM 2) (range 0-100%) (13) at admission and the Paediatric Logistic Organ Dysfunction (PELOD) score daily (range 0-71) (14). Since the PELOD score is a non-uniform ordered discrete scale, this score was also used to calculate the number of organs failing. If a patient scored the maximum score on an organ subscale (i.e. cardiovascular, renal, respiratory, hematological or hepatic), this was scored as organ failure 'yes'. The total number of organ failures was counted for each measurement (ranging from 0-5).

Pharmacokinetic analysis

Midazolam concentration-time data were analysed using non-linear mixed effects modelling version 7.3 (ICON, Globomax LLC, Ellicott, MD, USA), complying with the latest FDA and EMA guidelines (15, 16). Model development was in four steps: (1) selection of a structural model, (2) selection of an error model, (3) covariate analysis and (4) internal validation of the model. For model selection, we used the objective function value to compare models. The objective function of NONMEM is a statistical criterion for the goodness-of-fit of the model. It is proportional to the sum of squared differences between the observations and values predicted by the model, and is assumed to be Chi-square distributed. Smaller (or more negative) values represent a better fit. For example, when covariates are added to the model, it is expected that the model should provide a better fit to the data. This is assessed by the difference in successive objective function values between the model with the covariate and without the covariate, and which can be tested for statistical significance using a Chi-square table (17).

For the structural and error models, a decrease in objective function value (OFV) of 3.84 points was considered statistically significant ($p<0.05$). The optimal model was selected using standard methodology for population PK analysis with NONMEM. The details of model selection and validation can be found in the Supplemental Methods.

Once the base model was selected, covariates were tested for their influence on pharmacokinetic parameters. The continuous covariates evaluated were age, weight, CRP, cytokines, PRISM II, PIM 2, PELOD, number of organ failures, creatinine, ALAT and albumin. Since the concentration of IL-6 covered a large range, it was log-transformed and as such considered as covariate in the model. Categorical covariates included sex, diagnosis group, co-administration of CYP3A inhibitors (i.e. clarithromycin, voriconazole, fluconazole, erythromycin, haloperidole, metronidazole), study center and CYP3A genetic polymorphisms. Potential covariates were evaluated using forward inclusion and backward elimination with a level of significance of <0.005 (OFV -7.9 points) and <0.001 (OFV -10.8 points), respectively. In addition, inclusion of a covariate in the model had to result in a decline in unexplained inter-individual variability or unexplained inter-occasion variability before it was included in the final model (18, 19). Additional

covariates had to reduce the objective function and unexplained variability further to be retained in the model. Next, the model was internally validated as described in the Supplement.

Dose simulations

To explore the quantitative impact of relevant covariates on midazolam clearance, identified from the population PK analysis, simulations were performed as follows. Using the currently recommended starting dose in children (a loading dose of 100 µg/kg and a maintenance dose of 100 µg/kg/h for 48 hours) concentration-time profiles were visualized for representative critically ill children with varying body weight, CRP concentrations and organ failure.

RESULTS

Patients and data

Midazolam concentrations were obtained from 83 children admitted to the intensive care unit between October 2009 and August 2014. A total of 523 plasma samples were available with a median of 6 (range 1-15) samples per patient. Patients were between 1 day and 17 years old (median age 5.1 months) and body weight ranged from 2.5 to 63 kg (median 5.6 kg). See further Table 1.

Model development and covariate analysis

A two-compartmental model described the pharmacokinetics of midazolam well. Inter-individual variability (IIV) for clearance and volume of distribution of the central compartment could be estimated and adding these variability parameters improved the model. Then, the inclusion of inter-occasion variability (IOV) for clearance improved the model. A combined error model, combining a proportional and additive error, was superior over a proportional or additive error model. The inclusion of all these variances in the model resulted in lower residual unexplained errors and improved the model significantly (ΔOFV -119.6, $p<0.01$).

Body weight

The covariate analysis showed that body weight was the most significant covariate resulting in a 76.5 reduction in objective function ($p<0.005$). Using body weight as covariate, 32.9% and 43.9% of the IIV in clearance and volume, respectively, of the central compartment was explained (Table 2). Therefore, body weight was incorporated in the model (Figure 1a, b and Figure 2a) and with this pediatric base model other covariates were tested to explain more inter-individual and inter-occasion variability.

Table 1. Patient characteristics

Characteristic	Total
Number of patients (n)	83
Number of samples (n)	523
Samples/patient*	6 (1 – 15)
Sex (male/female, %)	48/35 (58/42%)
Age (months)*	5.1 (0.02 – 202)
Weight (kg)*	5.6 (2.5 – 63)
Reason admission ICU	
Respiratory disorder[#]	58 (70.0%)
Cardiac disorder[##]	5 (6.0%)
Sepsis	8 (9.6%)
Cardiac surgery	9 (10.8%)
Non-cardiac surgery	3 (3.6%)
CRP (mg/L)*	32 (0.3 – 385)
IL-6 (ng/L)*	25 (0.55 – 43140)
PRISM II (%)*	16.3 (0.8 – 98.4)
Predicted mortality PIM 2 (%)*	5.3 (0.25 – 33.2)
PELOD*	11 (0 – 41)
Number of failing organs*	2 (0 – 5)

* Data are in median (range); PRISM II=Pediatric Risk of Mortality; PIM 2=Pediatric Index of Mortality; PELOD=Pediatric Logistic Organ Dysfunction; # viral/bacterial pneumonia, ARDS and asthma; ## congenital heart disease and cardiomyopathy

Inflammation

The inclusion of the inflammation markers IL-6 and CRP as covariate on clearance resulted in a decrease in the objective function by 38.1 and 59.5 points, respectively (Table 2). Since IL-6 and CRP concentrations were highly correlated (Pearson, r=0.6, p<0.001), only CRP concentrations were included as covariate on clearance. Next to a decrease in OFV, incorporating CRP in the model resulted in better goodness-of-fit plots and a decrease in the IOV in clearance of 20.4% (Table 2, Figure 1c, d). For higher concentrations of CRP, midazolam clearance was lower (Figure 2b). Figure 3a shows that a CRP of 300 mg/L is associated with a 65.4% lower clearance than a CRP of 10 mg/L. Incorporation of other cytokines (e.g. IL1a, IL1b, IL2, IL4, IL8, IL10 and TNF-α) did neither improve the model significantly, nor explained variability in clearance any further.

Organ failure

There was no relation between clearance or volume of distribution and PRISM II or PIM 2 scores. The PELOD score correlated negatively with clearance. Including the number of organ failures as covariate in the pediatric model (Figure 1e, f) significantly improved

Table 2. Results of covariate analysis for the two-compartment pharmacokinetic model of midazolam

Covariate	Model	Relationship of covariate	No. of structural parameters	ΔOFV
-	Simple model (without IOV)	-	8	+193.7
Body weight	Pediatric base model (without IOV)	$CL_i=CL_{5kg}\bullet(WT/5)^{k1}$ $V1_i=V1_{5kg}\bullet(WT/5)^{k3}$	10	+117.2
Body weight	Pediatric base model	$CL_i=CL_{5kg}\bullet(WT/5)^{k1}$ $V1_i=V1_{5kg}\bullet(WT/5)^{k3}$	11	-
Organ failure	Pediatric model with organ failure	$CL_i=CL_{5kg}\bullet(WT/5)^{k1}$ with varying CL_{5kg} for varying number of organs failing	14	-34.7
IL-6	Pediatric model with inflammatory marker*	$CL_i=CL_{5kg}\bullet(WT/5)^{k1}\bullet(1+/1\bullet(IL\text{-}6/3.2))$	12	-38.1
CRP	Pediatric model with inflammation	$CL_i = CL_{5kg} \bullet (WT/5)^{k1} \bullet (CRP/32)^{k2}$	12	-59.5
CRP and organ failure	Pediatric model with inflammation and organ failure	$CL_i = CL_{5kg} \bullet (WT/5)^{k1} \bullet (CRP/32)^{k2}$ with varying CL_{5kg} for varying number of organs failing	15	-75.3

*IL-6: Interleukin-6 concentrations were log transformed
ΔOFV: Difference in objective function value compared to Pediatric base model

the model (OFV Δ-34.7 points, Table 2) and resulted in better goodness-of-fit plots. It lowered the IIV and IOV with 8.6% and 7.8% respectively. The clearance of midazolam decreased with an increasing number of organ failures (Figure 2c). Three failing organs was associated with a 34.7% lower clearance compared to one failing organ (Figure 3b).

Other covariates

Significant differences between study centers were not found. Fourteen patients received a CYP3A inhibitor; this had no effect on midazolam clearance. CYP3A polymorphisms, albumin, creatinine and ALAT concentrations were tested as covariates as well, but did neither improve the model nor explained variability in clearance or volume of distribution.

Final model

Incorporation of both inflammation and organ failure in the model resulted in a lower OFV (Table 2) and better description of the data compared to models including inflammation or organ failure only (goodness-of-fit plots, Suppl. Figure E1). Figure 3c shows that clearance is up to 77.4% lower when patients have both increased CRP and an increased number of organs failing.

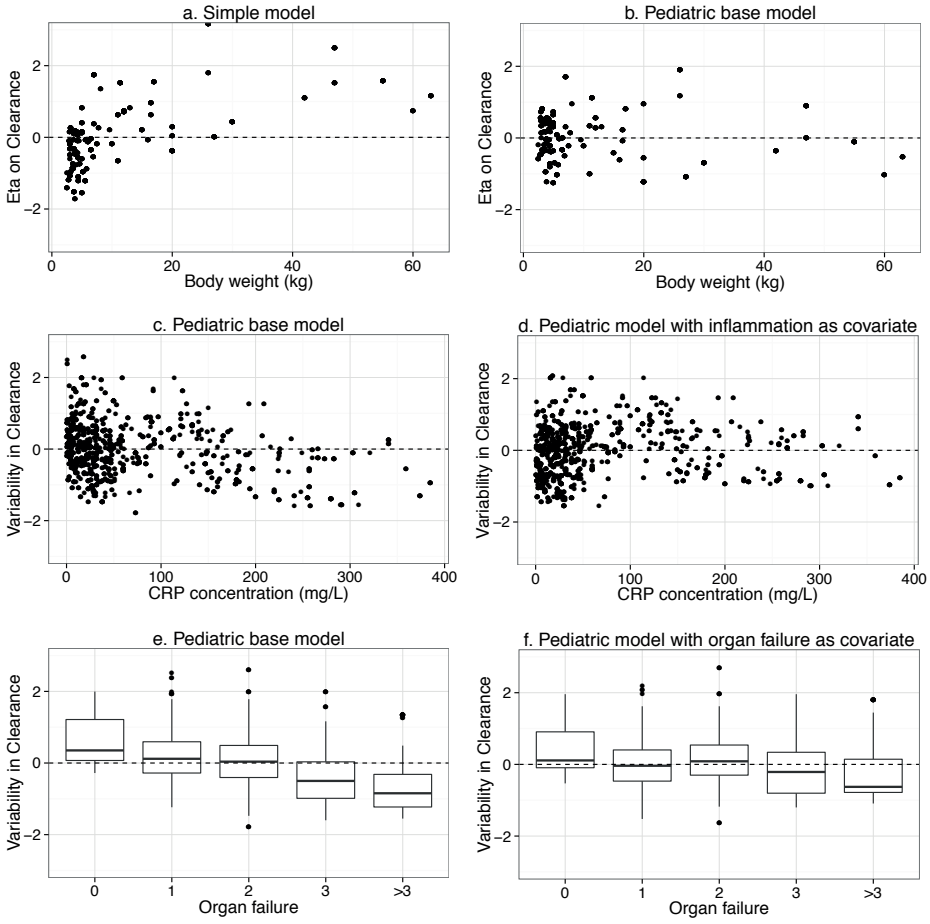

Figure 1. Variability in clearance versus the included covariates before (a,c,e) and after (b,d,f) inclusion of the different covariates

(a, b) Inter-individual variability on clearance versus body weight, before and after inclusion of body weight as covariate on clearance. **(c, d)** Variability on clearance before and after inclusion of CRP concentration as covariate on clearance. **(e, f)** Variability on clearance before and after inclusion of organ failure as covariate on clearance. Variability (c, d, e, f) includes inter-individual variability and inter-occasion variability.

Model evaluation

The final model was evaluated in a bootstrap analysis. Median parameter values as well as the 5th and the 95th percentiles were in agreement with the model estimations and standard errors (Table 3). Normal distribution of errors was shown in the normalized prediction distribution errors (NPDE), with no significant trends in NPDE versus time and NPDE versus predictions (Suppl. Figure E2).

Dose simulations

Figure 4 shows simulated midazolam concentrations over time in the final PK model for patients with a body weight of 3.5, 10 and 60 kg. The simulations accounted for different clinical scenarios of increased CRP concentrations, increased organ failures or both increased CRP concentrations and organ failures. At a CRP level of 300 mg/L the plasma

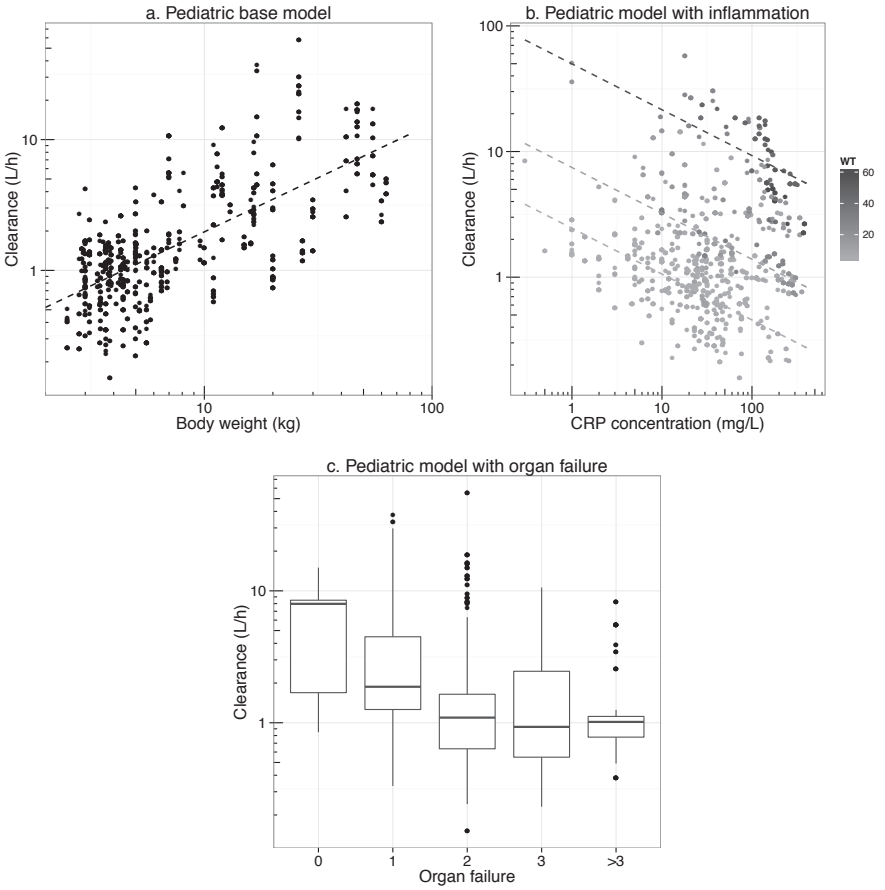

Figure 2. Post-hoc plots for clearance versus the included covariates body weight (a), inflammation marker CRP (b) and organ failure (c)

(a) Clearance versus body weight. • Individual estimated clearance value for each individual, -- Population predicted clearance, predicted with the Pediatric base model (Table 3).

(b) Clearance versus CRP concentration. • Individual estimated clearance value for each individual at each different CRP measurement in the study. Shaded grey colors indicate body weight (kg) with darker grey for increasing body weight. -- Population predicted clearance for an individual of 3.5 (light grey), 10 (intermediate grey) and 60 kg (dark grey), predicted with the model with inflammation (Table 3).

(c) Boxplot of the individual predicted clearance values for each individual on each day in the study versus number of organs failing. Of the 523 plasma samples, 10, 200, 209, 70 and 34 samples were taken from patients with 0, 1, 2, 3 and >3 organs failing, respectively.

midazolam concentration is 2.7 fold higher than at a CRP level of 10 mg/L (Figure 4a-c). With three organ failures the plasma concentration is 1.5 fold higher than with one organ failure (Figure 4d-f). Plasma concentrations are even higher in patients with both increased CRP concentration and higher number of organ failures (Figure 4g-l).

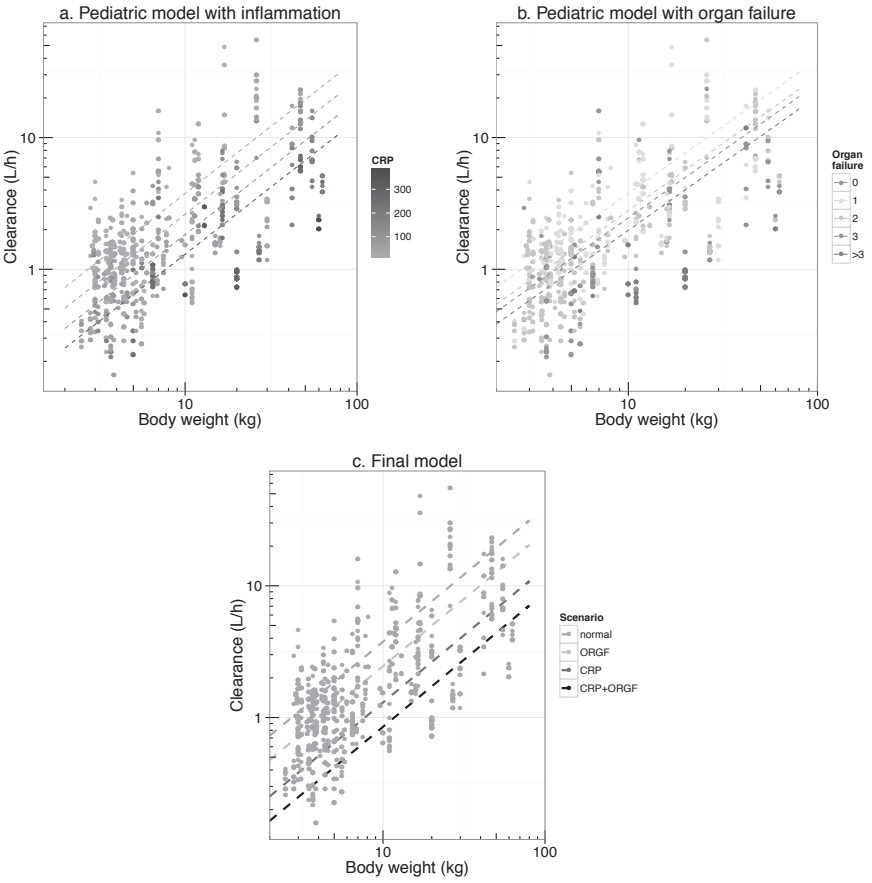

Figure 3. Post-hoc values for clearance versus body weight

Each point represents the posthoc clearance for an individual at a different time point in the study.

(a) Different colors reflect varying CRP concentrations while the four lines represent the model predictions for CRP concentrations of 10, 32, 100 and 300 mg/L respectively with darker grey lines for increasing CRP concentrations.

(b) Different colors reflect increasing organ failure while the four lines represent the model predictions for number of organs failing of 1, 2, 3 and >3 respectively with darker grey lines for increasing number of organs failing.

(c) Different colors of the lines reflect different scenarios as predicted by the model. The light grey line represents the scenario when the patient has a CRP concentration of 10 mg/L and 1 organ failure (ORGF), the intermediate greyline indicates 3 organ failures, the dark grey line indicates a CRP concentration of 300 mg/L and the black line indicates the scenario where both CRP and the level of organ failure are 300 mg/L and 3 respectively.

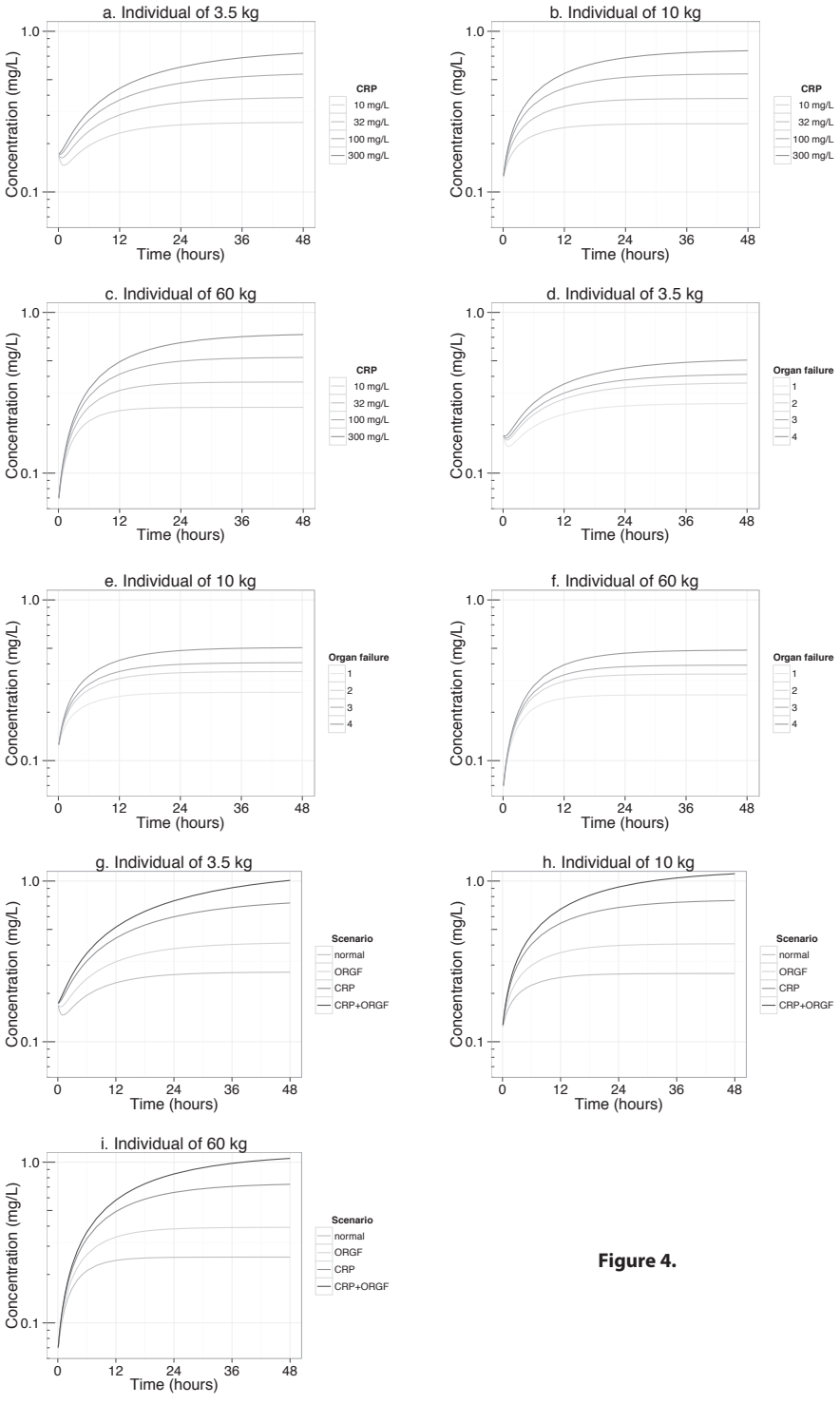
a. Individual of 3.5 kg
b. Individual of 10 kg
c. Individual of 60 kg
d. Individual of 3.5 kg
e. Individual of 10 kg
f. Individual of 60 kg
g. Individual of 3.5 kg
h. Individual of 10 kg
i. Individual of 60 kg
Concentration (mg/L)
1.0
0.1
0
12
24
36
48
Time (hours)
CRP
10 mg/L
32 mg/L
100 mg/L
300 mg/L
Organ failure
1
2
3
4
Scenario
normal
ORGF
CRP
CRP+ORGF

Figure 4.

Figure 4. Simulations of midazolam concentration over time for three typical individuals in the study of 3.5, 10 and 60 kg, receiving a continuous infusion of 100 µg/kg/h for 48 hours and a loading dose of 100 µg/kg

(a-c) Concentration-time profiles for different CRP concentrations ranging from 10-300 mg/L. **(d-f)** Concentration-time profiles for different levels of organ failure. **(g-i)** Concentration-time profiles for the combined effect of different CRP concentrations and levels of organ failure (ORGF). The light grey line represents the scenario when the patient has a CRP concentration of 10 mg/L and 1 organ failure, the intermediate grey line indicates 3 organ failures, the dark grey line indicates CRP concentration of 300 mg/L and the black line indicates the scenario where both CRP and the level of organ failure are 300 mg/L and 3, respectively.

Table 3. Parameter estimates of best models

Parameter	**Pediatric base model**	**Pediatric model with inflammation and organ failure included as covariates**	
	Model fit (CV%)	Model fit (CV%)	Bootstrap median (5th-95th percentile)
Clearance	$CL_i = CL_{5kg} \cdot (WT/5)^{k1}$	$CL_i = CL_{5kg} \cdot (WT/5)^{k1} \cdot (CRP/32)^{k2}$ with varying CL_{5kg} for different number of organs failing	
CL_{5kg} (L/h)	1.11 (8%)	ORGF1: 1.29 (14%)	ORGF1: 1.29 (1.05-1.70)
		ORGF2: 0.96 (13%)	ORGF2: 0.96 (0.78-1.25)
		ORGF3: 0.84 (27%)	ORGF3: 0.83 (0.54-1.30)
		ORGF>3: 0.68 (25%)	ORGF>3: 0.67 (0.43-0.99)
k1	0.828 (13%)	1.02 (13%)	1.03 (0.79-1.26)
k2	–	-0.312 (21%)	-0.324 (-0.42- -0.21)
Inter-compartmental clearance			
Q (L/h)	1.57 (43%)	1.52 (34%)	1.37 (0.09-3.43)
Volume of distribution	$V1_i = V1_{5kg} \cdot (WT/5)^{k3}$	$V1_i = V1_{5kg} \cdot (WT/5)^{k3}$	
$V1_{5kg}$ (L)	3.58 (43%)	3.28 (33%)	3.45 (1.79-8.20)
k3	1.32 (19%)	1.34 (17%)	1.30 (0.93-1.74)
V2 (L)	5.35 (21%)	5.44 (16%)	5.13 (0.94-6.71)
Inter-individual variability			
ω^2 CL	0.381 (25%)	0.345 (21%)	0.350 (0.226-0.513)
ω^2 V1	1.14 (59%)	1.19 (50%)	1.07 (0.14-2.06)
Inter-occasion variability			
π^2 CL	0.344 (24%)	0.197 (24%)	0.175 (0.103-0.265)
Residual error			
Proportional	0.096 (15%)	0.098 (15%)	0.095 (0.074-0.121)
Additive (µg/L)	0.121 (18%)	0.138 (19%)	0.139 (0.015-0.210)

CL clearance (L/h), with CL_i the individual predicted clearance of individual *i*, CL_{5kg} the population predicted clearance for a median subject of 5kg, k1 exponent to relate body weight to clearance, k2 exponent to relate CRP concentrations to clearance, Q inter-compartmental clearance (L/h), V1 volume of distribution in the central compartment (L), with $V1_i$ the individual predicted volume of individual *i*, $V_{5\,kg}$ the population predicted volume for a median subject of 5 kg, k3 exponent to relate body weight to volume of distribution, V2 volume of distribution in the peripheral compartment, ω^2 the variance for the inter-individual variability of the parameter mentioned, π^2 the variance for the inter-occasion variability of the parameter mentioned, WT body weight (kg), CRP C-reactive protein concentrations (mg/L), ORGF number of organs with organ failure, with failure defined by a maximum value on the PELOD score for that organ. A bootstrap was performed with 500 times of resampling the dataset.

DISCUSSION

This prospective population PK study shows that both inflammation, as reflected by CRP, and disease severity, as reflected by the number of organ failures, significantly affect midazolam clearance in critically ill children. These data suggest that critically ill patients may be at an increased risk of increased drug levels and associated toxicity when receiving CYP3A substrate drugs.

Our study importantly adds to existing data. In septic critically ill children, antipyrine clearance, as global marker of CYP450 metabolism was related to inflammation and severity of organ failure (5). By using midazolam as validated probe of CYP3A activity, our data may serve to predict more specifically the impact of inflammation and organ failure on CYP3A activity, and thereby the clearance of specific CYP3A substrates. A previous study found on average a lower midazolam clearance in 13 critically children than in children receiving midazolam for elective procedures (20). From these observations, we speculated that inflammation may contribute to decreased CYP activity and consequent reduced midazolam clearance.
Also, in a pilot study we showed that organ failure as reflected by PELOD score, but not CRP, was related to midazolam clearance (9). Most likely, the lack of correlation with CRP was due to the small sample size in this pilot study (n=17). Together, these studies suggest an important effect of inflammation and/or critical illness on CYP3A-mediated drug metabolism in children, but did not make clear to what extent inflammation and organ failure affect drug metabolism and consequent clearance. Furthermore, these studies were restricted by number and range of patients and data. The present study includes a much larger cohort of critically ill children, with a heterogeneous diagnosis mix covering an extensive variation in age, body weight, degree of inflammation and disease severity. In this study, we indeed showed a very strong correlation between inflammation and organ failure and midazolam clearance within a pediatric ICU population.

To support our hypothesis that inflammation-mediated mechanisms are related to the observed lower midazolam clearance, we determined cytokines and CRP. IL-6 is a principal inhibitor of CYP3A mRNA expression (21). In adult patients after elective surgery and bone marrow transplant, and in patients with rheumatoid arthritis and cancer, elevated IL-6 levels correlated with reduced CYP3A4 activity (22-25). Furthermore, inhibition of IL-6 by the IL-6 inhibitor tocilizumab seemed to reverse this IL-6 mediated CYP3A down-regulation in adult rheumatoid arthritis patients (26).
Indeed, in line with these studies and as we hypothesized, higher IL-6 levels were related to lower midazolam clearance. Moreover, C-reactive protein levels were also negatively correlated with midazolam clearance. CRP is an acute phase protein whose production

by the liver is triggered by proinflammatory cytokines such as IL-6 (27). This is apparent by the strong correlation between the IL-6 and CRP serum levels. As CRP explained more of the variability within patients, is clinically easily available and measured frequently, CRP was chosen as final parameter in our pharmacokinetic model.

Next to inflammation, the number of organ failures was significantly related to midazolam clearance and adding this covariate further improved the model. As midazolam has a low to intermediate hepatic extraction ratio, changes in hepatic clearance are predominantly dependent on CYP enzymes, but some impact of liver flow cannot be excluded (8, 28). Variation in liver flow in critically ill patients may result from changes in cardiac output consequent to cardiac failure and/or mechanical ventilation. Also, kidney failure has been associated with decreased hepatic drug metabolism (4). In contrast, in our study, creatinine levels, as markers of kidney function, were not significantly associated with reduced midazolam clearance, while in an adult study midazolam clearance was significantly lower in critically ill patients with acute kidney failure (29).
Hence, in addition to inflammation-mediated CYP3A downregulation, organ failure in itself may add to a reduction in midazolam clearance. This is supported by the 20% higher concentrations in the simulations when organ failure was added to the effect of CRP.

Apart from age and disease, genetic variation in CYP3A4/5 activity may contribute to variation in midazolam clearance. We could, however, not identify a significant effect of genetic polymorphisms of CYP3A4 and CYP3A5 on midazolam clearance. There was a trend but not significant lower clearance in patients with CYP3A4*22, possibly due to the low prevalence of this SNP in our cohort. Patients who expressed the CYP3A5*1 allele, i.e. who express functional CYP3A5, did not have a higher midazolam clearance. We also could not confirm that functional CYP3A5 compensates for CYP3A4 suppression, as previously suggested (29). We did not find an effect of co-administration of CYP3A inhibitors on midazolam clearance, most likely due to the low incidence (n=14) and the use of weak inhibitors only. Although an increase in IL-6 and CRP has been described in children on cardiopulmonary bypass (30), there were no differences in CRP and organ failure range between cardiac surgical patients and the whole study population in our study.

Some limitations of our study should be acknowledged. First, a controlled study was considered not feasible in this ICU setting. Therefore, an even spread of number of patients per age group, per inflammation, per organ failure and with different genetic polymorphisms was not possible. However, the present study includes a large cohort of critically ill children, with a heterogeneous diagnosis mix covering an extensive variation in age, body weight, degree of inflammation and disease severity, which is

representative of the usual case mix in PICUs around the world. Second, all patients had at least one organ failure (the lung) as mechanical ventilation was an inclusion criterion of the original study. Only in a few patients we could collect data in the absence of organ failure (i.e. after extubation). Third, we did not determine midazolam metabolite pharmacokinetics, which could have further supported our hypothesis that CYP3A metabolism is reduced in sicker patients. Lastly, our data show an association between inflammation and midazolam clearance but a definite causal relationship could not be established due to the nature of the study.

Despite these limitations, our results strongly indicate that critically ill patients are at an increased risk of drug toxicity or therapy failure due to important inflammation and organ failure mediated variation in clearance of CYP3A substrates. As CYP2D6, CYP1A2, CYP2C9 and CYP2C19 also appear downregulated in response to inflammation, our results may have an even wider impact and warrant further study for these enzymes and their substrates (31-34). In daily practice, our results may support more extensive therapeutic drug monitoring in patients with unexplained symptoms potentially related to drug toxicity. Finally, similar to drug metabolizing enzymes, drug receptors may also be subject to changes related to critical illness and in turn alter sensitivity to the drug's effect (24). Hence, further exploration of the pharmacokinetic-pharmacodynamic relationship in critical illness is recommended.

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SUPPLEMENTAL METHODS

Analytical methods

Midazolam plasma concentrations were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS), validated according to current ICH and FDA guidelines. The lower limit of quantification was 5.1 ng/ml.

Serum cytokine levels were determined using a customized Luminex Performance Assay (R&D Systems) containing the following analytes: MCP-1, MIP1a, MIP1b, RANTES, IL-8, FGF-b, G-CSF, GM-CSF, IFN-γ, IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-10, TNF-α. Samples were prepared according to the manufacturer's instructions, read on a BioPlex200 System, and analyzed in BioPlex Manager 6.0 software.

CRP was measured using an immunoturbidimetric assay (Modular analytics <P> Roche diagnostics, Mannheim, Germany) and values <5 mg/L were considered normal.

Genomic DNA was isolated from 200 µl EDTA blood or saliva on the MagNA Pure Compact System with the use of MagNA Pure Compact Nucleic Acid Isolation Kit I (Roche®). The genetic variants CYP3A4*1G (rs2242480), *22 (rs35599367) and CYP3A5*3 (rs776746) were determined on the 7500 Real-Time PCR System (Applied Biosystems®) with the use of Taqman® SNP Genotyping Assay C__26201900_30, C__59013445_10 and C__26201809_30 (Applied Biosystems®), respectively.

Analysis of pharmacokinetic data

Population pharmacokinetic (PK) data analysis was performed using first-order conditional estimation with interaction in NONMEM version 7.3 (ICON, Globomax LLC, Ellicott, MD, USA) with Pirana 2.9.0 and R version 3.1.1 for visualization of data. Of all measurements, 1.3% were below the limit of quantification (BLQ). BLQ observations were handled according to the M6 method (35), as other methods did not result in an improvement of the model.

Model development

Model development was in four steps: (1) selection of a structural model, (2) selection of an error model, (3) covariate analysis and (4) internal validation of the model. For the structural and error models, a decrease in objective function value (OFV) of 3.84 points was considered statistically significant ($p<0.05$). Visual improvement of the goodness-of-fit plots (observed vs. individual and population predicted concentration, conditional weighted residuals (CWRES) vs. time and CWRES vs. population predicted concentration) was evaluated. In addition, the confidence interval for the estimated parameters, the correlation matrix, η-shrinkage and the condition number (to find ill-conditioning or over-parameterization of the model) served to evaluate the models.

The individual pharmacokinetic parameters (post-hoc values) of the *i*th subject are modeled by use of Eq. 1:

(1) $P_i = P_{pop} \cdot e^{\eta i}$

where P_i is the individual value of the PK parameters of the *i*th individual, P_{pop} the population prediction and η_i the inter-individual variability, which is assumed to be a Gaussian random variable with a mean zero and variance of ω^2 with a log-normal distribution. Inter-occasion variability on the different parameters was tested for the subsequent days to assess changes in pharmacokinetic parameters between days. This resulted in the identification of inter-occasion variability (IOV) on clearance describing the changes in clearance within individuals during the study according to Eq. 2:

(2) $CL_{ij} = CL_{pop} \cdot e^{\eta i + m ij}$

where CL_{ij} is the individual parameter estimate at the *j*th occasion, CL_{pop} the population prediction of clearance, η_i the inter-individual variability and m_{ij} is a random variable for the *i*th individual at the *j*th occasion (IOV). Both η_i and m_{ij} were assumed to be independently normally distributed with a mean of zero and variances ω^2 and π^2, respectively. The IOV represents the variability between different occasions, where every 24 hours after the first dose was regarded as a new occasion.
The residual unexplained variability was described with a combined error model (proportional and additive error model) for all data. The observations of the *j*th observation of the *i*th individual are described according to Eq. 3:

(3) $Y_{ij} = C_{pred,ij} \cdot (1 + \varepsilon_1) + \varepsilon_2$

where Y_{ij} is the observed concentration, $C_{pred,ij}$ the predicted concentration for the *j*th observation in the *i*th individual and ε_1 and ε_2 the proportional and additive error samples respectively from a distribution with a mean of zero and variance of σ^2.

Covariate analysis

Tested covariates included patient characteristics (age, weight, sex, diagnosis group, co-administration of CYP3A inhibitors, study center, CYP3A polymorphisms), inflammation markers (CRP, cytokines) and disease severity (PRISM II, PIM 2, PELOD, number of organ failures, creatinine, ALAT and albumin). Individual post-hoc parameters, inter-individual variability and conditionally weighted residuals (CWRES) were plotted against the covariates to evaluate possible relationships. Continuous covariates were tested in a linear or power function (Eqs. 4 and 5):

$$P_i = P_{pop} \cdot \left(1 + \left(\frac{Cov_i}{Cov_{median}} \right) \cdot l \right) \quad (4)$$

$$P_i = P_{pop} \cdot \left(\frac{Cov_i}{Cov_{median}} \right)^k \quad (5)$$

where P_i and Cov_i are the values for the parameter and covariate, respectively, for the *i*th individual, P_{pop} is the population mean for parameter P and Cov_{median} is the standardized value of the covariate. In the linear function, the slope is depicted by *l*. For Eq. 5, *k* represents the scaling factor in the power function. For clearance, also a body weight dependent exponent *k* was tested (36). Since the concentration of IL-6 covered a large range, it was log-transformed and as such considered as covariate in the model. Categorical covariates such as co-administration of CYP3A inhibitors, sex and number of organs failing were tested as a fraction for each category or independently estimated for the different categories. When a CYP3A inhibitor (i.e. clarithromycin, voriconazole, fluconazole, erythromycin, haloperidole, metronidazole) was administered at the same day as midazolam, a factor affecting clearance was estimated for that day.
Potential covariates were evaluated using forward inclusion and backward elimination with a level of significance of <0.005 (OFV -7.9 points) and <0.001 (OFV -10.8 points), respectively. In addition, inclusion of a covariate in the model had to result in a decline in unexplained inter-individual variability or unexplained inter-occasion variability before it was included in the final model (18, 19). Additional covariates had to reduce the objective function and unexplained variability further to be retained in the model.

Model evaluation

The model was internally validated using bootstrap analysis in Perl-speaks-NONMEM (PsN version 4.2.0). Five hundred datasets were resampled from the original datasets and refitted to the model. Normalized prediction distribution errors (NPDE) were calculated with the NPDE package in R (37). For this method, the dataset used for model development was simulated a thousand times with inclusion of inter-individual and inter-occasion variability and residual error.

SUPPLEMENTAL FIGURES

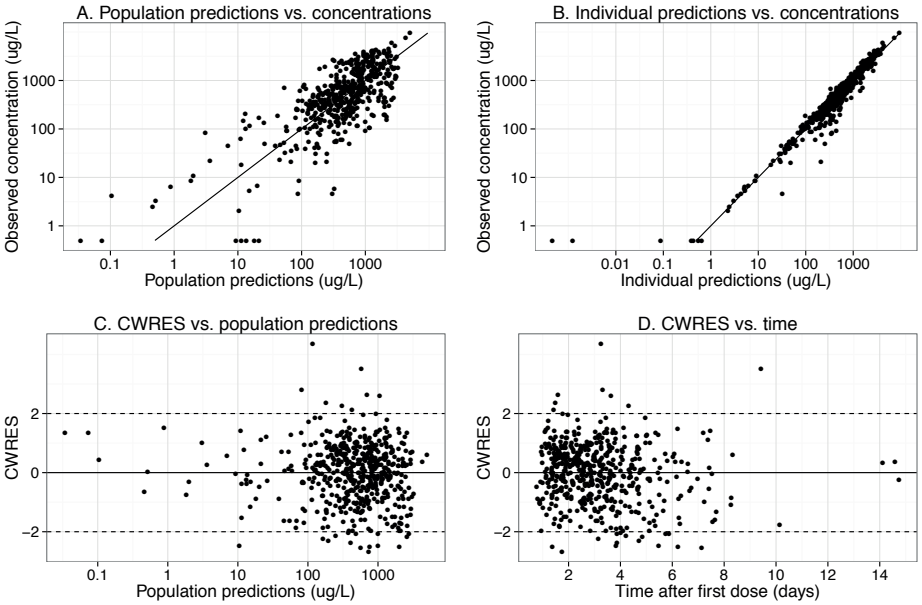


Figure E1. Goodness-of-fit plots for the final model with inflammation and organ failure included as covariates

(a) Log observed plasma concentrations vs. log population predicted concentrations. **(b)** Log observed plasma concentrations vs. log individual predicted concentrations on a log scale. **(c)** Conditional weighted residuals (CWRES) versus log population predictions. **(d)** CWRES versus time after first dose.

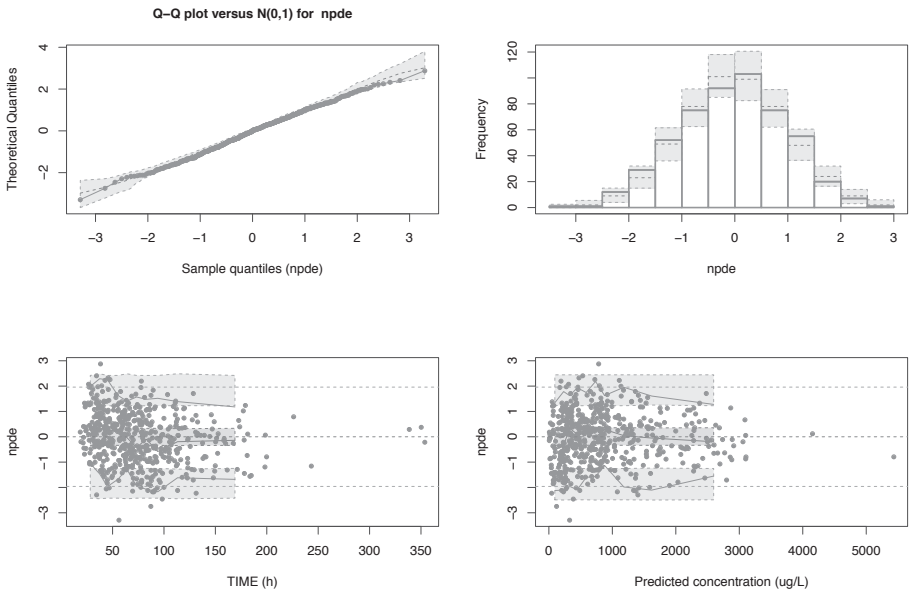
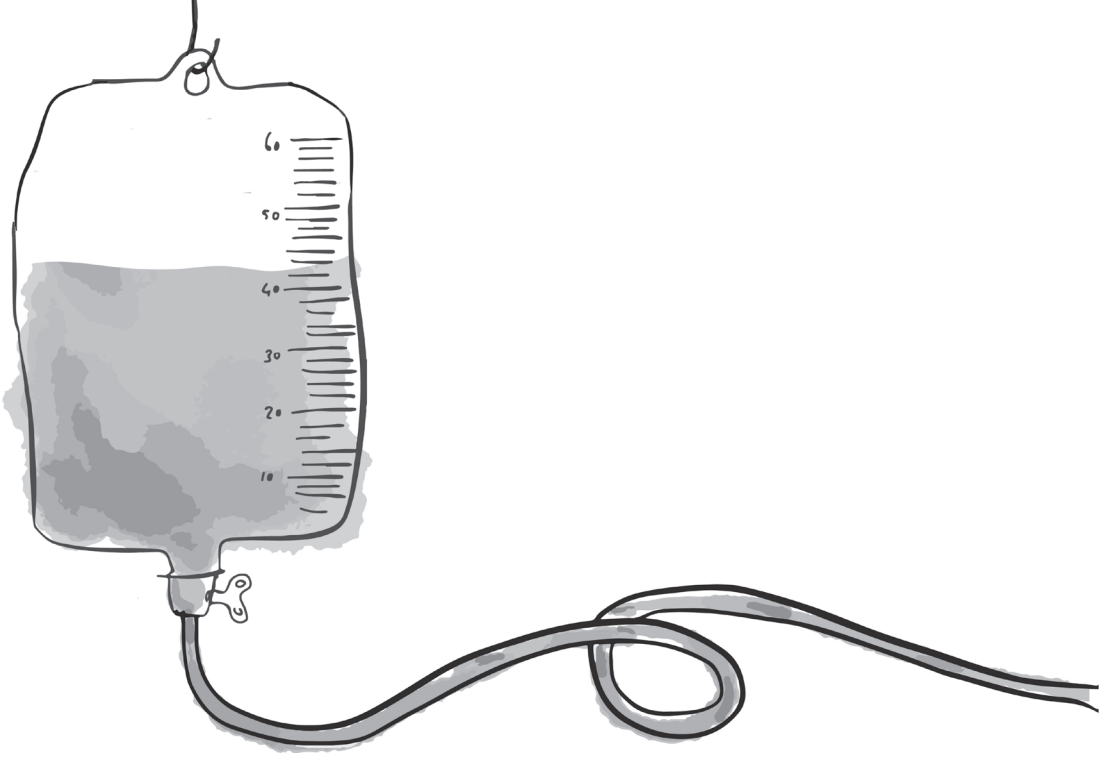


Figure E2. Normalized prediction distribution error (NPDE) results of the final model with inflammation and disease severity included as covariate plots

(a) Q-Q plot. **(b)** Histogram of the NPDE distribution. **(c)** NPDE versus time after first dose in hours. **(d)** NPDE versus predicted concentrations in µg/L.

PART III

Pharmacodynamics in pediatric critical illness – midazolam as sedative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Chapter 5

Optimal sedation in pediatric intensive care patients: a systematic review

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ABSTRACT

Purpose: Sedatives administered to critically ill children should be titrated to effect, because both under- and oversedation may have negative effects. We conducted a systematic review to examine reported incidences of under-, optimal, and oversedation in critically ill children receiving intensive care.

Methods: A systematic literature search using predefined criteria was performed in PubMed and Embase to identify all articles evaluating level of sedation in PICU patients receiving continuous sedation. Two authors independently recorded: study objective, study design, sample size, age range, details of study intervention (if applicable), sedatives used, length of sedation, sedation scale used, and incidences of optimal, under- and oversedation as defined in the studies.

Results: Twenty-five studies were included. Two studies evaluated sedation level as primary study outcome; the other 23 as secondary outcomes. Together, these studies investigated 1.163 children; age range 0-18 years. Across studies, children received many different sedative agents and sedation level was assessed with 12 different sedation scales. Optimal sedation was ascertained in 57.6% of the observations, undersedation in 10.6% and oversedation in 31.8%.

Conclusions: This study suggests that sedation in the PICU is often suboptimal and seldom systematically evaluated. Oversedation is more common than undersedation. As oversedation may lead to longer hospitalization, tolerance, and withdrawal, preventing oversedation in pediatric intensive care deserves greater attention.

INTRODUCTION

The provision of adequate sedation and analgesia to critically ill children is an important aspect of care in the pediatric intensive care unit. Sedatives and analgesics reduce anxiety, pain, and agitation, enhance synchronization with mechanical ventilation, and enable invasive procedures to be performed. Adequate sedation is defined as the level of sedation at which patients are asleep but easily arousable (1). Oversedation delays recovery, as greater sedatives consumption is associated with longer duration of ventilation as well as extubation failure (2). Oversedation also induces tolerance and withdrawal syndrome (3, 4). Undersedation, on the other hand, may lead to increased distress and adverse events such as unintentional extubation or displacement of catheters. All this may also lead to a longer ICU stay.

Children are usually sedated through a combination of hypnotics (e.g. midazolam) and analgesics (e.g. morphine or fentanyl) (5-7). Regrettably, there is little evidence from randomized trials on the efficacy of these drugs for sedation in critically children (8). Nevertheless, efforts are being made to improve sedation management, for example with the use of sedation algorithms and standardized sedation management (9, 10).

To achieve the optimal level of sedation in individual patients, doses of sedatives are individually titrated to effect. This process is guided by scores on a variety of observational sedation scales (5). The COMFORT score or COMFORT-behavior scale and the Hartwig sedation scale are widely used and validated for this setting (11, 12). Other scales used are the Ramsay scale (13), Richmond Agitation Sedation Scale (RASS) (14), State Behavior Scale (SBS) (15), and the University of Michigan Sedation Scale (UMSS) (16). In addition, methods derived from the electro-encephalogram (EEG), such as the Bispectral Index (BIS) and middle latency auditory-evoked potential index (AEP), are applied, although their use is not validated in young children (17).

The aim of this systematic literature review is to evaluate the reported incidences of under-, optimal, and oversedation in pediatric intensive care patients and to determine to what extent the goal of adequate sedation is met (18).

METHODS

Search strategy

A systematic literature search was performed in the PubMed and Embase databases from inception to July 2012, using the terms sedation, child, intensive care unit, and sedation quality/sedation level. We used a comprehensive search strategy to identify all published articles evaluating the level of sedation, measured with an observational scale, in pediatric intensive care patients. For Embase, appropriate search terms were

applied. Full details of the search strategy are presented in Appendix I. Furthermore, reference lists of retrieved articles were searched to identify other relevant papers that complied with the inclusion criteria.

Selection criteria

We used the following inclusion criteria:

1) Study population of PICU patients (0-18 years) on mechanical ventilation and receiving continuous sedation.
2) Reporting level of sedation and/or the incidence of under-, over-, and optimal sedation, as defined in the study.

Studies published in any language with an English language abstract were eligible for review. Exclusion criteria were:

1) Procedural sedation.
2) Preterm patients.
3) Patients treated with muscle relaxants, which preclude the use of sedation scores.
4) Studies using only the BIS monitor in children aged <1 year, since this method is not validated for this patient group (17).

Two authors (NV, EI) independently reviewed titles and abstracts of all retrieved citations to identify eligible studies. Of all included studies, the full-text articles were again reviewed to ensure that they met inclusion criteria. Disagreements between reviewers were resolved by consensus.

Data extraction

Two authors (NV, EI) each independently recorded the following data: country of origin, study objective, study design, study population, age of patients, sample size, details of study intervention (if applicable), sedatives used (drug, dose), length of sedation, sedation scale used, and the incidence of optimal sedation, and under- and oversedation. We used the definitions for optimal sedation as used by the researchers in the individual studies (as percentage of number of observations, patients or time) to be able to pool the data, despite different sedation assessment methods (Table 1).

Quality assessment

Study quality was determined with the "Quality Assessment Tool for Quantitative Studies" by the McMaster University, School of Nursing (19) as strong, moderate or weak.

Table 1. Summary of included studies reporting the incidence of optimal, under-, and oversedation

Authors	Country	Study design	Study population	*n*	Sedatives used	Sedation scale	Definition optimal sedation	Incidence of optimal sedation	Incidence of under-sedation	Incidence of over-sedation	Comments
Parkinson et al. (34)	UK	RCT of sedative drugs	Critically ill children 1 day-15 years	44	Midazolam vs. chloral hydrate and promethazine	Clinical sedation scale	2-4, depending on patients condition	96% and 90% (413/432 and 332/367 obs)	4% and 9% (19/432 and 32/367 obs)	0% and 1% (0/432 and 3/367 obs)	
Amigoni et al. (22)	Italy	Observational study of sedation scales	Critically ill children 1 month-18 years	46	Not reported	Comfort behavior scale nurse (and BIS)	COMFORT-B 11-22 (BIS 40-80)	34.8% (16/46 pts) 73.9% (34/46 pts)	0% (0/46 pts) 4.3% (2/46 pts)	65.2% (30/46 pts) 21.7% (10/46 pts)	
Ista et al. (9)	The Netherlands	Observational study, before-after introduction of sedation protocol	Critically ill children 0-3 years	131	Midazolam, morphine	COMFORT behavior scale and NISS	COMFORT-B 11-22 with a NISS of 2	64% (2273/3573 obs)	12.9% (461/3573 obs)	19.7% (704/3573 obs)	
Ista et al. (11)	The Netherlands	Observational study of sedation scale	Critically ill children 0-18 years	78	Midazolam, morphine, ketamine, fentanyl	COMFORT behavior scale and NISS	COMFORT-B 11-22 with a NISS of 2	48.8% (411/843 obs)	11.2% (94/843 obs)	40.1% (338/843 obs)	
Froom et al. (23)	UK	Observational study of sedation scales	Critically ill children 0-16 years	19	Midazolam, morphine, chloral hydrate	COMFORT score	17-26	14.8% (4/27 obs)	3.7% (1/27 obs)	81.5% (22/27 obs)	
Triltsch et al. (24)	Germany	Observational study of sedation scales	Critically ill children <18 years	40	Benzodiazepines, opioids, propofol, ketamine	COMFORT score	17-26	27.5% (11/40 pts)	0%	72.5% (29/40 pts)	

Table 1. Summary of included studies reporting the incidence of optimal, under-, and oversedation (continued)

Authors	Country	Study design	Study population	*n*	Sedatives used	Sedation scale	Definition optimal sedation	Incidence of optimal sedation	Incidence of under-sedation	Incidence of over-sedation	Comments
de Wildt et al. (40)	The Netherlands	Observational PKPD study	Critically ill children 2 days-17 years	21	Midazolam	COMFORT score	17-26	46.1% (244/497 obs)	6% (30/497 obs)	44.9% (223/497 obs)	
Arenas-Lopez et al. (35)	UK	Observational study of sedative drug	Critically ill children <5 years	14	Morphine and clonidine	COMFORT score	13-23	81.9% (837/1022 hrs)	10.8% (110/1022 hrs)	7.3% (75/1022 hrs)	
Marx et al. (20)	USA	Observational study of sedation scale	Critically ill children 1-102 months	85	Opiates, benzodiazepines, barbiturates	COMFORT score	17-26	57.1% (32/56 obs)	12.5% (7/56 obs)	30.4% (17/56 obs)	
Brunow de Carvalho et al. (12)	Brazil	Observational study of sedation scales	Critically ill children 16 days-5 years	18	Opiates, benzodiazepines, barbiturates	COMFORT score Hartwig sedation scale	COMFORT 17-26 Hartwig 15-18	CF 60% (18/30 obs) Hartwig 56.7% (17/30 obs)	CF 6.7% (2/30 obs) Hartwig 16.7% (5/30 obs)	CF 33.3% (10/30 obs) Hartwig 26.7% (8/30 obs)	
Aneja et al. (25)	USA	Observational study of sedation scales	Critically ill children 3 months-18 years	24	Opioids, benzodiazepines, propofol	Ramsay	2-3	33.8% (155/458 obs)	9.2% (42/458 obs)	Deeply 38.8% (179/458 obs) Oversedated 18.2% (82/458 obs)	
Berkenbosch et al. (26)	USA	Observational study of sedation scales	Critically ill children 1 month-20 years	24	Midazolam, fentanyl, propofol	Ramsay	2-4	50.9% (217/426 obs)	8.7% (37/426 obs)	40.4% (172/426 obs)	

Table 1. Summary of included studies reporting the incidence of optimal, under-, and oversedation (continued)

Authors	Country	Study design	Study population	*n*	Sedatives used	Sedation scale	Definition optimal sedation	Incidence of optimal sedation	Incidence of under-sedation	Incidence of over-sedation	Comments
Curley et al. (15)	USA	Observational study of sedation scales	Critically ill children 6 weeks-6 years	91	Opioids, benzodiazapines	State Behavioral Scale	0 and -1	42.9% (85/198 obs)	4% (8/198 obs)	53% (105/198 obs)	
Johansson et al. (27)	Sweden	Observational study of sedation scales	Postoperative patients 0-10 years	40	Midazolam, morphine	NISS	NISS of 2	70%	17%	13%	
Ambrose et al. (36)	UK	Observational study of sedative drug	Critically ill children <10 years	20	Midazolam and clonidine	Clinical sedation score	2-7	89%	-	-	
Playfor et al. (21)	UK	Observational study of sedation scale	Critically ill children 1 month-16 years	28	Midazolam, morphine, chloral hydrate, antihistamines	Clinical sedation score (response to tracheal suction)	1, 2 or 4	79% ideal 11% acceptable (64/81 obs and 9/81 obs)	10% (8/81 obs)	-	
Hartwig et al. (37)	Germany	Observational PKPD study	Critically ill children 26 days-5 years	24	Midazolam, fentanyl	Clinical sedation score	15-18	60% (9/15 points)	6.7% (1/15 points)	33.3% (5/15 points)	
Lamas et al. (28)	Spain	Observational study of sedation scales	Postoperative cardiac and non-cardiac surgery patients <14 years	50	Midazolam, fentanyl (vecuronium)	BIS monitor MLAEPs Ramsay score COMFORT score	BIS ≥ 60 MLAEPs ≥ 30 Ramsay ≤ 5 COMFORT ≥ 18	8% (4/50 pts)	-	BIS 56% MLAEPs 73.3% Ramsay 83.9% COMFORT 92.9%	40% of the obs in paralyzed patients

Table 1. Summary of included studies reporting the incidence of optimal, under-, and oversedation (continued)

Authors	Country	Study design	Study population	*n*	Sedatives used	Sedation scale	Definition optimal sedation	Incidence of optimal sedation	Incidence of under-sedation	Incidence of over-sedation	Comments
Lamas et al. (29)	Spain	Observational study of sedation scales	Critically ill children 6 months-19 years	50	Opioids, benzodiazepines	BIS MLAEPs	BIS ≥ 60 MLAEPs ≥ 30	44% (62/141 obs)	-	56% (79/141 obs)	39% of the obs in paralyzed patients
Lamas et al. (30)	Spain	Observational study of sedation scales	Critically ill children <19 years	77	Midazolam, fentanyl (vecuronium)	BIS monitor AEPs Ramsay score COMFORT score	BIS ≥ 60 AEPs ≥ 30 Ramsay 1-5 COMFORT 18-40	BIS 35% AEPs 32.5% Ramsay 27% COMFORT 18%	-	BIS 65% AEPs 67.5% Ramsay 73% COMFORT 82%	40% of the obs in paralyzed patients
Twite et al. (31)	USA	Observational study of sedation scales	Critically ill children 1 month-13 years	75	Fentanyl, midazolam	BIS	BIS 61-80	26.5% (230/869 obs)	9.5% (83/869 obs)	64% (556/869 obs)	
Courtman et al. (32)	UK	Observational study of sedation scales	Critically ill children 1 month-16 years	40	Midazolam, morphine	BIS	BIS 60-80	63%	-	24%	
Crain et al. (33)	USA	Observational study of sedation scales	Critically ill children	31	Opioids, benzodiazepines, propofol	BIS	BIS 61-80	27.4% (17/62 obs)	22.6% (14/62 obs)	50% (31/62 obs)	
Chrysostomou et al. (38)	USA	Retrospective study of sedative drug	Postoperative cardiothoracic surgery patients	38	Dexmedetomidine	Sedation scale	0-2	93%	-	-	33 patients not on MV
Rosen et al. (39)	USA	Retrospective study of sedative drug	Critically ill children	55	Midazolam	Five-point activity scale for sedation	3	±90%	<10%	-	

Studies are categorized by study design and sedation scale used
Obs=observations, pts=patients h=hours

Statistical analysis

We analyzed studies separately on study design, sedation scale used and proportion of under-, over-, and optimal sedation. Proportion was expressed as percentage of number of observations, patients or time (hours). If similar outcome measures were used, the results of individual studies were quantitatively pooled to calculate a weighted mean, using descriptive statistics. The large heterogeneity in study aims and study designs precluded further statistical analysis.

RESULTS

Study selection

After filtering out duplicate studies, our search yielded 392 potentially relevant articles. Of these studies, 348 were excluded on the grounds of information in title and abstract (Figure 1). Of the remaining 44 articles, the full-text was retrieved and assessed for eligibility. Nineteen studies were excluded for lack of quantitative data on sedation level or incidence of optimal, under-, or oversedation, or for absence of a definition of optimal sedation. Details of the remaining 25 studies are presented in Table 1.

Study characteristics

One study was a randomized controlled trial (comparing two sedative regimens); 22 studies were prospective observational studies; and two were retrospective studies on a sedative drug. Of all 25 studies, only two determined the level of sedation as primary study outcome (20, 21). Fifteen studies investigated one or more sedation scales or sedation monitoring systems (such as the BIS) (11, 12, 15, 22-33); six studies investigated a sedative drug (34-39); one was a pharmacokinetic-pharmacodynamic study (40); and one study described the effect of implementation of a sedation protocol on amount of sedatives administered (9). Although assessment of level of sedation was not the primary objective in the latter 23 studies, they reported incidences of under-, optimal-, and oversedation.

Since sedation practices may differ between countries, we also looked at the country of origin. Of the 25 studies, eight were conducted in the United States, 16 in six European countries, and one in Brazil.

All studies together investigated a total of 1.163 critically ill children. The most frequently used drugs were benzodiazepines (midazolam, in 22 studies) and opioids (morphine, in 14 studies). Other drugs used were fentanyl, ketamine, clonidine, propofol, barbiturates, chloral hydrate, first-generation antihistamines, and dexmedetomidine in different combinations.

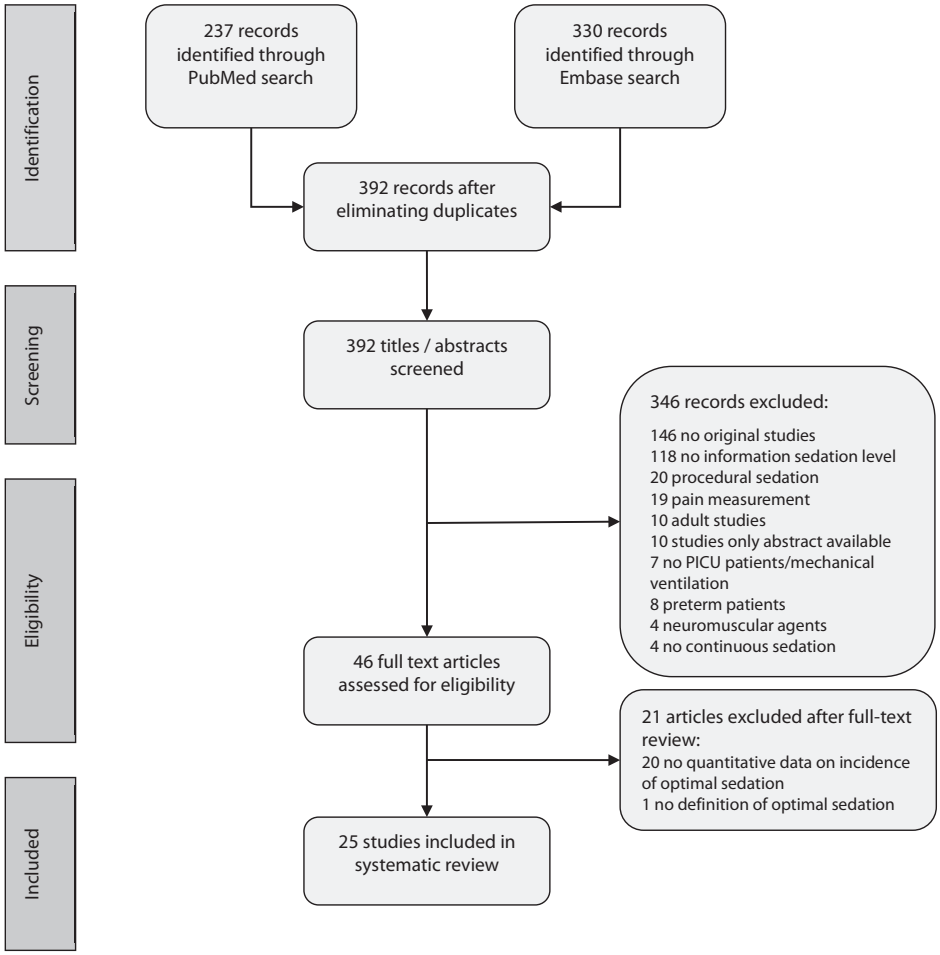

Figure 1. Flowchart search results

Quality assessment

Only two studies had level of sedation as their primary outcome, all other studies varied by aim and study design. Therefore, assessment of study quality with the "Quality Assessment Tool for Quantitative Studies" was not possible, and this makes direct comparison between the studies difficult.

Sedation scales

Across all studies, 12 different observational sedation scores were used, of which four were validated for the PICU setting, i.e. the COMFORT score, the COMFORT-B scale, the Hartwig sedation scale, and the State Behavior Scale. Most frequently (11/25) used were the COMFORT score and COMFORT-behavior scale (COMFORT-B), followed by the Ram-

say score, the State Behavioral Scale, and the Hartwig sedation scale. Six studies (23%) used the BIS monitor. In 13 studies two or more sedation scales or monitors were used. All studies defined optimal sedation in terms of cut-off values (Table 1). The definition of optimal sedation differed between studies, even when the same sedation scale was used. For example, a COMFORT score between 17 and 26 is thought to indicate adequate sedation (20). However, one study applied the 13-23 range to define adequate sedation (35). This range was chosen a priori to target a level of sedation that would produce a patient who was under analgesics, calm, with minimal risk of self-extubation, but able to maintain an appropriate cough reflex and spontaneous respiratory effort to achieve ventilator synchrony. Furthermore, different cut-off values for the Ramsay score were used: i.e. 2-3 (25); 2-4 (26); and 1-5 (28, 30). Assessment frequency also varied considerably between studies; from once daily to hourly.

Level of sedation

Reported incidences of optimal, under-, and oversedation are presented in Table 1.
Studies varied in the way incidence was reported (as a proportion of observations, patients or hours). Fifteen studies reported the incidence as a proportion of observations, as summarized in Figure 2. Optimal sedation was ascertained in 15-93% of observations, undersedation in 0-22%, and oversedation in 0-82% of observations. In these 15 studies, patients were optimally sedated in 57.6% of the observations, undersedated in 10.6% of the observations, and oversedated in 31.8% of the observations.
Two studies reported proportions of patients; in these two studies together, 68.6% of patients were oversedated at any time during admission (Figure 3).
The two studies that used both an observational score and the BIS score reported considerably different results (28, 30). The incidence of oversedation measured with the BIS was lower than that measured with a validated observational scale (56% vs. 92.9% and 65% vs. 82%).

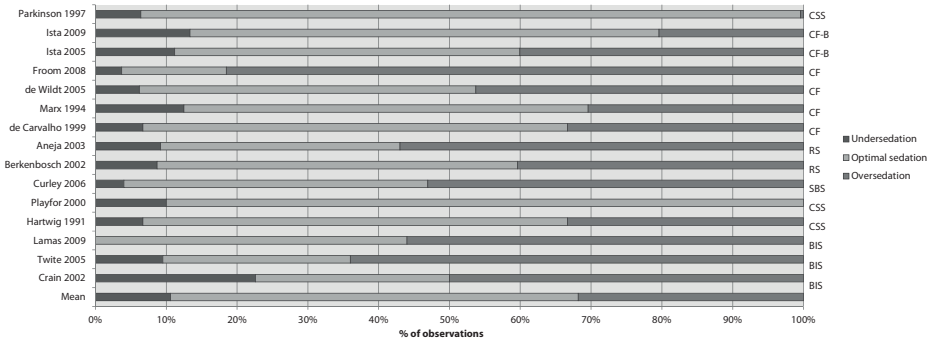

Figure 2. Incidence of under-, optimal, and oversedation (% of observations)
CSS=clinical sedation scale; CF-B=COMFORT behavior scale; CF=COMFORT score; RS=Ramsay; SBS=State Behavior Scale; BIS=Bispectral Index Monitor

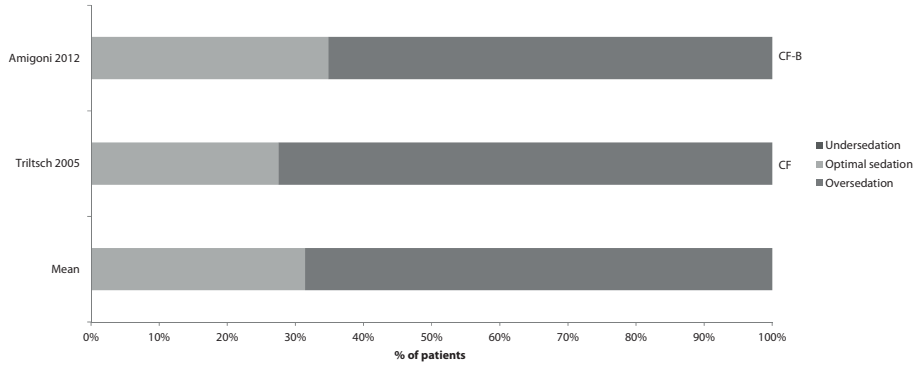

Figure 3. Incidence of under-, optimal, and oversedation (% of patients)
CF-B=COMFORT behavior scale; CF=COMFORT score

DISCUSSION

This review shows that the level of sedation in critically ill children is often suboptimal during their ICU stay, at least in ICUs that apply sedation assessment in daily practice. Patients are optimally sedated in only 60% of assessments. Under- and oversedation occur in 10% and 30% of the assessments, respectively. However, across all studies, there is a large variation in incidence of oversedation, i.e. from 0 to 82% of assessments. Most studies, however, report incidence in the range of 40 to 65%, which corresponds to that reported in adult ICU patients (41-43).

Our results indicate that in critically ill children oversedation is more common than undersedation. We suggest several reasons for the relatively high incidence of oversedation. First, there may be a tendency to avoid undersedation at all cost, as this may lead to discomfort and potential adverse effects as self-extubation and removal of lines and catheters. Since children, especially preverbal infants, cannot clearly communicate their well-being and are often bewildered by the ICU setting, nurses and doctors may also tend to avoid undersedation. Second, nurses believe that mechanical ventilation is uncomfortable and stressful, and this perception might lead to higher sedation level than necessary (42, 44). Third, sedation protocols are not fully adhered to, so that sedatives are not tapered off when possible (45). These tendencies are unwanted, as oversedation may be even more detrimental to patients.
Continuous sedation as such is an independent predictor of prolonged mechanical ventilation in adults, and consequently leads to longer ICU and hospital stay (46). Oversedation, in addition, is also associated with tolerance, withdrawal, and delirium. Especially longer duration of use and high drug doses are risk factors for development

of withdrawal symptoms in children (4). Moreover, longer use of sedatives has been associated with symptoms of depression and post-traumatic stress symptoms in adults (47). In a study in children, almost one-third of children reported delusional memories, and these were the children with the longest duration of administration of opiates/benzodiazepines and the highest risk of posttraumatic stress (48). The administration of sedatives to children may also be associated with adverse neurodevelopmental outcomes at later age, probably by inducing neuroapoptosis (49-51).
The implementation of sedation algorithms aimed at less sedation has led to shorter duration of mechanical ventilation, ICU stay, and hospital stay in adults (52). Also, daily sedation interruption significantly improved short- and long term outcomes in adults (53). A more recent "no-sedation" protocol is even more promising in this respect (54). All evidence indicates that the use of sedative drugs should be reduced. In children, daily sedation interruption seems feasible and safe, but effectiveness needs to be demonstrated in large trials (55).

This review also shows a great variety of assessment instruments used in clinical practice. No more than four of the 12 observational sedation scores have been validated for PICU patients, i.e. the COMFORT score, the COMFORT-B scale, the Hartwig sedation scale, and the State Behavior Scale. This is remarkable, as there is consensus that the level of sedation should be assessed and documented using a validated sedation assessment scale (5). The reliability of the other scales is questionable. Furthermore, six studies used the BIS monitor. There is insufficient evidence, however, to support the use of the BIS monitor, or any other neurophysiological sedation scoring technique, such as auditory evoked potentials, in children below the age of 6 months (56). The suitability of the adult-derived EEG algorithm to assess children's BIS values is doubted. Furthermore, pre-awakening BIS values in children aged <1 year are lower than in older children (57). This could explain why in some pediatric studies BIS monitoring resulted in a lower incidence of oversedation than did application of the COMFORT score (28, 30).

In all studies the authors defined optimal level of sedation. Remarkably, different studies applied different cut-off values of the COMFORT score and Ramsay score (25, 26, 28, 30). This variation may be explained by the uncertainty in what constitutes optimal sedation, but may also be the result of patient-specific factors. For example, a deeper level of sedation is often aimed for in patients with pulmonary hypertension, traumatic brain injury or difficult airway. Playfor et al. (21) used a clinical sedation score based on the response to tracheal suction, categorizing the response on a five-point scale. A score of 1 (no response to tracheal suction) was considered as the desired level of sedation for children with severe head injury; a score of 2 for children receiving a high level of intensive care with frequent invasive procedures, and a score of 4 for children prior to extubation.

In addition, the relatively high incidence of suboptimal sedation shown in this review reflects the fact that titrating the correct amount of sedation for each child can be complex. There may be several reasons for this. First, PICU populations are quite heterogeneous with respect to disease type and severity, age, and neurodevelopmental stage, so optimal sedation management may differ widely. Second, pharmacokinetics and pharmacodynamics, largely insufficiently studied, may be unpredictable, particularly in patients with multiorgan failure (58). Dosing regimens are often based on healthy adult volunteers and do not take into account factors such as altered protein binding, distribution, and clearance in critically ill children. Also, sedation requirements may change over the course of illness (59).

With the risks of oversedation and the difficulties of reaching adequate sedation in mind, a critical appraisal of sedation strategies in critically ill children is needed. Optimal sedation could perhaps be achieved with the use of validated sedation scales and standard sedation protocols and by studying promising interventions such as daily sedation interruption. These studies are needed in pediatric intensive care.

CONCLUSIONS

This review shows that optimal sedation for critically ill children remains challenging for health professionals. These children are often oversedated and consequently run the risk of adverse outcomes. It is high time to find conclusive evidence on optimal sedation strategies in the PICU setting.

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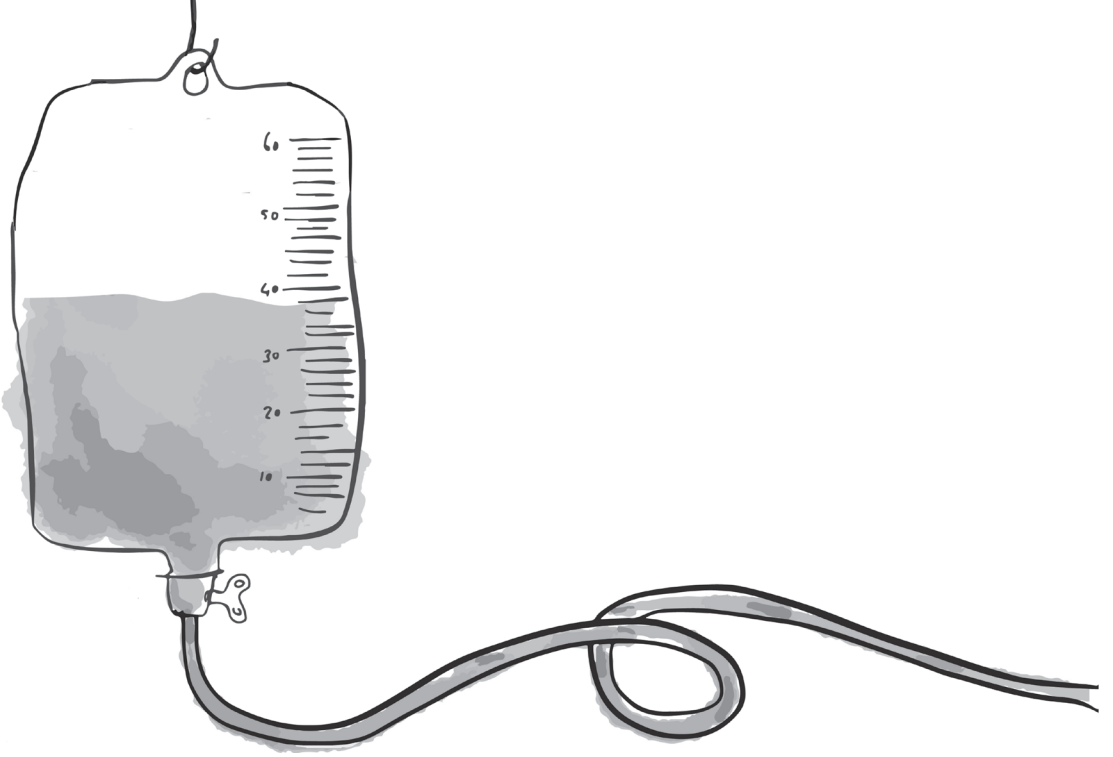
APPENDIX I. SEARCH STRATEGY

Pubmed

(child*[tw] OR infan*[tw] OR pediatr*[tw] OR paediatr*[tw])
AND
(intensive car*[tw] OR critical car*[tw] OR critically ill*[tw] OR ICU[tw] OR PICU[tw])
AND
(sedat*[tw] OR midazolam[tw] OR lorazepam[tw] OR diazepam[tw] OR benzodiazepin*[tw] OR fentanyl[tw] OR remifentanyl[tw] OR morphine[tw] OR ketamine[tw] OR clonidine[tw] OR pentobarbital[tw] OR opioid*[tw] OR propofol[tw])
AND
(sedation qualit*[tw] OR quality of sedation[tw] OR sedation level*[tw] OR level of sedation[tw] OR sedation score*[tw] OR sedation scale*[tw] OR sedation assess*[tw] OR assessing of sedation[tw] OR sedation protocol*[tw] OR sedation guideline*[tw] OR sedation algorithm*[tw] OR assessment tool*[tw] OR conscious sedation/standards[mesh] OR conscious sedation/methods[mesh] OR nursing assessment[mesh] OR nursing assess*[tw] OR nursing diagn*[tw] OR COMFORT score*[tw] OR COMFORT scale*[tw] OR COMFORT behavio*[tw] OR bispectral inde*[tw] OR state Behavior Scale*[tw] OR state behaviour scale*[tw] OR pharmacodynamic*[tiab])

Embase

(child*:ti,ab,de OR infan*:ti,ab,de OR pediatr*:ti,ab,de OR paediatr*:ti,ab,de) AND (((intensive OR critical*) NEAR/2 (car* OR ill*)):ti,ab,de OR ICU:ti,ab,de OR PICU:ti,ab,de) AND (sedat*:ti,ab,de OR midazolam:ti,ab,de OR lorazepam:ti,ab,de OR diazepam:ti,ab,de OR benzodiazepin*:ti,ab,de OR fentanyl:ti,ab,de OR remifentanyl:ti,ab,de OR morphine:ti,ab,de OR ketamine:ti,ab,de OR clonidine:ti,ab,de OR pentobarbital:ti,ab,de OR opioid*:ti,ab,de OR propofol:ti,ab,de) AND ((sedation NEAR/2 (qualit* OR level* OR score* OR scale* OR assess* OR protocol* OR guideline* OR algorithm*)):ti,ab,de OR (assess* NEAR/2 tool*):ti,ab,de OR 'conscious sedation':de OR 'nursing assessment'/exp OR (nurs* NEAR/2 (assess* OR diagn*)):ti,ab,de OR (COMFORT NEAR/1 (score* OR scale* OR behavio*)):ti,ab,de OR (bispectral NEAR/1 inde*):ti,ab,de OR (('state Behavior' OR 'state behaviour') NEAR/1 scale*):ti,ab,de OR pharmacodynamic*:ti,ab)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Chapter 6

Daily interruption of sedation in critically ill children: study protocol for a randomized controlled trial

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Trials 2014, 15:55

ABSTRACT

Background: In adult patients who are critically ill and mechanically ventilated, daily interruption of sedation (DSI) is an effective method of improving sedation management, resulting in a decrease of the duration of mechanical ventilation, the length of stay in the intensive care unit (ICU) and the length of stay in the hospital. It is a safe and effective approach and is common practice in adult ICUs. For critically ill children it is unknown if DSI is effective and feasible. The aim of this multicenter randomized controlled trial is to evaluate the safety and efficacy of daily sedation interruption in critically ill children.

Methods/Design: Children between 0 and 18 years of age who require mechanical ventilation, with an expected duration of at least 48 hours and need for sedative infusion, will be included. After enrollment patients will be randomly assigned to DSI in combination with protocolized sedation (intervention group) or protocolized continuous sedation (control group). A sedation protocol that contains an algorithm for increasing and weaning of sedatives and analgesics will be used. The sedative infusion will be restarted if the patient becomes uncomfortable or agitated according to the sedation protocol. The primary endpoint is the number of ventilator-free days at 28 days.

Trial registration: NTR2030

BACKGROUND

Critically ill children are often sedated in order to prevent discomfort or anxiety and to facilitate care. The sedative drug of choice for the majority of critically ill children is midazolam, often given together with analgesics such as morphine or fentanyl (1). Doses are individually titrated, based on sedation assessments, to reach the optimal level of sedation. Both inadequate and excessive sedation may have deleterious effects. Oversedation delays recovery, promotes tolerance and leads to distressing symptoms on withdrawal of the drugs (2). Undersedation may result in increased distress and increased adverse events, such as unplanned extubation, accidental displacement of catheters and fighting the ventilator.

Despite the use of sedation algorithms, excessive sedation is a common problem in critically ill children receiving continuous sedation (3). In adults, the administration of sedatives by continuous infusion is an independent predictor of a longer duration of mechanical ventilation as well as a longer stay in the intensive care unit (ICU) and in the hospital overall (4).

In adults, daily sedation interruption (DSI) improves clinical outcome. Every day, sedative drug infusions are interrupted and patients are allowed to 'wake up' from their medicine-induced sleep. During this period, patients are assessed for neurological recovery and readiness for extubation, or re-sedated if required (5). In adult intensive care patients, DSI resulted in a significant decrease in the duration of mechanical ventilation, the length of stay in the ICU and the length of stay in the hospital (6). DSI is also a safe approach: self-extubation and removal of catheters did not occur more frequently in patients treated with DSI. Follow-up studies showed that DSI reduces the incidence of complications associated with mechanical ventilation and reduced symptoms of post-traumatic stress disorder (7, 8). In the last few years, some studies have confirmed the safety and efficacy of DSI (9, 10), while other studies did not find a positive effect of DSI on clinical outcome (11,12). Nevertheless, DSI is now routine practice in adult ICUs (5, 13). An even more drastic approach of no sedative drugs at all has also been shown to improve clinical outcome in adult intensive care patients (14).

For critically ill children, it is unknown if DSI is effective, feasible and safe. Data from adult ICU studies cannot be automatically extrapolated to children. Important differences in the use of sedative drugs between children and adults have been described. In adult ICU patients, propofol and remifentanyl are the drugs of choice, besides midazolam, morphine or fentanyl. In children, propofol is contraindicated for prolonged (>24 hours) sedation because of the risk for propofol infusion syndrome (1). Another important difference is that the elimination half-life of many drugs varies between adults and children, due to age-related changes in drug metabolism and renal excretion. Also, the assessment of the sedative level differs between adults and children. For example,

to assess wakefulness adult patients are asked to perform actions on request, such as squeeze a hand or stick out their tongue. In most pediatric ICUs (PICUs), 80% of admissions are children <3 years of age. Younger children cannot perform such instructions on request and the assessment of their sedation level should include other parameters, such as non-verbal communication. Specific instruments, such as the COMFORT scale, have been developed and validated for assessing sedation levels in critically ill children (15). Finally, since younger children cannot clearly communicate, their behavior is different and there might be a greater intolerance of discomfort.

We identified two studies evaluating the feasibility of DSI in children. In a pilot study in 30 ventilated children DSI was compared with standard care (16). DSI appeared feasible and safe (similar rate of unintended extubations and line removals) and reduced the amount of sedatives administered. However, this trial was not sufficiently powered to detect differences in clinical outcomes. The second study performed by our group showed that in 20 neonates on extracorporeal membrane oxygenation (ECMO), midazolam and morphine could be discontinued following cannulation for a median of 10 hours without adverse events (17).
Recently, a study was published comparing DSI with continuous sedation in children on mechanical ventilation (18). This study showed that DSI also improves outcomes in pediatric patients. The length of mechanical ventilation and duration of intensive care stay were significantly reduced in the interrupted sedation group (10.3 vs. 7.1 days, p=0.021 and 14.1 vs. 10.7 days, p=0.002, respectively). There were no differences in adverse events between groups. Given the large differences in patient population and ICU practices between this Indian ICU and the Western setting, these results need further validation (19). In this Dutch multicenter study, efficacy and safety of daily interruption of sedation in critically ill children will be investigated.

METHODS/DESIGN

In this multicenter randomized controlled trial, we will compare DSI combined with protocolized sedation with standard of care (protocolized sedation only). This study is a collaborative study between PICUs in The Netherlands.

Study population

Patients will be recruited from five tertiary medical-surgical PICUs (Erasmus MC-Sophia Children's Hospital, Radboud University Nijmegen Medical Centre, Academic Medical Centre of Amsterdam, Leiden University Medical Centre and University Medical Centre Groningen).

Children between 0 and 18 years of age admitted to the pediatric intensive care unit, who require mechanical ventilation, with an expected duration of at least 48 hours, and need for sedative drugs can be included.
Inclusion criteria: age between 0 to 18 years, at least 37 weeks of post conceptual age, anticipated duration of mechanical ventilation of at least 48 hours, need for sedative/analgesic drugs.
Exclusion criteria: anticipated death within 48 hours or withdrawal of life support, patients in whom level of sedation cannot be scored due to underlying neurologic condition, neurological, respiratory or cardiac instability that may not tolerate inadequate sedation (for example, traumatic brain injury, pulmonary hypertension), therapeutic hypothermia after cardiopulmonary resuscitation, difficult airway, fixed duration of mechanical ventilation, admission for ECMO, admission to our PICU after transfer from another PICU where the patient is already ventilated/sedated for >2 days, withdrawal of informed consent.

Randomization

Within 24 hours after intubation, parental informed consent will be obtained. The morning after enrollment, patients will be randomly assigned in a 1:1 ratio to DSI combined with protocolized sedation (intervention group) or protocolized sedation alone (control group). Stratified randomization will be used in combination with random permuted blocks. Randomization will be stratified with regards to age in three groups, respectively 0 up to 30 days, 30 days up to 2 years, and 2 years up to 18 years. A biostatistician will carry out computer randomization in advance. During the study period, the pharmacist will have access to group allocation for preparation of study medication, and each assignment is designated on a paper enclosed in a numbered, opaque sealed envelope. After informed consent is obtained, the appropriate envelope is placed in a study binder at the patient's bedside.

Intervention

After enrollment, patients will be randomly assigned to one of two strategies: protocolized continuous sedation combined with daily interruption of infusion of sedatives beginning 24 hours after start of infusion (intervention group) or protocolized continuous sedation alone (control group).

Protocolized sedation / standard of care
All study centers use a standardized sedation protocol that contains an algorithm for increasing and weaning of sedatives and analgesics. It standardizes sedation management and allows nurses to adapt medication based on validated sedation scores (COMFORT-behavior scale (COMFORT-b), Nurse Interpretation of Sedation Score (NISS)).

The COMFORT-b is an adapted version of a scale that was originally developed by Ambuel and colleagues in 1992 for the assessment of distress in paediatric patients, except for premature neonates and children with neurological diseases and limited motor function (20). It consists of six behavioral items: alertness, agitation, crying or in case of artificial ventilation breathing reaction, body movements, muscle tone and muscle tone in the face. A trained intensive care nurse observes a patient for a 2-minute period, during which all items are assessed on a five-point numerical scale (scored 1 to 5). The most distressed behavior during the 2-minute period is scored. The total COMFORT-b score is the total of all item scores, with a minimal score of 6 and a maximal score of 30. The cut-off points for sedation scores were established (21). In all participating PICUs, nurses have been trained to use this scale. Interobserver variability was satisfactory, with Cohen's $\kappa > 0.65$ for all nurses.

Upon admission to the ICU patients are evaluated for the need of sedatives and analgesics according to standard medical treatment protocols. In this protocol, initially, midazolam is titrated (up to 300 μg/kg/h) according to predefined COMFORT-b scores. Adequate sedation is defined as a COMFORT-b score ≥ 11 and ≤ 22. A COMFORT-b score of <11 implies oversedation, a score >22 undersedation. When sedation is considered insufficient, morphine (up to 30 μg/kg/h) is given in addition to midazolam. In cases of continuing distress and where sedation is still inadequate, other drugs, such as ketamine, clonidine, fentanyl, lorazepam, propofol, and alimemazine are added. When pain is also suspected, as defined by a high numeric rating scale score (NRS$\geq$4), additional morphine is given. All study centers use this protocol, with only local differences in the choice of additional agents to midazolam and morphine (Appendix 1).

Intervention group

After the first 24 hours of mechanical ventilation, the patient is assessed for a safety screen every morning at 10.00 AM, after routine care. This safety screen ensures that interruption of sedation is safe for the patient. If the patient passes the screen, the sedative/analgesic infusions will be discontinued immediately; this can be delayed for planned procedures. Analgesics needed for active pain will be continued (for example, pleural drain, <24 hours after surgery). A patient passes the screen unless: he/she receives a sedative infusion for active seizures, receives escalating sedative doses due to ongoing agitation, receives neuromuscular blockers, has evidence of increased intracranial pressure or if there is cardiorespiratory instability. Patients who fail the test will be reassessed after 24 hours (Figure 1).

During interruption, the patient may wake up, and therefore, patients will be monitored frequently. Patient comfort will be assessed routinely every 2 hours using the COMFORT-b/NISS and NRS scores and at any time the patient appears distressed. The COMFORT-b score will be used to assess the level of sedation/wakefulness.

The sedative infusion will be started again: (a) if the patient becomes uncomfortable or agitated, according to the sedation protocol; or (b) if deemed necessary by the clinical team for instability in cardiorespiratory parameters, defined as the need to increase the ventilatory support or cardiovascular treatment (inotropes/fluid bolus), not associated with the underlying disorder.

After a loading dose of midazolam (0.1 mg/kg, intravenously), the sedative infusions will be restarted at half the previous dose and then titrated according to the sedation protocol by the nurse to achieve adequate sedation.

Control group

In the control patients, following the safety screen, a blinded infusion will be started at the same rate and dose as the patient was receiving. The level of sedation will be assessed in a manner similar to the interruption group. When assessments indicate distress, the study infusion will be ceased and replaced by the sedative infusion at a similar rate as before the interruption.

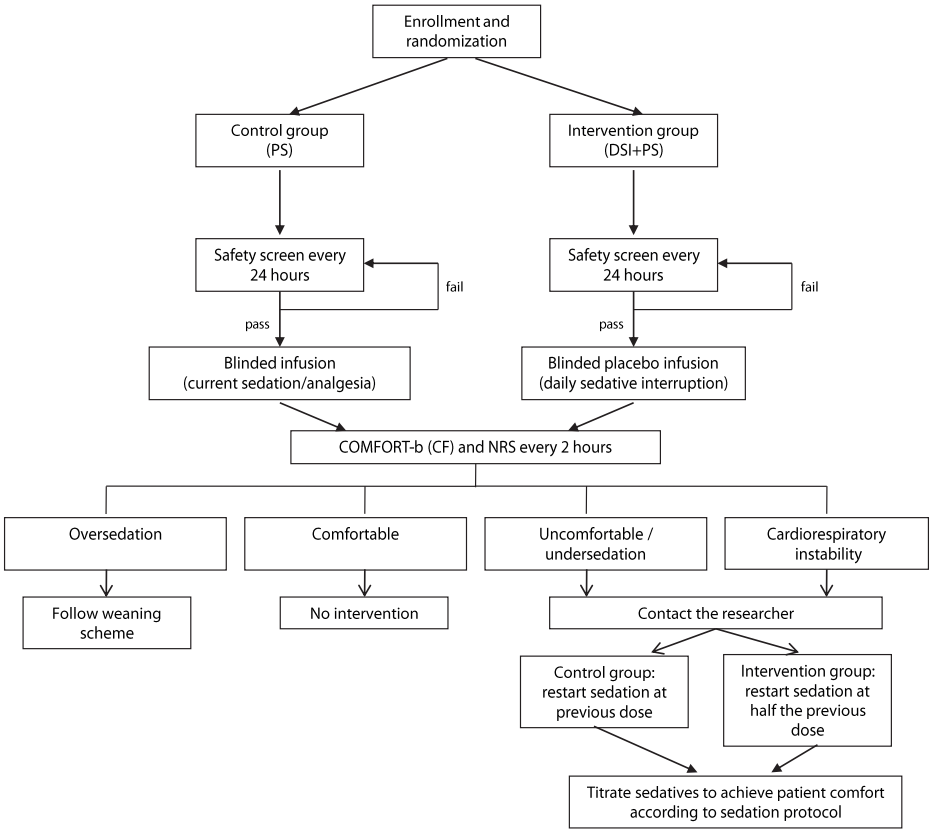

Figure 1. Flowchart of study design

Blinding

Complete blinding after randomization was considered unsafe. It would mean blinded multiple infusion concentration/rate changes over time, leaving patients prone to drug dosing mistakes. However, during interruption, all patients will receive one or more blinded infusions (placebo in the intervention group and current sedation in the control group) prepared by the study pharmacist to minimize bias. In this way the caregiving nurse will be blinded for placebo or current sedation during the interruption period. This will minimize bias in assessing the sedation level of the patient. At the end of the interruption period, the caregiving nurse will open the envelope that is placed in the study binder at the patient's bedside to identify group allocation and sedation will be resumed at 50% (intervention group) or 100% (control group) of the previous intravenous infusion rate. This infusion rate is visible for the caregiving nurse and is therefore not blinded. This procedure will be repeated on every study day.

Follow-up

Quality of life and symptoms of posttraumatic stress disorder (PTSD) will be assessed 3 months after pediatric intensive care treatment using validated questionnaires.

Patients will be approached by telephone by the investigators. Quality of life will be determined using the Child Health Questionnaire (CHQ). The CHQ is a generic health profile measure covering physical and psychosocial domains that refer to the perceived health status for the collective 4 weeks prior to completing the questionnaire. Its structure and methodological approach are similar to those of the Short Form 36 (SF-36), the most used quality of life measure in adults. We will ask the parents to complete the CHQ for patients aged 2 months to 18 years. Patients aged 12 to 18 years will also be asked to complete the CHQ by themselves.

Symptoms of posttraumatic stress will be measured with the Dutch Children's Responses to Trauma Inventory (CRTI). This is a 26-item self-report questionnaire for children aged 8 to 18 years. The questionnaire covers three subscales (intrusion, avoidance, hyperarousal) according to the diagnostic symptoms as per the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) for PTSD and one subscale for non-specific reactions. The total score of symptoms of PTSD can be used as an overall index of a child's stress reaction following a stressful event.

Endpoints

The main study endpoint is the number of ventilator-free days at 28 days, defined as the number of days a patient breathes without mechanical assistance for at least 48 hours consecutively from day 1 to day 28 after randomization.

Secondary outcomes are: total and average dose of midazolam and morphine administered (mg/kg); number of COMFORT behavior scores <11 (oversedation) and >22

(undersedation); use of additional sedative or analgesic drugs during ventilation; total number of safety screen assessments and number and reason for failure to pass; total number and reasons for protocol deviations; adverse events (auto-extubation and reintubation, accidental displacement of catheters and feeding tubes, pain, changes in blood pressure, heart rate, respiratory rate or alarms in those parameters (bradycardia/apneas) that need medication or adjustments in ventilator settings, need for soft wrist restrainers); incidence of withdrawal symptoms (Sophia Observation withdrawal Symptoms (SOS) scale); length of stay in the intensive care unit (days); length of stay in the hospital (days); organ failure free days, defined as the number of days from day 1 to day 28 in which the patient is without clinically significant organ dysfunction (the Paediatric Logistic Organ Dysfunction score (PELOD) will be used to define pediatric organ dysfunction); 30-day mortality; costs at 28 days; quality of life at 3 months, assessed by the Child Health Questionnaire; and incidence of PTSD at 3 months.

Statistical methods

Sample size calculation

Our institutional admission data from 2008 showed that 168 children were mechanically ventilated for at least 48 hours in our pediatric intensive care unit with mean ventilator-free days of 16.5 days (SD 9.9). Using these data, we calculated that a sample size of 100 patients per group is sufficient to detect a clinically significant difference of 25% in ventilator-free days (that is, mean 20.6 days in the intervention group versus 16.5 days in the control group), with a power of 80%, based on a two-tailed Mann-Whitney test with a significance level of 5%.

Final evaluation

Data will be analyzed with an intention-to-treat approach.

Demographic and clinical characteristics will be described using standard statistical analysis methods. Descriptive data will be presented as percentages, means ± SD for normally distributed variables, and medians ± interquartile ranges for non-normally distributed variables.

We will use chi-square tests or Fisher's exact tests to compare the distribution of categorical variables between the study groups, and the Mann-Whitney test to compare continuous variables, including the primary outcome ventilator-free days.

The number of ventilator-free days will also be compared with correction for baseline variables (age, sex, PELOD score and type of disease), using multiple linear regression analysis.

To compare the effects of the two treatment protocols on length of stay in the intensive care unit and in the hospital, time-to-event analysis will be used. Kaplan-Meier analysis and the log-rank test will be used to assess the effect of the treatment protocols. These

tests will also be used to assess the effect of the treatment on 30-day mortality. Cox proportional hazards analysis will be used to assess differences between the study groups after adjustment for the baseline variables mentioned previously.
All statistical tests will be two-tailed and the significance level will be set at 0.05.

Ethical considerations

The study protocol has been evaluated and approved by the institutional review board of Erasmus Medical Centre, Rotterdam and by the local ethics committees of all participating centres: Radboud University Nijmegen Medical Centre, Academic Medical Centre of Amsterdam, Leiden University Medical Centre and University Medical Centre Groningen. Written parental consent will be obtained from participants. The study will be conducted according to the principles of the declaration of Helsinki (version 2004) and in accordance with the Medical Research Involving Human Subjects Act (WMO).
This trial is registered in the Dutch Trialregister, located at http://www.trialregister.nl, under number NTR2030.

Data and Safety Monitoring Board (DSMB)

All adverse events reported spontaneously by the subject or observed by the investigator or staff will be recorded. A continuous evaluation on adverse effects will be performed by an independent DSMB. Adverse events are defined as any undesirable experience occurring to a subject during the clinical trial. If it appears that a disproportionate number of adverse events occur in the intervention group, the DSMB can decide that the study must be terminated.

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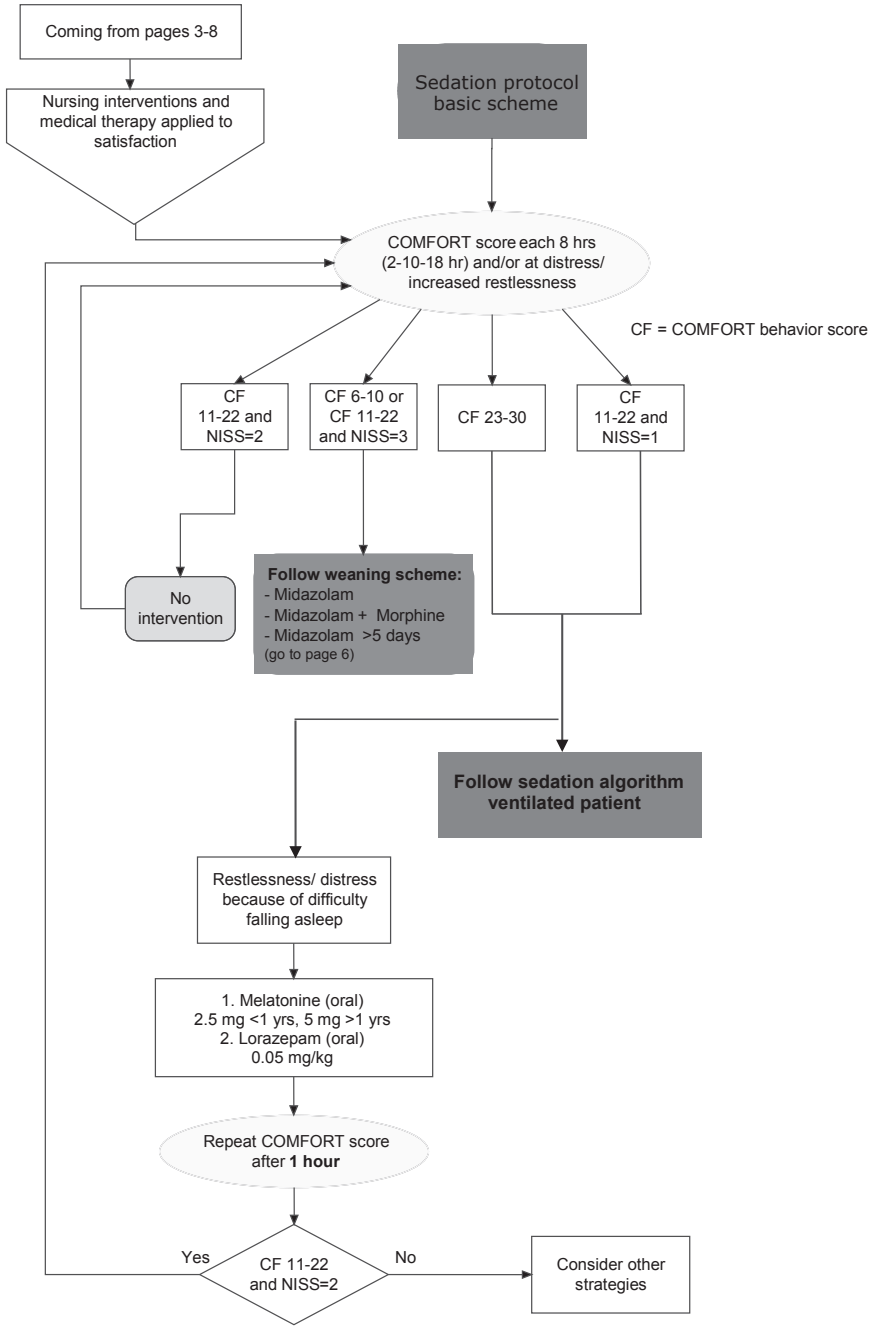
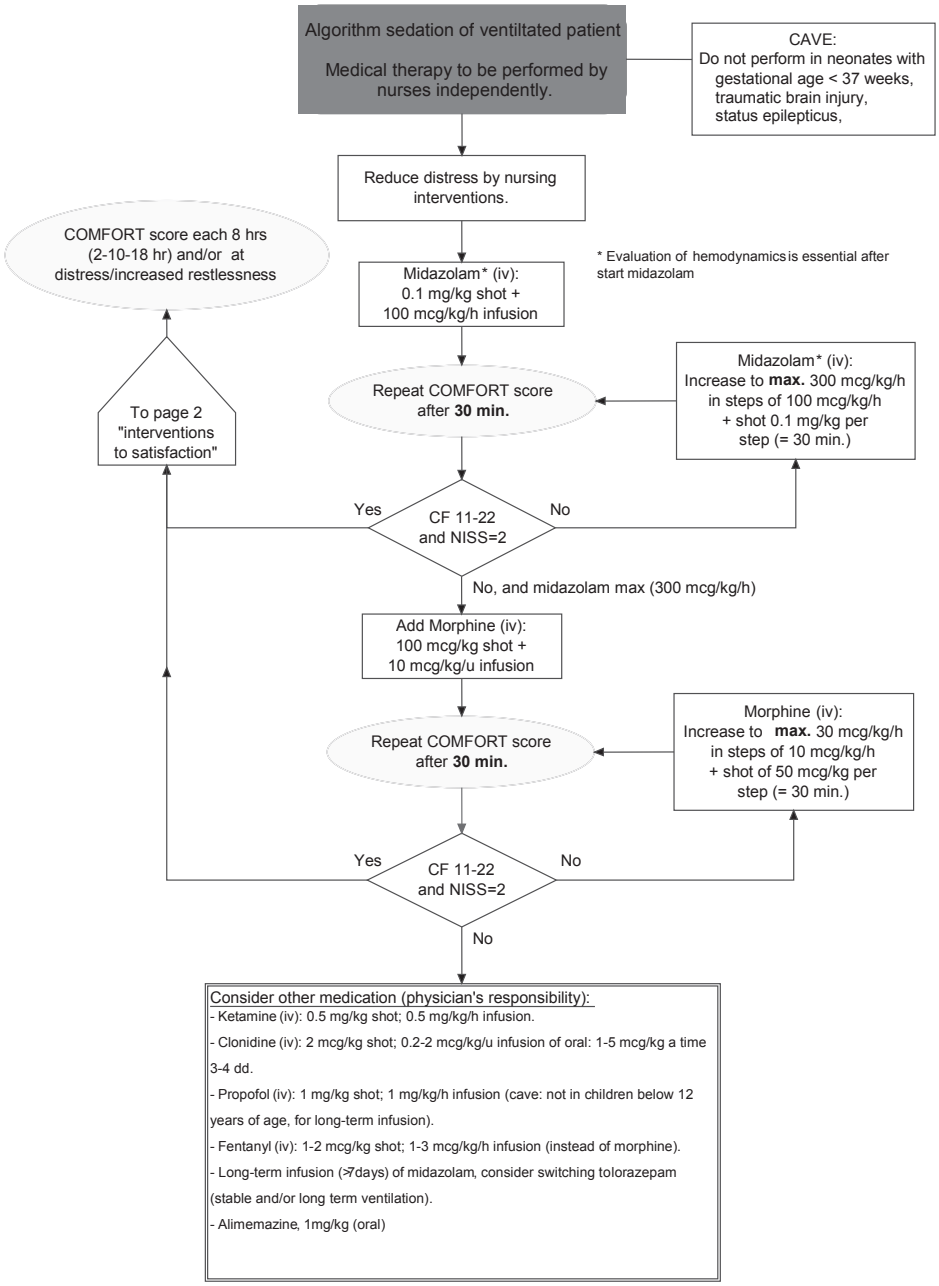
APPENDIX

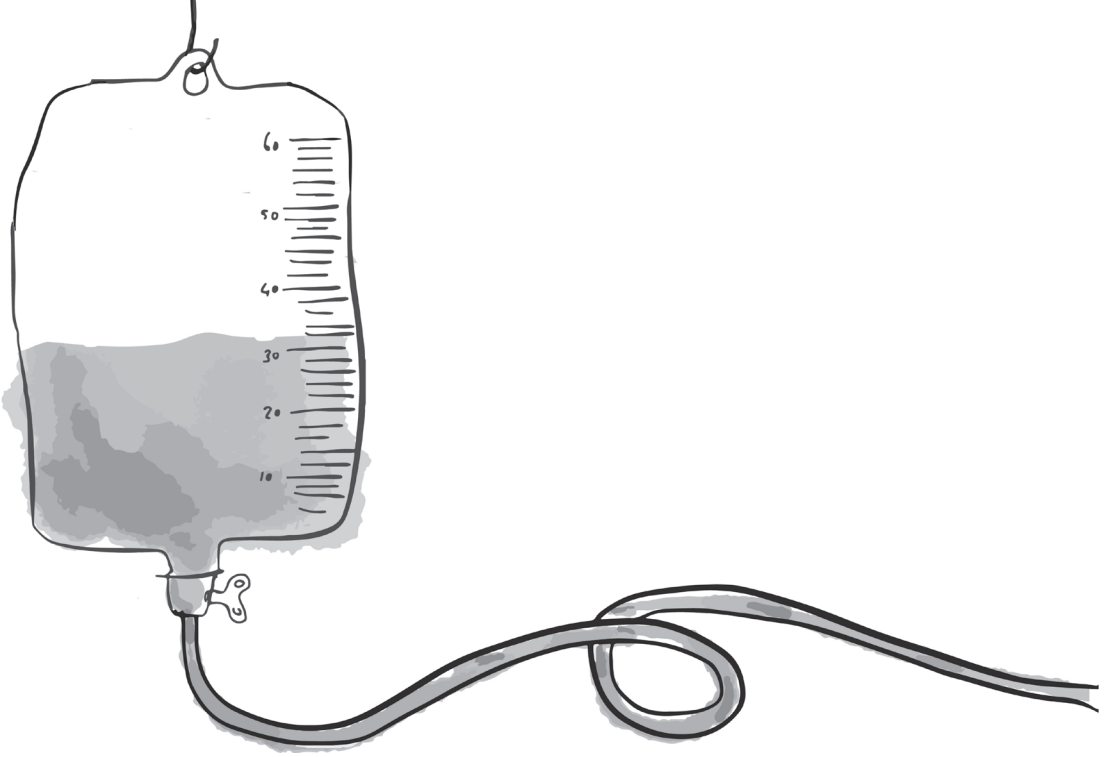
Sedation protocol



a. Sedation protocol, basic scheme



b. Sedation protocol, increasing decision tree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Chapter 7

A randomized controlled trial of daily sedation interruption in critically ill children

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Intensive Care Medicine 2016, 42(2):233-44

ABSTRACT

Purpose: To compare daily sedation interruption plus protocolized sedation (DSI+PS) to protocolized sedation only (PS) in critically ill children.

Methods: In this multicenter randomized controlled trial in three pediatric intensive care units in the Netherlands, mechanically ventilated critically ill children with need for sedative drugs were included. They were randomly assigned to either DSI+PS or PS only. Children in both study arms received sedation adjusted on the basis of validated sedation scores. Provided a safety screen was passed, children in the DSI+PS group received daily blinded infusions of saline; children in the PS group received blinded infusions of the previous sedatives/analgesics. If a patient's sedation score indicated distress, the blinded infusions were discontinued, a bolus dose of midazolam was given and the 'open' infusions were resumed: DSI+PS at half of infusion rate, PS at previous infusion rate. The primary endpoint was the number of ventilator-free days at day 28. Data were analyzed by intention to treat.

Results: From October 2009 to August 2014, 129 children were randomly assigned to DSI+PS (n=66) or PS (n=63). The study was terminated prematurely due to slow recruitment rates. Median number of ventilator-free days did not differ: DSI+PS 24.0 days (IQR 21.6-25.8) versus PS 24.0 days (IQR 20.6-26.0); median difference 0.02 days (95% CI -0.91 to 1.09), p=0.90. Median ICU and hospital length of stay were similar in both groups: DSI+PS 6.9 days (IQR 5.2-11.0) versus PS 7.4 days (IQR 5.3-12.8), p=0.47, and DSI+ PS 13.3 days (IQR 8.6-26.7) versus PS 15.7 days (IQR 9.3-33.2), p=0.19, respectively. Mortality at 30 days was higher in the DSI+PS group than in the PS group (6/66 versus 0/63, p=0.03), though no causal relation to the intervention could be established. Median cumulative midazolam dose did not differ: DSI+PS 14.1 mg/kg (IQR 7.6-22.6) versus PS 17.0 mg/kg (IQR 8.2-39.8), p=0.11.

Conclusion: In critically ill children, daily sedation interruption in addition to protocolized sedation did not improve clinical outcome and was associated with increased mortality compared with protocolized sedation only.

INTRODUCTION

Commonly, mechanically ventilated critically ill children are sedated to enhance their comfort and safety. Moreover, a state of sedation facilitates synchronization with mechanical ventilation and enables invasive procedures to be performed.
Although sedation is helpful in the care of critically ill children, it has numerous negative effects. Especially, oversedation should be avoided, as it is associated with longer duration of ventilation, longer hospital stay and adverse patient outcomes, such as withdrawal, delirium and long-term psychological morbidity in adults (1-4). In recent years, efforts have been made to improve sedation management in children, for example with the use of sedation algorithms and protocols (5-7). Nonetheless, optimal sedation remains challenging and oversedation is common in pediatric intensive care (8).
In adults, daily sedation interruption (DSI) was found to be an effective method of improving sedation management. Clinical trials have shown that DSI can reduce the duration of mechanical ventilation, hospital stay and amount of sedatives administered, without compromising patient comfort or safety (9). Several later studies have confirmed this beneficial effect (10), whereas other studies, in different settings, found no benefit (11, 12). For critically ill children, it is unknown if DSI will improve outcome. Two studies showed that DSI in children is feasible, but these studies were not sufficiently powered to detect differences in clinical outcomes (13, 14). In a recent study from India comparing DSI with continuous sedation in children, DSI led to improved clinical outcomes, including shorter durations of mechanical ventilation and ICU stay (15). However, given the differences in patient population and ICU practices between the Indian and the Western setting, these results need further verification (16). Furthermore, it is unknown if the combined use of DSI and protocolized sedation is beneficial in children, as this appears not the case in adults (11). We hypothesized that mechanically ventilated children managed with DSI combined with protocolized sedation have more ventilator-free days at day 28 than patients managed with protocolized sedation alone.

METHODS

Patients

We recruited patients from three tertiary medical-surgical PICUs in the Netherlands: Erasmus MC-Sophia Children's Hospital, Radboud University Nijmegen Medical Center and Academic Medical Center Amsterdam. Approval from each institutional review board and written informed consent from parents or legal representatives was obtained. The trial has been registered in the Dutch Trial Register (http://www.trialregister.nl/trialreg/index.asp), no. NTR2030.

Eligible patients were children between 0 and 18 years of age, and at least 37 weeks of postconceptual age, requiring mechanical ventilation with an expected duration of at least 48 hours and need for sedative drugs. Exclusion criteria were: anticipated death or withdrawal of life support within 48 hours; impossibility of assessing level of sedation due to an underlying neurologic condition; neurological, respiratory or cardiac instability that may not tolerate inadequate sedation; therapeutic hypothermia after cardiopulmonary resuscitation; difficult airway; fixed duration of mechanical ventilation (e.g., until planned operation); admission for ECMO; already having been ventilated/sedated for >2 days in a transferring PICU; and no informed consent.

Study design

The study design of this randomized controlled trial has previously been described in detail (17). In short, within 24 hours after intubation, informed consent was obtained and, the morning after enrollment, the patient was assigned to either DSI combined with protocolized sedation (DSI+PS group) or protocolized sedation only (PS group).

Randomization and blinding

Patients were randomly assigned in a 1:1 ratio to either DSI+PS or PS, using blocked randomization with stratification by center and age group (0-30 days, 30 days-2 years, and 2-18 years). An independent biostatistician carried out computer randomization in advance.

In both groups, the syringes containing sedatives/analgesics were replaced each morning with blinded syringes, provided a safety screen was passed. The pharmacist had access to group allocation to be able to prepare blinded infusions. In the DSI+PS group, the infusions were replaced with saline infusions, in the PS group, the infusions were replaced with blinded infusions containing the same sedative and analgesic drug concentrations. In this way, the caregiving nurse was blinded for group allocation, so as to minimize bias in assessing the sedation level. If a patient's sedation score indicated distress, the blinded infusions were discontinued, a bolus dose midazolam was given and the original 'open' infusions were restarted at 50% of the rate for the DSI+PS group and at the original rate for the PS group. This infusion rate was visible for the caregiving medical team. For restart of the 'open' infusions, the bedside nurse opened an envelope placed in the study binder at the patient's bedside to identify group allocation. The envelope was then closed again and returned to the study binder. This procedure was repeated on every study day. Effectively, only the first start of the blinded infusions resulted in a complete blinding of treatment for the medical team. After the first restart, they could be aware of the patient's allocation, if they deduced that the full or 50% resumption of the infusion rate the day before indicated group assignment. For safety reasons, complete blinding was deemed not to be feasible.

Protocolized sedation

All study centers used a standardized sedation protocol for adjustment of sedatives and analgesics, based on scores on validated instruments for this population (COMFORT behavior scale (COMFORT-B), Nurse Interpretation of Sedation Score (NISS), numeric rating scale (NRS)) (18, 19). All nurses had been trained to use these instruments. Inter-observer variability was satisfactory, with $\kappa > 0.65$ for all nurses. Adequate sedation was defined as a COMFORT-B score ≥11 and ≤22. A COMFORT-B score of <11 implied oversedation, a score >22 implied undersedation. Upon a patient's admission to the PICU, the need of sedation was assessed. If sedation was needed, midazolam was initiated and titrated up to a maximum of 300 µg/kg/h. When sedation was still considered insufficient, morphine (up to 30 µg/kg/h) was added to the midazolam treatment. If a patient remained distressed and sedation still seemed inadequate, other sedative drugs were added according to local standard practice (see Figure 1a, b).

Intervention group (DSI+PS)

After having been on mechanical ventilation for 24 hours, a patient was assessed for a safety screen daily at 1000 h, after routine care. A patient passed the screen unless he/she received a sedative infusion for active seizures, escalating sedative doses due to ongoing agitation, neuromuscular blockers, had evidence of increased intracranial pressure or in cases of cardiorespiratory instability as judged by the bedside clinician. Patients who did not pass the screen were reassessed after 24 hours. If the patient passed the screen, all sedative and opioid infusions were replaced with blinded infusions containing saline. Analgesics needed for active pain were continued (e.g., pleural drain, <24 hours after surgery). During blinded infusions, the patient was strictly monitored and comfort was assessed at least every 2 hours using the COMFORT-B and NRS scores or earlier if distress was apparent. The sedative and opioid infusions were restarted if the patient appeared uncomfortable or if this was deemed necessary in view of cardiorespiratory instability. After a loading dose of midazolam (0.1 mg/kg, intravenously), sedative infusions were restarted at half the previous dose and then titrated according to the sedation protocol to achieve adequate sedation (Figure 2).

Control group (PS)

In the control patients, following the safety screen, blinded infusions were started at the same infusion rate as the patient was receiving, containing the same medication, effectively continuing the sedation. Level of sedation was assessed in the same way as in the DSI+PS group. When assessments indicated distress, a loading dose of midazolam was given, and the blinded infusions were replaced with the sedative infusions at a similar rate as before the start of blinded infusions and subsequently titrated according to the sedation protocol to achieve adequate sedation.

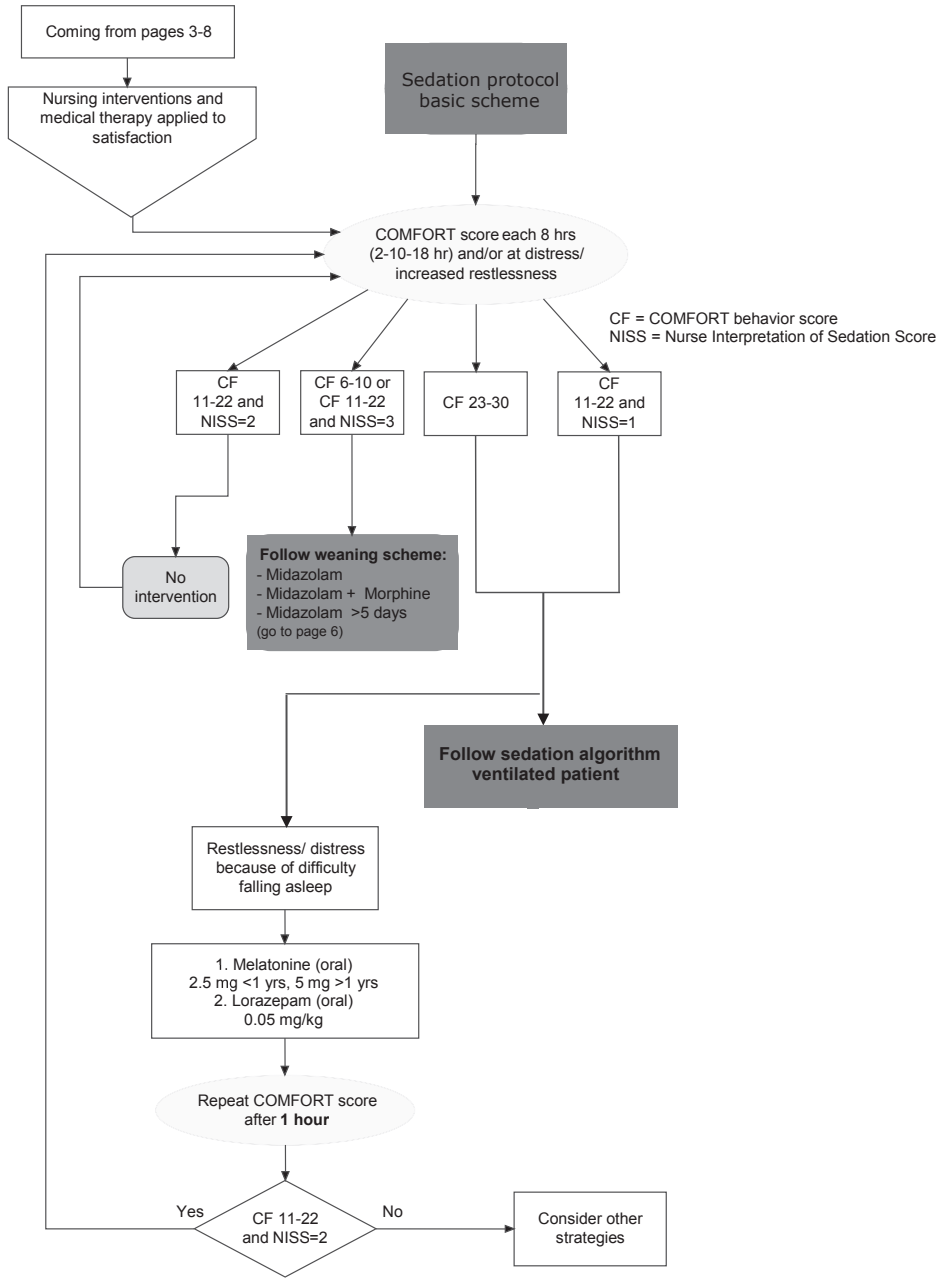

Figure 1a. Sedation protocol, basic scheme

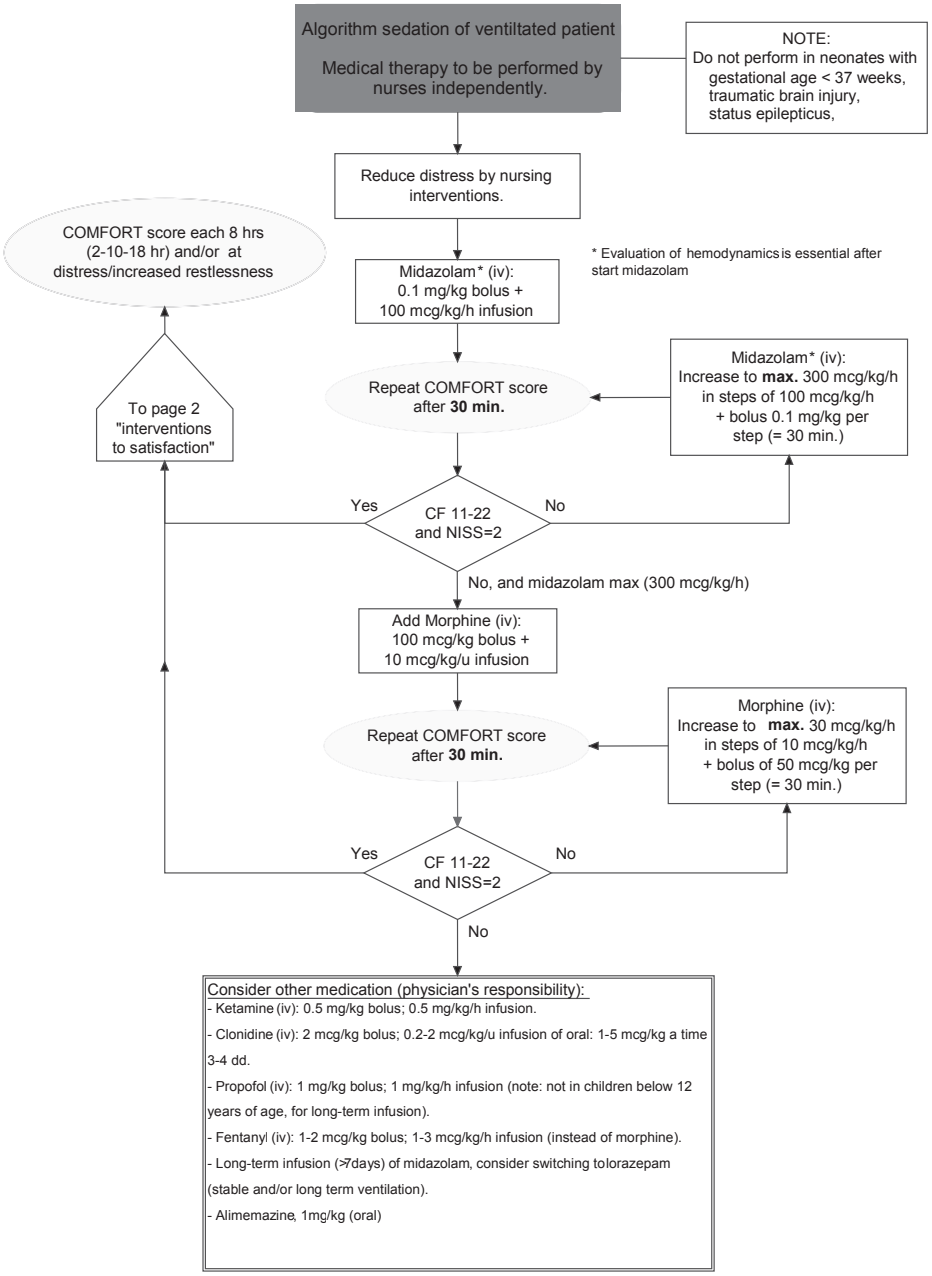

Figure 1b. Sedation protocol, increasing decision tree

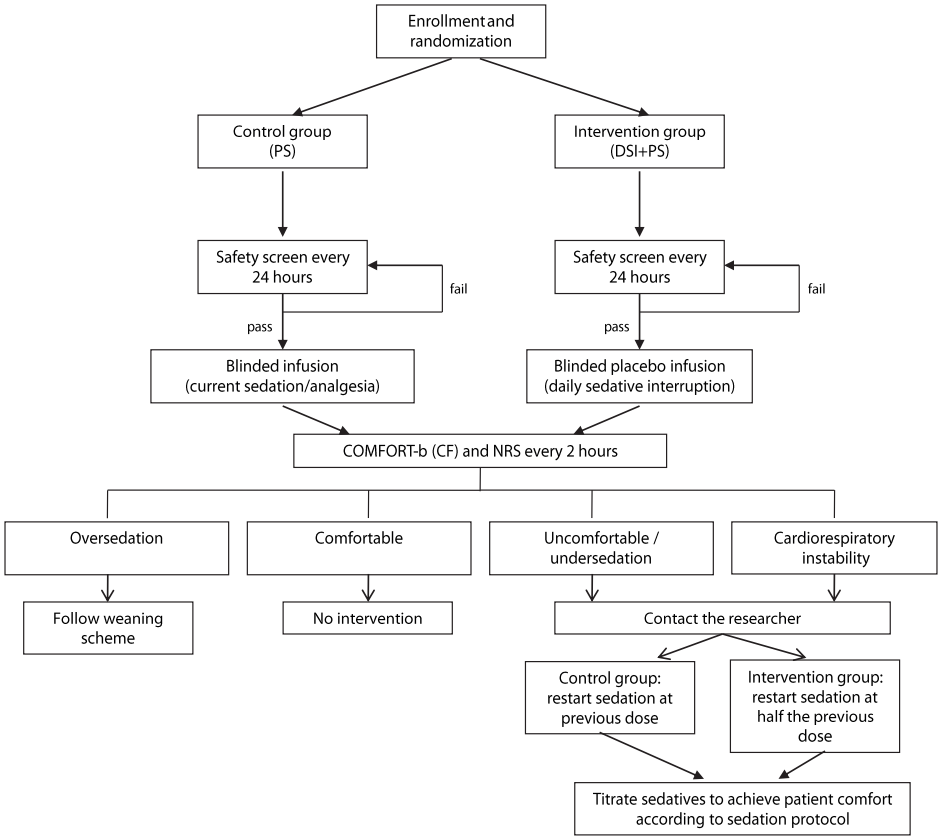

Figure 2. Flowchart of study design

Endpoints

The primary endpoint was the number of ventilator-free days at day 28, defined as the number of days a patient had breathed without mechanical ventilation for at least 48 hours continuously during a 28-day period after randomization. Patients who died during this 28-day period were assigned zero ventilator-free days.

Secondary outcomes included: length of stay in the ICU and hospital (days); 30-day mortality; total and median dose of midazolam and morphine (mg/kg); number of COMFORT-B scores <11 and >22; use of additional sedative drugs during ventilation; incidence of withdrawal symptoms (Sophia Observation withdrawal Symptoms (SOS) scale (20)); adverse events; total number of safety screen assessments; and number and reason for failure to pass.

Statistical analysis

The Erasmus MC institutional admission data for the year 2008 showed that 168 children were mechanically ventilated for at least 48 hours in our PICU with a mean number of

16.5 (SD 9.9) ventilator-free days. On this basis, including 100 patients per group would be sufficient to detect a clinically significant difference of 25% in ventilator-free days (i.e. mean 20.6 days in the DSI+PS group versus 16.5 days in the PS group), with a power of 80%, based on a Mann–Whitney test with a significance level of 5%.

Data were analyzed blinded, with an intention-to-treat approach. Descriptive data are presented as percentage, mean ± SD for normally distributed variables, and median ± IQR for non-normally distributed variables. Distribution of categorical variables between groups was compared with Fisher's exact tests; continuous variables with Mann–Whitney tests. The primary outcome was also compared between groups with correction for baseline variables (age, sex, Pediatric Logistic Organ Dysfunction (PELOD) score and type of disease), using robust multiple linear regression analysis to account for the non-normal distribution of the model residuals. Effects of treatment on length of stay in the ICU and hospital were assessed with time-to-event analysis, i.e. Kaplan-Meier analysis and log-rank test. These tests also served to assess the effect on 30-day mortality. Penalized Cox analysis was used to assess differences between the groups after adjustment for the baseline variables mentioned above. All statistical tests were two-tailed and the significance level was set at 0.05. Statistical analyses were performed using SPSS (v. 21) and R (v. 3.1.2) for robust regression analysis.

An interim analysis was not scheduled, but an independent data and safety monitoring board (DSMB) continuously evaluated possible adverse events.

RESULTS

Participants

Of 1059 eligible patients, 132 patients were included in the study between October 2009 and August 2014. Recruitment rates were lower than foreseen, and the study was terminated prematurely, before the recruitment of 200 patients. Three patients were excluded from the analysis because they were on mechanical ventilation for <48 hours or informed consent was withdrawn before the start of the study (Figure 3). Consequently, 129 children were analyzed, 66 in the DSI+PS group and 63 in the PS group.

Eight patients (12%) in the DSI+PS group discontinued the protocol. Three of those were placed on ECMO, two were withdrawn by the medical team (one because of clinical instability and one because deeper sedation was thought necessary), two patients were withdrawn by parents (concerned that their child was insufficiently sedated), and one patient was transferred to the neonatology ward. In the PS group, four patients (6%) discontinued the protocol. Two of those were placed on ECMO, one was withdrawn by the medical team (because of clinical instability), and one was withdrawn by the parents.

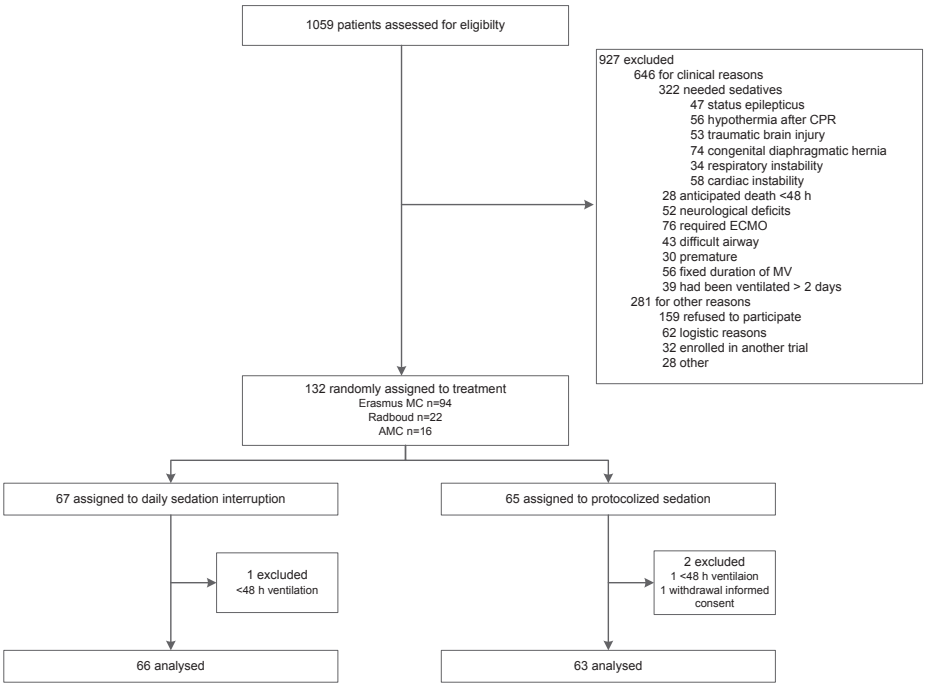

Figure 3. Flowchart of recruited patients

Baseline characteristics of the two groups were similar (Table 1). Most patients (67%) were admitted for a non-surgical condition such as respiratory disorders.

Main outcomes

Table 2 shows that the median number of ventilator-free days was 24.0 days in both groups (median difference 0.02 (95% CI -0.91 to 1.09), p=0.90). Adjustment for baseline variables gave similar results (mean difference 0.04 (95% CI -1.04 to 1.11), p=0.95). In the PS group, more re-intubations were needed (9 vs. 2, p=0.03). The number of accidental extubations was not different between groups (DSI+PS group n=1/66, PS group n=4/63, p=0.20). ICU and hospital length of stay did not differ significantly between the groups (Table 2).

Mortality at 30 days was significantly higher in the DSI+PS group (6 (9.1%) vs. 0 (0%), p=0.02 using log-rank test), also after adjustment for baseline variables. The DSMB reviewed the causes of mortality and could not determine a causal relation between intervention and outcome for these six deaths in the DSI+PS group. The intervals between last blinded infusion and death were 1, 7, 20, 23 and 27 days, while one patient did not receive blinded infusion at all. Three of these six patients were withdrawn prematurely from the study because of the start of ECMO. Two others died from ongoing sepsis with progressive deterioration and multiple organ failure, and one patient suffered from a pneumonia in aplasia with critical illness neuropathy.

Table 1. Baseline characteristics

	DSI+PS (n=66)	PS (n=63)
Age (months)	2.8 (1.1-17.1)	2.7 (1.3-14.0)
0 – 30 days (group A)	12 (18.2%)	11 (17.5%)
30 days – 2 years (group B)	40 (60.6%)	38 (60.3%)
2 years – 18 years (group C)	14 (21.2%)	14 (22.2%)
Gender (male/female)	38/28 (57.6/42.4%)	41/22 (65.1/34.9%)
Weight (kg)	5.0 (3.7-10.0)	4.6 (3.7-11.0)
PRISM II	16.5 (13-24)	16 (11-21)
Predicted mortality PIM 2 (%)	4.3 (1.6-10.0)	3.2 (1.5-7.6)
PELOD	11 (8-20)	11 (11-20)
Diagnosis on admission:		
Respiratory disorder[a]	47 (71.2%)	40 (63.5%)
Cardiac disorder[b]	3 (4.5%)	4 (6.3%)
Sepsis	7 (10.6%)	6 (9.5%)
Surgery		
Cardiac	7 (10.6%)	7 (11.1%)
Non-cardiac	1 (1.5%)	2 (3.2%)
Other	1 (1.5%)	4 (6.3%)
Sedation before randomization (mg/kg)[c]		
Midazolam	3.6 (2.4-5.7)	3.1 (2.4-5.2)
Morphine	0.25 (0.12-0.43)	0.35 (0.14-0.46)

Data are in median (IQR) or n (%); PRISM II=Pediatric Risk of Mortality; PIM 2=Pediatric Index of Mortality; PELOD=Pediatric Logistic Organ Dysfunction; [a] Viral/bacterial pneumonia, ARDS and asthma; [b] Congenital heart disease and cardiomyopathy; [c] Cumulative dose (infusion and bolus) in the first 24 hours after intubation

Sedative medication

Sedation profiles are presented in Table 3. As a reflection of the protocol, mean infusion rates were lower in patients treated with DSI+PS. However, cumulative dose was not different between the groups, as patients treated with DSI+PS received more boluses of midazolam (median cumulative midazolam dose (infusion+boluses) 14.1 mg/kg (IQR 7.6-22.6) vs. 17.0 mg/kg (IQR 8.2-39.8), p=0.11). Also, for the other sedative drugs, no significant difference was found in cumulative dose. Median number of days of exposure to midazolam and number of agents received were not different. The median duration of blinded infusions was 25.9 hours (IQR 10.1-48.8 h) in the DSI+PS group versus 41.4 hours (IQR 23.8-75.7 h) in the PS group, p=0.003. In nine patients in the DSI+PS group, there was no need to restart sedation after the first interruption. These patients were comfortable without sedation for a median of 48.5 hours (range 23.5-74.5 h) until extubation.

Table 2. Main study outcomes

	DSI+PS (n=66)	PS (n=63)	*p* value
Ventilator free days at 28 days (days)	24.0 (21.6-25.8)	24.0 (20.6-26.0)	0.90
Duration of mechanical ventilation (days)	5.1 (3.7-7.3)	5.2 (3.6-9.0)	0.71
Reintubation <24 h	2 (3.0%)	9 (14.3%)	0.03
Tracheostomy	1 (1.5%)	1 (1.6%)	1.00
Length of stay ICU (days)	6.9 (5.2-11.0)	7.4 (5.3-12.8)	0.47
Length of stay hospital (days)	13.3 (8.6-26.7)	15.7 (9.3-33.2)	0.19
30-day mortality	6 (9.1%)	0 (0%)	0.03
Adverse events:			
Self-extubations	1	4	0.20
of which requiring reintubation	0	2	0.24
Oversedation – flumazenil	0	1	0.49
Fixation (need for soft wrist restrainers)	1	0	1.00

Data are in median (IQR) or n (%)

Distress assessments

Median COMFORT-B scores were slightly lower in the PS group than the PS+DSI group, indicating that they were more deeply sedated (12 (IQR 10-14) vs. 12 (IQR 11-15), p=0.048) (Table 3). The median (IQR) number of assessments per subject was not different between groups. Univariate analysis revealed that 824 (24.3%) of the scores in the DSI+PS group indicated oversedation (COMFORT-B<11), versus 998 (25.4%) of the scores in the PS group (p=0.27). Undersedation (COMFORT-B>22) was more frequent in the DSI+PS group (3.2% (n=107) vs. 2.4% (n=93), p=0.04).

All patients were oversedated at some point during the study period, whereas 62 of 129 patients (n=34 patients in the DSI+PS group and 28 in the PS group) were undersedated at some point.

Median SOS scores were comparable between groups (Table 3). Total number of SOS assessments was significantly higher in the PS group (540 vs. 317 scores, p=0.001). In total, 25 patients had a SOS score of ≥4 during the study period (n=10 in DSI+PS group, n=15 in PS group, not significant), indicating withdrawal symptoms.

Safety screen

Two-thirds of all safety screens were passed, 198 (65.6%) of 302 in the DSI+PS group and 261 (73.7%) of 354 in the PS group. Agitation and cardiorespiratory instability were the main reasons for failing the safety screen (Table 4). Approximately 60% of the patients passed all safety screens performed (60.6% in DSI+PS group and 63.5% in PS group).

Table 3. Sedation profiles

	DSI+PS (n=66)	PS (n=63)	*p* value
Midazolam	n=66	n=63	
Cumulative dose infusion (mg/kg)	13.0 (6.9-22.3)	17.0 (8.1-39.8)	0.08
Mean infusion rate (mcg/kg/hr)	126 (59-185)	134 (90-221)	0.02
Cumulative dose bolus (mg/kg)	0.74 (0.24-1.21)	0.52 (0.20-1.19)	0.21
Total cumulative dose (mg/kg)	14.1 (7.6-22.6)	17.0 (8.2-39.8)	0.11
Number of exposure days	4.5 (3.4-6.7)	4.9 (2.8-8.7)	0.79
Morphine	n=54	n=52	
Cumulative dose infusion (mg/kg)	0.89 (0.5-1.4)	1.15 (0.6-2.8)	0.12
Mean infusion rate (mcg/kg/hr)	9.7 (6.3-13.0)	11.9 (10.0-16.4)	0.004
Cumulative dose bolus (mg/kg)	0.15 (0.06-0.36)	0.10 (0.02-0.14)	0.03
Total cumulative dose (mg/kg)	0.92 (0.60-1.56)	1.16 (0.65-2.86)	0.17
Clonidine	n=13	n=11	
Cumulative dose infusion (mcg/kg)	55.2 (15.8-95.1)	92.6 (43.2-208.3)	0.04
Mean infusion rate (mcg/kg/hr)	0.56 (0.42-0.92)	0.98 (0.66-1.52)	0.01
Cumulative dose bolus (mcg/kg)	4.08 (2.24-4.73)	6.43 (3.04-10.50)	0.15
Total cumulative dose (mcg/kg)	47.4 (8.0-86.7)	75.7 (41.2-204.8)	0.10
Ketamine	n=9	n=17	
Cumulative dose infusion (mg/kg)	15.3 (6.8-108.0)	35.8 (6.4-94.9)	0.85
Mean infusion rate (mg/kg/hr)	0.54 (0.27-1.14)	0.74 (0.30-0.97)	0.83
Cumulative dose bolus (mg/kg)	0.92 (0.50-1.89)	1.09 (0.50-3.48)	0.72
Total cumulative dose (mg/kg)	4.51 (0.52-26.20)	35.63 (3.11-56.17)	0.11
Fentanyl	n=34	n=28	
Cumulative dose (mcg/kg)	4.1 (2.1-12.3)	2.3 (1.2-7.9)	0.15
Propofol	n=24	n=29	
Cumulative dose (mg/kg)	6.5 (2.8-26.2)	10.8 (2.6-40.7)	0.57
Number of different sedatives received	2 (2-3)	2 (2-4)	0.31
Number of patients with >2 sedatives	24 (36.4%)	26 (41.3%)	0.57
COMFORT-B scale			
Total number of assessments	3389	3924	
Median number of assessments per patient	41 (28-59)	47 (26-76)	0.45
Median COMFORT-B score	12 (11-15)	12 (10-14)	0.048
Oversedation (COMFORT-B<11), n(%)	824 (24.3%)	998 (25.4%)	0.27
Undersedation (COMFORT-B>22), n(%)	107 (3.2%)	93 (2.4%)	0.04
SOS score			
Number of patients	19	20	
Total number of assessments	317	540	
Median number of assessments per patient	9 (3-21)	16.5 (9-39)	0.07
Median SOS	1.0 (0.5-2.0)	1.0 (1.0-2.8)	0.23
SOS ≥ 4, n(%)	32 (10.1%)	66 (12.2%)	0.35

Data are in median (IQR) or n (%); n= the number of patients receiving the drug

Table 4. Safety screen

	DSI+PS (n=66)	PS (n=63)
Median number of assessments per patient	4 (3-5)	4 (3-6)
Total number of assessments	302	354
Pass	198 (65.6%)	261 (73.7%)
Fail	69 (22.8%)	76 (21.5%)
No sedation	35 (11.6%)	17 (4.8%)
Reason for failure		
Active seizures	0 (0%)	3 (3.9%)
Ongoing agitation	24 (34.8%)	33 (43.4%)
Neuromuscular blockade	7 (10.1%)	24 (31.6%)
Increased ICP	0 (0%)	0 (0%)
Cardiorespiratory instability	38 (55.1%)	16 (21.1%)
No. of patients with		
0 fail	40 (60.6%)	40 (63.5%)
1 fail	10 (15.2%)	8 (12.7%)
2 fail	6 (9.1%)	8 (12.7%)
3 fail	3 (4.5%)	1 (1.6%)
4 fail	3 (4.5%)	2 (3.2%)
5 fail	3 (4.5%)	2 (3.2%)
>5 fail	1 (1.5%)	2 (3.2%)

Data are in median (IQR) or n (%)

DISCUSSION

This multicenter randomized controlled trial showed no difference in ventilator-free days and ICU or hospital length of stay for children treated with daily interruption of sedation combined with protocolized sedation compared with children receiving protocolized sedation alone. Additionally, DSI+PS was not associated with the administration of less sedative drugs compared with the use of PS.

These findings contradict those of two earlier studies on DSI in children, in both of which DSI was associated with shorter durations of mechanical ventilation, shorter ICU stays and less use of sedatives (13, 15).

This discrepancy can perhaps be explained as follows. First, we compared DSI in the setting of a protocolized sedation strategy for all patients, the latter being standard of care in the participating PICUs. A nurse-driven sedation protocol is assumed to be beneficial to minimize sedation, although this was recently questioned in a study in critically ill children (6, 21). The effect of protocolized sedation itself on the clinical endpoints might have outweighed the effect of DSI. This is in line with an adult study in which DSI offered

no benefit over a nurse-driven protocol already targeting light sedation (11). Also, the previous pediatric pilot study used no sedation protocol and patients in the control group were deeply sedated (13), which could explain the beneficial effect of DSI.
Second, there are important differences between the present study and that of Gupta and colleagues which could explain the different study outcomes (15). In the latter, around 70% of the patients had neurological illnesses, while we did not include patients with neurological problems. Moreover, mean duration of mechanical ventilation was 10.3 days in the continuous group, versus 5.2 days in our population. Lastly, the daily dose of midazolam was almost twice that in the present study (mean 11.0 vs. 6.1. mg/kg/day in the control groups and mean 7.1 vs. 4.4 mg/kg/day in the DSI groups).

In the present study, cumulative drug doses did not significantly differ between the two groups. The need for intermittent bolus administration in the DSI+PS group counterbalanced the reduction in continuous sedation. However, in nine patients in the DSI+PS group, there was no need to restart sedation. It seems that there are two groups of patients: 1) patients who may not need sedation at all and 2) patients who become agitated after sedation interruption and even need more (bolus) medication to become comfortable again. Therefore, a continuous critical appraisal of the need to continue sedation is warranted. Active tapering of sedation is still needed as this may improve outcome, in particular in the first group.

More reintubations were needed in the PS group. Patients in the DSI+PS group were possibly more alert and therefore extubation may have been more successful, as also demonstrated in adult DSI studies (10). Overall, around a quarter of the distress assessments indicated oversedation. This is somewhat lower than described in the literature (8), possibly due to the use of a sedation protocol. Judging from the higher number of SOS assessments in the PS group, these patients showed more clinical withdrawal symptoms, although no statistically significant difference was found in the number of scores ≥4, sedative drug doses, and length of exposure to midazolam between the two groups.

This study shows that DSI in children is feasible. Around 60% of patients passed all safety screens, and DSI was not related to more adverse events, in line with earlier studies. However, the higher mortality in the first 30 days in the DSI+PS group (9.1%) compared to the control group was totally unexpected, as also was the absence of mortality in the control group (0%). Reassuringly, overall 30-day mortality in our total patient cohort (6/129; 4.6%) was not higher than the reported ICU mortality in the Netherlands (22). Moreover, an independent DSMB could not identify a causal relationship between the study intervention and cause of death for individual patients. All six patients were

seriously ill, with a high mortality risk in advance. Furthermore, the timeframe between active participation in the study and death makes a causal relation unlikely.
In previously published DSI studies, mortality was never increased. In adult studies, reported ICU mortality was 29.8% in the DSI group and 31% in the usual care group (RR 0.96, 0.77-1.21) (23). Pooled adult data also demonstrated no difference in overall mortality (RR 0.88, 0.75-1.05) and 28-day mortality (RR 0.82, 0.5-1.12) between DSI and control groups (23). In children, Gupta reported a mortality of 26.1% in the DSI group and 26.8% in the control group (15). Both percentages are higher than our reported mortality due to a different ICU setting and different population, but mortality was not increased in DSI patients. In the pediatric pilot study, all patients survived until PICU discharge (13). We could not establish a theoretical framework explaining the increased mortality found in our study. Considering all this, and given that meta-analyses of trials had not previously identified an adverse mortality risk with DSI, it is highly unlikely that there is a relationship with DSI. Nevertheless, while our finding may be due to a type I error, we cannot exclude that the increased mortality in our study is due to an unexpected impact of the study protocol.

A limitation of our study is the smaller-than-planned sample size. The planned inclusion of 200 patients was not reached due to slow recruitment rates. The number of eligible patients was lower than expected and around 50% of parents declined to provide consent (24). The reasons for these refusals were not recorded, but it is not unreasonable to assume that these parents found the concept of discontinuing drugs given to promote comfort not acceptable, as also suggested in an adult DSI trial with the same consent rate (25). It would probably take another 2.5 years to finish recruitment of all planned 200 patients. This timeframe was deemed not feasible by the study group, and at this point it was decided to stop the study. The decision was not influenced by interim results as data were still blinded at the time of the decision. Still, we believe our results are valuable. A post hoc power analysis resulted in a power of 62% with 129 patients, although the expected mean number of ventilator-free days in the sample size calculation was lower than observed in the study, likely due to the selection of relatively more stable patients. Since we did not even find a trend in the number ventilator-free days or the length of stay between both groups, it is unlikely that we would find a clinically meaningful difference with 200 patients. Furthermore, this study can provide useful data to assist others who might be planning a trial or performing a meta-analysis. Another consideration of the study is that, in the DSI+PS group, 22.8% of the safety screens were not passed, and for that day sedation was not interrupted. This could have diminished the differences between the two groups. However, this reflects clinical practice and is comparable with adult DSI studies (11). Furthermore, there may be a Hawthorne effect in the control group (26), as sedation practice was closely monitored in both groups

possibly leading to a better adherence to the sedation protocol. A strength of this study is the multicenter design. This reflects actual practice in different PICUs and enhances the generalizability of these findings.

CONCLUSIONS

Based on this multicenter study, there is no beneficial effect of daily sedation interruption in addition to protocolized sedation for critically ill children. Daily sedation interruption did not reduce the duration of mechanical ventilation, the length of stay, or the amounts of sedative drugs administered, but was associated with a higher 30-day mortality. Therefore, daily sedation interruption is not the sedation strategy of choice in critically ill children provided protocolized sedation is implemented in the pediatric intensive care.

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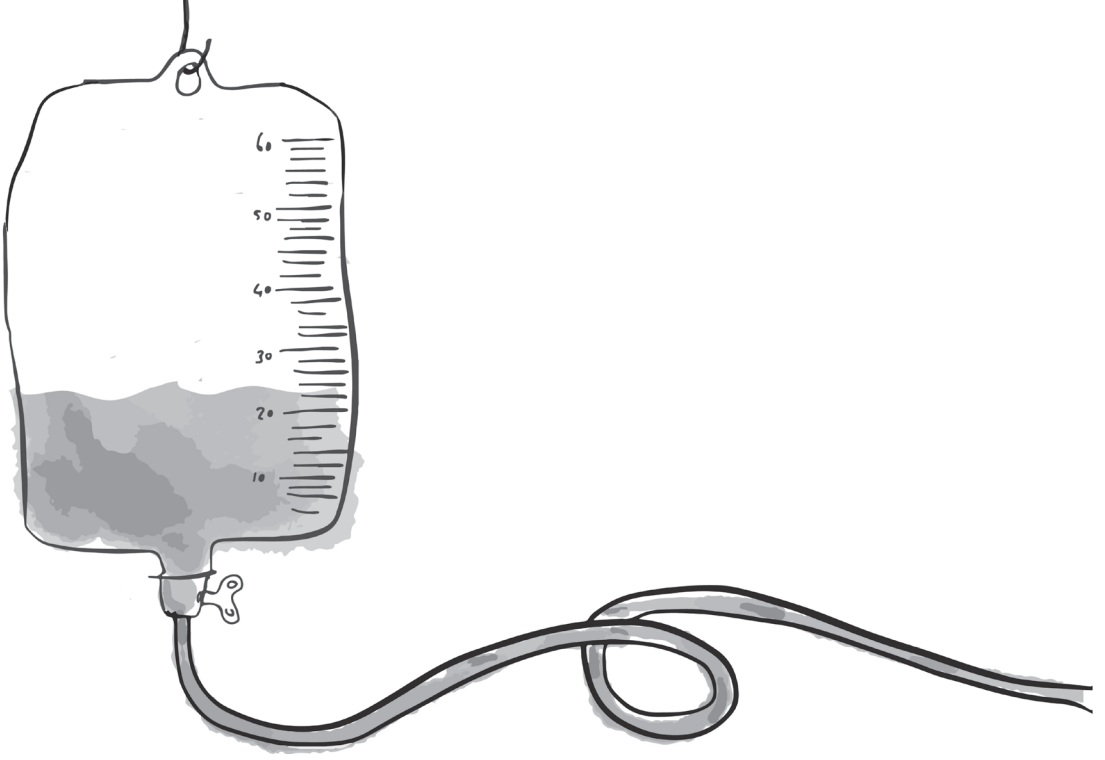
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Chapter 8

Short-term health-related quality of life of critically ill children following daily sedation interruption

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ABSTRACT

Objective: Our earlier pediatric daily sedation interruption (DSI) trial showed that DSI in addition to protocolized sedation (PS) in critically ill children does not reduce duration of mechanical ventilation, length of stay or amounts of sedative drugs administered as compared with protocolized sedation only, but undersedation was more frequent in the DSI+PS group. We now report the preplanned analysis comparing short-term health-related quality of life (HR-QoL) and posttraumatic stress symptoms between the two groups.

Design: Preplanned prospective part of a randomized controlled trial.

Setting: Two tertiary medical-surgical pediatric intensive care units in the Netherlands.

Patients: Critically ill children requiring mechanical ventilation.

Interventions: None.

Measurements and main results: Eight weeks after a child's discharge from the pediatric intensive care unit, HR-QoL was assessed with the validated Child Health Questionnaire and, only for children above 4 years of age, posttraumatic stress was assessed with the Dutch Children's Responses to Trauma Inventory. Additionally, HR-QoL of all study patients was compared with Dutch normative data. Of the 113 patients from two participating centers in the original study, 96 patients were eligible for follow-up and 64 patients were included (response rate 67%). No difference was found with respect to HR-QoL between the two study groups. None of the eight children >4 years showed posttraumatic stress symptoms.

Conclusions: DSI in addition to protocolized sedation for critically ill children did not seem to have an effect on short-term HR-QoL. Also in view of the earlier found absence of effect on clinical outcome, we cannot recommend the use of DSI+PS.

INTRODUCTION

Critically ill children admitted to a pediatric intensive care unit (PICU) and who are mechanically ventilated often receive sedative drugs to ensure their comfort. It is common practice in many PICUs to moderately or heavily sedate children (1). There is a tendency to avoid undersedation, not only because this may lead to discomfort and potential adverse effects such as self-extubation, but also the children, especially pre-verbal infants, otherwise may be bewildered by what is happening to them. Moreover, concerns have been raised that remembering such experiences may lead to adverse psychological outcome (2). A study from the UK found that almost one-third of children reported delusional memories three months after discharge from a PICU (3). Delusional memories were positively associated with post-traumatic stress symptoms, but the suggestion that coexistence of factual memory might be protective psychologically was not confirmed. In addition, this study showed an association between duration of sedation and the presence of delusional memory, which association has also been reported in adults (4, 5).

Recently we conducted a multicenter randomized controlled trial to study the efficacy and safety of daily sedation interruption combined with protocolized sedation (DSI+PS) compared to protocolized sedation (PS) in mechanically ventilated critically ill children. Our primary hypothesis was that children treated with DSI+PS would show an improved clinical outcome during PICU stay, an improved short-term health-related quality of life (HR-QoL) and less post-traumatic stress 8 weeks after PICU discharge. Nevertheless, as the trial found no differences in duration of mechanical ventilation, length of PICU stay and amounts of sedative drugs administered between the DSI+PS group and the PS group the hypothesis had to be rejected regarding the clinical outcome. However, undersedation was more frequent in the DSI+PS group (3.2% (107 of the 3389 scores) vs. 2.4% (93 of the 3924 scores), p=0.04). Children treated with DSI+PS had more fluctuation in level of sedation, while children in the PS group had a smoother course of sedation with the same amount of sedatives. We now report the preplanned analysis comparing short-term HR-QoL and posttraumatic stress symptoms between the two groups, also in relation to Dutch normative data.

MATERIALS AND METHODS

Setting and patients

In this preplanned prospective part of the randomized controlled trial referred to above, we assessed HR-QoL and post-traumatic stress disorder (PTSD) symptoms 8 weeks after PICU discharge (6).

For this study, patients from only two of the three participating tertiary medical-surgical PICUs in the Netherlands were enrolled: Erasmus MC-Sophia Children's Hospital and Radboud University Nijmegen Medical Center. Patients enrolled at Academic Medical Center Amsterdam were excluded as this center has a different follow-up program. Approval from each institutional review board and written informed consent from parents or legal representatives had already been obtained in the context of the original trial.
The following inclusion criteria applied to the original trial: age between 0 and 18 years; at least 37 weeks of postconceptual age; requiring mechanical ventilation with an expected duration of at least 48 hours and need for sedative drugs. The following exclusion criteria were applied: anticipated death or withdrawal of life support within 48 hours; impossibility of assessing level of sedation due to an underlying neurologic condition; neurological, respiratory or cardiac instability that may not tolerate inadequate sedation; therapeutic hypothermia after cardiopulmonary resuscitation; difficult airway; fixed duration of mechanical ventilation, admission for ECMO; already having been ventilated/sedated for >2 days in a transferring PICU. In addition, those with insufficient command of the Dutch language were excluded for this substudy.

Intervention

A detailed description of the study design is provided elsewhere (6). In brief, patients were randomized to DSI+PS or PS only. Throughout the study, patients in both treatment groups were managed with protocolized sedation. All study centers used a standardized sedation protocol for adjustment of sedatives and analgesics to achieve adequate sedation based on the scores on a validated assessment instrument (COMFORT behavior scale (7)). Midazolam and morphine were initiated sequentially and titrated first; other sedatives were added if sedation was still inadequate.

Intervention group (DSI+PS)

After having been on mechanical ventilation for 24 hours, a patient was assessed each morning for a safety screen. If the patient passed the screen, the sedative/analgesic infusions were discontinued, either immediately or later after planned procedures had been performed, and replaced by a blinded saline infusion at the same pump rate. Analgesics needed for active pain control were continued. During interruption, patients were strictly monitored and comfort was assessed at least every 2 hours or earlier if distress was apparent. The sedative infusion was restarted if the patient became uncomfortable or if deemed necessary by the clinical team in view of cardiorespiratory instability. After a loading dose of midazolam (0.1 mg/kg, intravenously), sedative infusion was restarted at half the previous dose and then titrated according to the sedation protocol to achieve adequate sedation.

Control group (PS)

In the control patients, following the safety screen, blinded midazolam and where applicable other analgesic/sedative infusions were started at the same rate as the patient was receiving. Level of sedation was assessed in the same way as in the DSI+PS group. When assessments indicated distress, the blinded infusion was replaced by the sedative infusion at a similar rate as before the interruption.

Outcome assessment

Health-related quality of life

HR-QoL was assessed with the validated Child Health Questionnaire (CHQ) (8, 9). The CHQ is a generic health profile measure covering physical and psychosocial domains that refer to perceived health status for the collective 4 weeks prior to completing the questionnaire. Designed specifically for children, it includes valuable domains like behavior and the effect of the child's health on parents. Its structure and methodological approach are similar to those of the SF-36, the most used HR-QoL measure in adults (10). The CHQ-IT97 (0-3 years) and CHQ-PF50 (4-17 years) were filled out by parents about their child, and the CHQ-CF87 (12-17 years) was filled out by children about themselves (8, 11, 12).

We assessed HR-QoL baseline status at study enrollment, and next 8 weeks after PICU discharge. Before discharge we told the parents that they would receive the HR-QoL questionnaires by regular mail in 8 weeks and invited them to complete these at home and return them by pre-paid envelope. The choice of respondent (mother, father or together) was left to the parents themselves. If the questionnaires were not returned within 3 weeks, we called the parents to inform whether they had received the questionnaires and if yes, kindly asked them to return them. If it appeared that parents had not received the questionnaire, we resent the questionnaire.

We compared HR-QoL of all study patients with normative data. Normative data were derived from representative samples of the general Dutch population (8, 11, 13).

Posttraumatic stress

Post-traumatic stress at 8 weeks after discharge was measured with the validated 34-item questionnaire Dutch Children's Responses to Trauma Inventory (CRTI), filled out by parents of children aged 4-18 years and by children aged 8-18 years themselves (14). We sent the CRTI questionnaire together with the HR-QoL questionnaire. The questionnaire covers 3 subscales (intrusion, avoidance, hyperarousal) according to the diagnostic DSM-IV symptoms of PTSD and one subscale for other child-specific reactions. The items are rated on a five-point scale. The total score, which can range from 34 to 170, can be used as an overall index of a child's stress reaction following a stressful event. Total scores between 92 and 105 indicate subclinical PTSD possibly requiring professional

support); scores of 106 and higher indicate severe symptoms that can possibly fulfil the criteria for PTSD. Psychometric properties of the questionnaire proved to be satisfactory in a sample of Dutch groups of children after violence and disaster (15). The internal consistency (Cronbach's alpha) was good (0.92). Convergent validity was high; the CRTI correlated strongly with the Children's Impact of Event Scale (CRIES) (r=0.77) (15).

Interview by telephone

Families who returned questionnaires were contacted by phone and asked to participate in a telephone interview with one of the investigators. This interview was in a semi-structured format using a standard questionnaire on health consequences in the weeks after PICU discharge. It included a total of 16 questions on healthcare consumption, current physical and behavioral functioning (such as fatigue, headache, pain, and sleep disturbances), and daily activities. Severity of complaints was scored on a 5-point scale (very mild to very severe).

Socioeconomic status

Socioeconomic status (SES) was categorized as "low" (elementary occupations), "middle" ('middle' occupations), or "high" ('highest' professional occupations) (16). SES was calculated based on a combined status score of the Netherlands Institute for Social Research based on home address (17). The latter score consists of average income in neighborhood, percentage of people with low income, percentage of less educated people, and percentage of people not working. A status score of 0 (±1.16 SD) was classified middle SES, <-1.16 was classified low SES, and >+1.16 was classified high SES.

Statistical analysis

A separate power analysis for this substudy was not performed. The sample size was calculated from the study's primary outcome, the number of ventilator-free days (6). Data were analyzed with an intention-to-treat approach; patients with follow-up data were analyzed in the group to which they were randomized.

Categorical data are presented as number and percentage and continuous data as median ± IQR.

The distribution of categorical variables between groups was compared with Fisher's exact test; continuous variables with Mann–Whitney tests.

Normality of the data was examined with the Kolmogorov-Smirnov test. In case of normal distribution, the HR-QoL data were compared with normative data using a one-sample t-test. A one-sample Wilcoxon signed-rank test was used for non-normally distributed HR-QoL data. Effect sizes were reported with Cohen's d (18). Baseline and post PICU discharge HR-QoL was compared using a paired Wilcoxon signed-rank test.

Statistical significance was considered with 2-tailed *p* values of <0.05. All analyses were performed in SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Patient sample

Of the 113 patients enrolled in the original trial from the two participating PICUs in this substudy, 96 patients were eligible for follow-up (44 in the DSI+PS group and 52 in the PS group) (Figure 1). Thirty-two patients did not participate: 31 patients did not return the questionnaires (reason unknown) and the parents of one patient withdrew consent. In total, 64 families returned the questionnaires (32 patients in both groups). The overall response rate was 67% (64/96). Participants and non-participants did not differ (Supplemental Table 1).

Baseline and in-hospital characteristics of the study groups are presented in Table 1.

The median follow-up interval after PICU discharge did not differ between the two groups (62 days (IQR 47-105) in the DSI+PS group vs. 58 days (IQR 47-90) in the PS group, *p*=0.71).

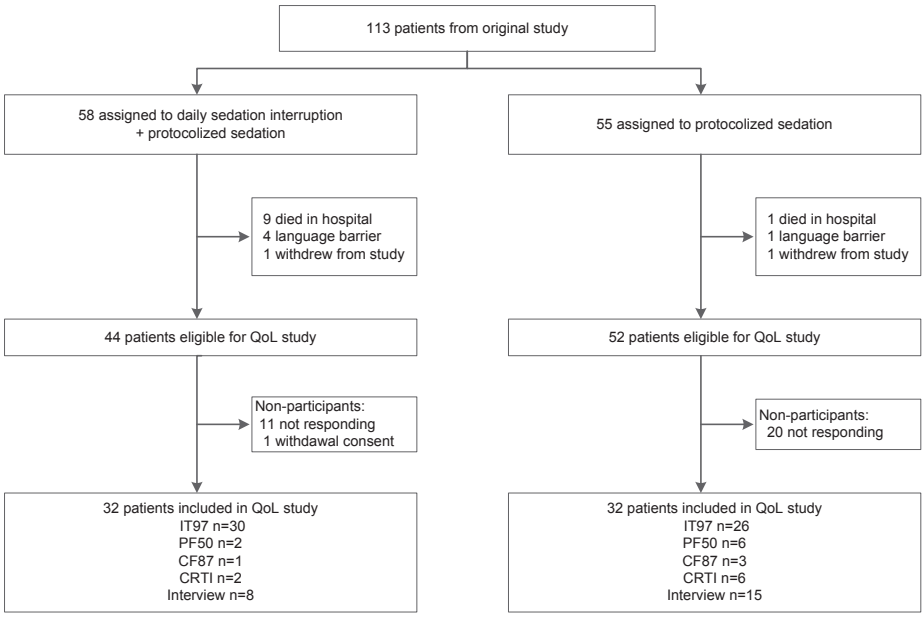

Figure 1. Flowchart of recruited patients

Table 1. Baseline and in-hospital characteristics

	DSI+PS (n=32)	PS (n=32)	*p* value
Age (months)	1.8 (0.9-5.0)	3.1 (1.3-22.7)	0.14
0 – 30 days (group A)	8 (25.0%)	4 (12.5%)	
30 days – 2 years (group B)	21 (65.6%)	20 (62.5%)	0.20
2 years – 18 years (group C)	3 (9.4%)	8 (25.0%)	
Gender (male/female)	18/14 (56/44%)	18/14 (56/44%)	1.00
PRISM II	16 (14-23)	19 (12-23)	0.83
Predicted mortality PIM 2 (%)	2.6 (1.5-6.3)	4.5 (2.1-8.8)	0.10
PELOD	11 (1-13)	12 (11-21)	0.03
Diagnosis on admission:			
Respiratory*	22 (68.8%)	18 (56.3%)	
Cardiac**	2 (6.3%)	2 (6.3%)	
Sepsis	1 (3.1%)	4 (12.5%)	
Surgery			0.83
Cardiac	5 (15.6%)	6 (18.8%)	
Non-cardiac	1 (3.1%)	1 (3.1%)	
Other	1 (3.1%)	1 (3.1%)	
Duration of mechanical ventilation (days)	4.5 (3.6-5.6)	4.8 (3.4-10.0)	0.55
Length of stay PICU (days)	6.5 (5.1-9.1)	7.5 (5.4-17.3)	0.19
Length of stay hospital (days)	12.2 (8.9-17.1)	19.3 (12.1-37.2)	0.01
Sedative exposure			
Midazolam	n=32	n=32	
Cumulative dose infusion (mg/kg)	12.9 (7.6-20.5)	15.1 (6.4-40.1)	0.23
Cumulative dose bolus (mg/kg)	0.68 (0.23-0.92)	0.40 (0.18-0.97)	0.38
Total cumulative dose (mg/kg)	13.7 (7.8-21.5)	15.8 (6.5-40.3)	0.23
Morphine	n=26	n=25	
Cumulative dose infusion (mg/kg)	0.77 (0.56-1.4)	1.2 (0.64-3.2)	0.21
Cumulative dose bolus (mg/kg)	0.15 (0.08-0.33)	0.12 (0.02-0.28)	0.54
Total cumulative dose (mg/kg)	0.86 (0.63-1.40)	1.17 (0.65-3.24)	0.27
COMFORT-B scale			
Total number of assessments	1559	2170	
Median number of assessments per patient	43 (29-60)	44 (26-93)	0.62
Oversedation (COMFORT-B<11), n(%)	325 (20.8%)	554 (25.5%)	0.001
Undersedation (COMFORT-B>22), n(%)	71 (4.6%)	44 (2.0%)	<0.001

Data are in median (IQR) or n (%); PRISM II=Pediatric Risk of Mortality; PIM 2=Pediatric Index of Mortality; PELOD=Pediatric Logistic Organ Dysfunction; * viral/bacterial pneumonia, ARDS and asthma; ** congenital heart disease and cardiomyopathy

Health-related quality of life

Fifty-six parents completed the CHQ-IT97 for children 0-3 years (30 in the DSI+PS group and 26 in the PS group). Eight parents completed the CHQ-PF50 for children 4-17 years (2 in the DSI+PS group and 6 in the PS group) and 4 children (between 12 and 18 years) the CHQ-CF87 (1 in the DSI+PS group and 3 in the PS group).

HR-QoL in the age group 0-3 years did not differ between the two study groups (Table 2). The older age groups were too small to compare the CHQ-PF50 and CHQ-CF87 results by study group. Overall, the HR-QoL scores were below the Dutch normative scores, indicating poorer quality of life (Table 3). Parent-reported HR-QoL scores were significantly lower with large effect sizes on physical functioning, growth and development, general health perceptions, and parental impact (time), The general behavior scores were significantly higher than the normative scores (p=0.02). Self-report scores on the CHQ-CF87 (children 12-17 years; n=4) were similar to the normative scores (Table 3).

Eighteen parents (11 in the DSI+PS group and 7 in the PS group) completed the CHQ-IT97 for children 0-3 years at baseline and after discharge. Subanalysis showed that only parental impact (emotional) was significantly higher after discharge (p=0.003) (Table 4).

Posttraumatic stress

The CRTI was completed for 8 of the 11 eligible patients above 4 years of age (73%, 2 in the DSI+PS group and 6 in the PS group); seven parents and four children completed the CRTI. Overall, the scores were low (median 60; range 36-78). None of the scores exceeded 92 indicating PTSD. Due to the small numbers, we did not compare the study groups.

Table 2. Health-related quality of life post discharge

	DSI+PS	PS	*p* value
Child Health Questionnaire – Infant Toddler 97 (0-3 yr)	n=30	n=26	
Physical functioning	86.1 (65.3-100.0)	86.7 (73.8-100.0)	0.76
Growth and development	75.0 (70.0-82.5)	75.0 (62.5-85.0)	0.66
Bodily pain/discomfort	75.0 (50.0-83.3)	83.3 (66.7-100.0)	0.10
Temperament and moods	72.2 (58.0-79.9)	76.4 (66.0-87.5)	0.12
General behavior (n=4/3)	81.2 (75.3-94.2)	89.2 (77.7-..)	1.00
Getting along (n=4/3)	77.5 (72.1-81.7)	71.7 (70.0-..)	0.63
General health perceptions	44.6 (36.3-61.3)	46.7 (21.7-67.5)	0.58
Parental impact: emotional	89.3 (72.3-95.5)	92.9 (79.5-100.0)	0.11
Parental impact: time	83.3 (71.4-94.0)	85.7 (76.2-95.2)	0.62
Family cohesion	85.0 (60.0-100.0)	85.0 (60.0-96.3)	0.84
Change in health	75.0 (43.8-100.0)	87.5 (56.3-100.0)	0.42

Data are in median (IQR)
Low scores imply worse functioning

Table 3. Health-related quality of life post discharge, compared to normative data

	Study patients	Norm	*p* value	Cohen's d
Child Health Questionnaire – Infant Toddler 97 (0-3 yr)	n=56	n=410		
Physical functioning (PF)	80.7 (21.5)	97.2 (9.8)	**<0.001**	**1.40**
Growth and development (GD)	74.9 (15.2)	86.5 (10.6)	**<0.001**	**1.03**
Bodily pain/discomfort (BP)	73.2 (23.2)	83.8 (16.8)	**0.002**	0.60
Temperament and moods (TM)	72.9 (14.1)	77.2 (10.5)	**0.037**	0.39
General behavior (GB)	84.8 (8.7)	72.8 (12.7)	**0.018**	**0.98**
Getting along (GA)	76.4 (6.1)	71.4 (8.8)	0.062	0.59
General health perceptions (GH)	46.4 (20.4)	79.0 (14.5)	**<0.001**	**2.13**
Parental impact: emotional (PE)	86.2 (13.2)	92.1 (10.5)	**0.021**	0.54
Parental impact: time (PT)	81.7 (16.1)	93.0 (11.0)	**<0.001**	**0.96**
Family cohesion (FC)	78.9 (20.6)	75.3 (18.8)	0.178	0.19
Change in health (CH)	73.9 (29.4)	56.1 (18.4)	**0.013**	**0.89**
Child Health Questionnaire – Parent Form 50 (4-17 yr)	n=8	n=353		
Physical functioning (PF)	69.4 (36.9)	99.1 (4.3)	**0.035**	**4.44**
Role functioning: emotional/behavior (REB)	70.8 (36.6)	97.9 (7.2)	0.091	3.09
Role functioning: physical (RP)	56.3 (40.8)	95.8 (15.6)	0.091	2.40
Bodily pain (BP)	71.3 (22.3)	85.7 (17.2)	0.122	0.83
General behavior (GB)	77.7 (19.1)	78.5 (13.1)	0.779	0.06
Mental health (MH)	76.3 (13.8)	81.4 (12.1)	0.260	0.42
Self-esteem (SE)	73.4 (16.4)	79.2 (11.0)	0.262	0.52
General health perceptions (GH)	51.0 (27.2)	82.9 (13.4)	**0.017**	**2.31**
Parental impact: emotional (PE)	78.1 (17.2)	86.3 (15.2)	0.261	0.54
Parental impact: time (PT)	80.6 (16.5)	94.0 (13.0)	0.122	1.02
Family activities (FA)	89.1 (15.3)	91.5 (11.9)	0.887	0.20
Family cohesion (FC)	72.5 (24.2)	72.2 (19.4)	0.573	0.02
Physical summary (PHS)	35.4 (18.7)	56.4 (5.7)	**0.017**	**3.38**
Psychosocial summary (PSS)	51.0 (9.8)	53.2 (6.4)	0.674	0.34
Child Health Questionnaire – Child Form 87 (12-17 yr)	n=4	n=457		
Physical functioning (PF)	84.3 (24.1)	96.0 (6.9)	0.705	1.64
Role functioning: emotional/behavior (REB)	87.5 (11.5)	89.4 (17.2)	0.461	0.11
Role functioning: Physical (RP)	80.6 (14.0)	95.0 (12.9)	0.141	1.12
Bodily pain (BP)	70.0 (14.1)	73.5 (22.7)	0.713	0.15
General behavior (GB)	87.7 (7.7)	80.9 (10.6)	0.066	0.64
Mental health (MH)	79.3 (12.9)	76.5 (15.4)	0.715	0.18
Self-esteem (SE)	71.9 (14.6)	74.7 (12.2)	1.000	0.23
General health perceptions (GH)	65.9 (26.3)	73.5 (16.5)	0.715	0.46
Family activities (FA)	80.2 (16.4)	80.0 (17.7)	1.000	0.01
Family cohesion (FC)	65.0 (26.1)	70.6 (23.5)	1.000	0.24

Data are in mean (SD)

Low scores imply worse functioning

Scores on the CHQ-PF50 scale "change in health" are not presented since individual normative data were not available for this scale

Cohen's d's are presented as absolute numbers. According to Cohen's criteria, an effect size of ≤.49 is considered small, .50 - .79 medium, and ≥ .80 large

Table 4. Health-related quality of life, baseline vs. post discharge

	Baseline	Post discharge	*p* value
Child Health Questionnaire – Infant Toddler 97 (0-3 yr)	n=18	n=18	
Physical functioning	83.3 (80.0-93.3)	83.3 (66.3-90.0)	0.37
Growth and development	72.4 (63.8-81.5)	72.5 (65.0-90.4)	0.07
Bodily pain/discomfort	58.3 (50.0-75.0)	75.0 (58.3-83.3)	0.14
Temperament and moods	71.5 (61.7-82.3)	73.6 (57.6-79.9)	0.71
General behavior	81.2 (71.9-94.7)	81.2 (78.2-94.2)	0.27
Getting along	74.2 (66.3-78.3)	76.7 (71.7-81.7)	0.07
General health perceptions	34.0 (23.6-51.9)	34.2 (20.2-44.2)	0.91
Parental impact: emotional	73.2 (48.2-90.2)	87.5 (75.0-92.6)	**0.003**
Parental impact: time	83.3 (71.4-90.5)	81.0 (71.4-97.6)	0.23
Family cohesion	92.5 (60.0-100.0)	85.0 (60.0-100.0)	0.37
Change in health	50.0 (25.0-75.0)	75.0 (37.5-87.5)	0.16

Data are in median (IQR)
Low scores imply worse functioning

Telephone interview

As 41 parents could not be reached by telephone, 23 of the 64 parents (36%) were interviewed by telephone (8 in the DSI+PS group and 15 in the PS group).

One or more complaints were reported for 16 children (70%): fatigue (n=2 in DSI+PS group and n=7 in the PS group), pain (headache n=1 in the DSI+PS group; other n=1 in the PS group), sleep disturbances, including nightmares (n=1 in DSI+PS group and n=6 in the PS group), behavioral/emotional problems (n=1 in DSI+PS group and n=4 in the PS group) and loss of appetite (n=4 in DSI+PS group and n=2 in the PS group). Seven parents (30%; n=3 in DSI+PS group and n=4 in the PS group) reported limitations in their own daily activities (e.g. job, holidays, hobbies and social visits) since their child's discharge from the PICU. Overall, complaints seemed more prevalent in the PS group (12 vs. 24 complaints); we refrained from statistical comparison due to the small numbers.

DISCUSSION

This multicenter randomized controlled trial is the first study using validated instruments to investigate the short-term outcome of DSI in critically ill children undergoing mechanical ventilation. We found that DSI had no effect on short-term HR-QoL. However, the parent-reported HR-QoL of their children was significantly worse compared with normative data.

Our results are in line with those from adult DSI follow-up studies. Adults managed with DSI reported similar cognitive, psychological, and quality-of-life outcomes after discharge from ICU as those managed with continuous sedation (19-21). Still, DSI was associated with fewer post-traumatic stress symptoms PTSD (20). The latter finding was also demonstrated in a study comparing light sedation with deep sedation (22).
In our original trial duration of mechanical ventilation, length of stay in the PICU and amounts of sedative drugs administered were similar between both study groups. In the adult studies, however, all these factors were lower in the intervention group. The lack of difference in clinical outcomes between the DSI+PS and PS group has likely contributed to a lack of differences in HR-QoL in the present study. Undersedation was more frequent in the DSI+PS group, which could have contributed to a lower HR-QoL in the DSI+PS group, but this was not found.

The finding of significantly worse parent-reported HR-QoL (physical scales) with large effect size compared with normative data is consistent with earlier studies reporting reduced HR-QoL and reduced mental wellbeing in children after PICU experience (23-25). Surprisingly, parents reported better general behavior of the child compared to normative data. The response shift phenomenon could possibly explain this finding. Response shift is "the change of the internal standards and values after a life-threatening or traumatic event" (26). If this should occur, it might result in a possibly too positive perception of problems. Since our results are consistent with earlier reports in children, this confirms that HR-QoL is reduced after pediatric critical illness. In addition, participation in a sedation study with closely monitoring of sedation levels and possibly a better adherence to sedation protocol does not influence HR-QoL.

As expected, 8 weeks post PICU discharge parents experienced more emotional worries/concerns than at baseline. Yet we were surprised to find no differences in the other HR-QoL scales. One would expect that 8 weeks after a PICU stay including mechanical ventilation, HR-QoL would be lower. We speculate that it is difficult for parents to objectively rate their child's HR-QoL before PICU admission, while their child is critically ill. This may be due to a lack of clear instructions of what is meant by 'baseline'. Consequently, baseline HR-QoL results should be interpreted carefully, taking into account potential bias due to anxiety of parents at the time of early PICU admission.

Several limitations of this study should be addressed. First, the response rate was not high (67%), which reduced sample size and thereby statistical power. Still, this response rate is similar to that in other studies in this field of research (23, 25). As participants and non-participants did not differ in baseline characteristics, selection bias based on these characteristics is unlikely. The response rate for the telephone interview was much lower,

only 37%. For one thing, despite multiple attempts, it was hard to contact the parents by telephone. And then, once parents were contacted and agreed to participate, it was a challenge to receive in-depth information by telephone. This may have been due to the fact that the phone call had not been scheduled and parents may have been reluctant to recall the experiences. To overcome these challenges, we suggest to embed HR-QoL measurement by way of formal diagnostic instruments in a visit to the outpatient clinic as part of patient care. Considering the worse HR-QoL after PICU discharge compared with normative data in our study, routine psychological screening during standard follow-up visits, both short-term and long-term seems warranted to be able to provide families with additional care when needed.

A second limitation is the small number of patients above 4 years of age. For this reason we were unable to compare HR-QoL in this age group, as well as incidence of PTSD in the study group.

Third, patients and parents completed questionnaires only once, approximately at 8 weeks after discharge. We planned to evaluate short-term outcome, as possible differences might resolve over time (19, 23). However, the timing of questionnaires might have influenced the results, reporting worse HR-QoL when compared with normative data, because they might not yet have fully recovered.

Fourth, the DSI+PS group had lower severity of illness, as reflected by PELOD score, and shorter hospital length of stay compared with the PS group. Severity of illness may be a predictor of health status in critically ill children, although the PELOD score, measuring organ dysfunction, seems not associated with worse HR-QoL (25). Whether a reduced hospital stay impacts HR-QoL is not clear.

CONCLUSIONS

Based on this multicenter prospective study, DSI, when added to protocolized sedation, is not associated with an improved health-related quality of life for critically ill children. Additionally, this study showed that HR-QoL of children surviving PICU is significantly worse compared with normative data. Also in view of the earlier found absence of effect on clinical outcome, we cannot recommend the use of DSI+PS in critically ill children.

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SUPPLEMENTAL

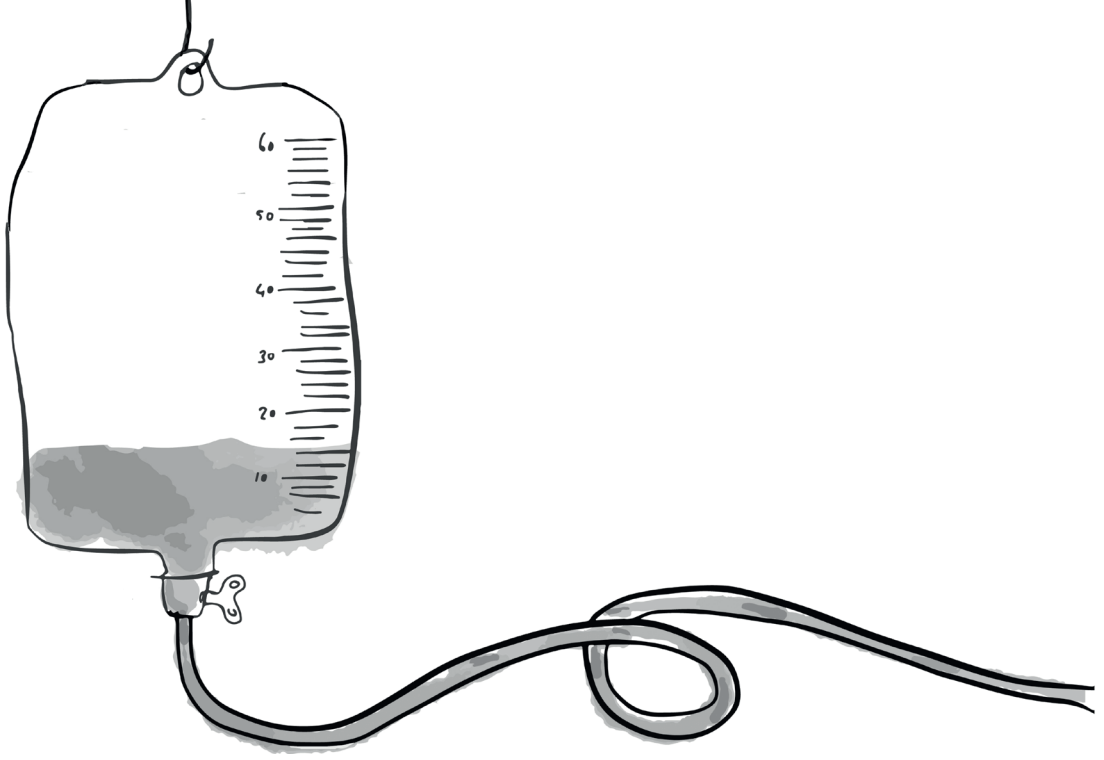
Supplemental Table 1. Characteristics of participants and non-participants

	Participants (n=64)	**Non-participants (n=32)**	***p* value**
Age (months)	2.3 (1.0-7.9)	2.5 (1.1-23.1)	0.55
0 – 30 days (group A)	12 (18.8%)	8 (25.0%)	
30 days – 2 years (group B)	41 (64.1%)	17 (53.1%)	0.59
2 years – 18 years (group C)	11 (17.2%)	7 (21.9%)	
Gender (male/female)	36/28 (56/44%)	22/10 (69/31%)	0.27
PRISM II	17 (13-23)	17 (10-22)	0.64
Predicted mortality PIM 2 (%)	-3.43 (-4.10- -2.42)	-2.79 (-3.98- -2.21)	0.37
PELOD	11 (11-18)	11 (10-12)	0.23
Diagnosis on admission:			
Respiratory*	40 (62.5%)	24 (75.0%)	
Cardiac**	4 (6.3%)	1 (3.1%)	
Sepsis	5 (7.8%)	3 (9.4%)	
Surgery			0.36
Cardiac	11 (17.2%)	1 (3.1%)	
Non-cardiac	2 (3.1%)	1 (3.1%)	
Other	2 (3.1%)	2 (6.3%)	
Duration of mechanical ventilation (days)	4.6 (3.5-7.5)	5.2 (3.8-6.6)	0.80
Length of stay PICU (days)	6.7 (5.4-12.2)	7.2 (5.3-9.9)	0.82
Length of stay hospital (days)	14.7 (10.1-26.0)	10.9 (8.0-21.4)	0.06
Sedative exposure			
Cumulative midazolam dose (mg/kg)	n=64 15.0 (7.7-25.0)	n=32 15.6 (6.1-32.2)	0.77
Cumulative morphine dose (mg/kg)	n=51 0.94 (0.63-1.43)	n=25 1.16 (0.64-2.16)	0.47
Socioeconomic status at baseline			
Level 1: low	8 (12.5%)	4 (12.5%)	
Level 2: middle	39 (60.9%)	24 (75.0%)	0.27
Level 3: high	17 (26.6%)	4 (12.5%)	

Data are in median (IQR) or n (%); PRISM II=Pediatric Risk of Mortality; PIM 2=Pediatric Index of Mortality; PELOD=Pediatric Logistic Organ Dysfunction; * viral/bacterial pneumonia, ARDS and asthma; ** congenital heart disease and cardiomyopathy

PART IV

Reflection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Chapter 9

General discussion

Research in pediatric intensive care

Pediatric intensive care is a unique and young subspecialty in medicine. The first pediatric intensive care unit (PICU) was established in 1955 in Sweden, and pediatric intensive care was only recognized as a distinct subspecialty 30 years ago (1). Major advances in the treatment of critically ill children have been made since then. Not only improved care for major conditions such as acute respiratory distress syndrome, sepsis, and traumatic brain injury, but also new technologies, continuous monitoring and specialized training in critical care have contributed to improved outcomes and survival (1). Nevertheless, most clinical decision making in the PICU is not related to evidence-based medicine based on clinical research, but rather based on physiology and knowledge acquired during training and from personal experience (2).

The PICU can be an ideal environment for clinical research. A dedicated multidisciplinary team is immediately available, and in addition to information in the medical record, extensive physiological monitoring data are usually available, and samples can be obtained easily from invasive devices (2). Still, the complex PICU environment also raises specific challenges to design and conduct of research. It may be difficult to identify good outcome measures due to the combination of low prevalence of major adverse events (e.g. severe morbidity, mortality) and small sample size (3). Second, ethical challenges include timely informed consent and the balance between burden and risk of research against the possible benefit of the trial (4). Children in the PICU generally are not able to participate in the decision as they are too young, too ill or too heavily sedated and parents or surrogates are asked to have their child participate in research under stressful circumstances of admission. It is not always possible to achieve written informed consent before start of the study in emergency settings, and deferred consent can then be a good alternative (5).

To date, more than 80% of all randomized controlled trials in the PICU setting are single center studies (3). These are logistically easier to set up, less expensive, do not require prolonged negotiation for study design, and enroll a less heterogeneous population (6). On the other hand, generalizability of their results is limited. Furthermore, because most diseases in PICU can be viewed as rare diseases (7), many clinical trials have problems with recruitment to ensure adequate power (3).
These limitations could be overcome through collaboration in larger (inter)national PICU research networks, such as the Canadian Critical Care Trials Group (Pediatric Interest Group), the Collaborative Pediatric Critical Care Research Network, the Pediatric Acute Lung Injury Sepsis Investigators Network (PALISI) and in the Netherlands, the so-called *Stichting Kinder Intensive Care* (SKIC). Collaborative research efforts will over time identify the best practices to improve PICU outcomes. Yet, the mindset in every academic PICU

should be that we can learn from every individual patient. Ideally, each patient admitted to the PICU participates in one or more research protocols.
Although heterogeneity of patients in the PICU is large, one common denominator is safe and effective drug therapy, which is the focus of the research presented in this thesis.

Drug research in critically ill children

Drug research is essential for determining the efficacy and safety of medications in children. Without this type of research, we need to resort to extrapolation from adult studies or off-label use for indications that have not been studied in children, with the inherent risk of adverse effects.
Major changes in pharmacokinetics and pharmacodynamics occur with increasing age due to changes in body composition, ontogeny of drug metabolism and transport and renal function (8). The relative lack of knowledge on drug disposition in children can lead to therapy failure (9) or adverse effects (10, 11). Extrapolation from adult data has caused harm in the past, for example the grey baby syndrome in neonates treated with chloramphenicol (12).
Similarly, drug dosing for critically ill children cannot always be derived from research in the general pediatric population. Both critical illness (e.g. shifts in body fluid, inflammation, liver, renal and heart failure) and its treatment modalities (e.g. mechanical ventilation, extra-corporeal membrane oxygenation (ECMO) (13), hypothermia (14, 15), continuous renal replacement therapy (16)) are likely to influence pharmacokinetics and pharmacodynamics of drugs. In addition, oral drug absorption is often altered in critically ill children (17), making the intravenous administration route preferred. As all medications are often given via the same intravenous catheter, this may give rise to drug interactions, which are hardly taken into account in daily practice.
Therefore, drug dosing for critically ill children, is a real challenge. The effects of factors such as inflammation, disease and therapy on both pharmacokinetics and its relation to pharmacodynamics need to be studied across the pediatric age range.

To better understand the interplay of different covariates in relation to drug therapy, a 'systems' pharmacology approach may be helpful. A key element of the systems approach is the distinction between 'drug-specific' and 'system-specific' parameters in pharmacokinetic models to describe variation in drug disposition and response. System-specific parameters relate to parameters describing physiological processes, such as organ perfusion and the expression/function of drug-metabolizing enzymes and transporters. Knowledge of the changes in the system-specific parameters characterizing the absorption, distribution, metabolism and excretion of drugs, such as maturation or inflammation-related changes, may aid to predict the disposition of drugs (8, 18, 19).

This knowledge can be obtained by analyzing changes in the pharmacokinetics of a paradigm compound cleared by this specific pathway. The drug metabolizing enzyme cytochrome P450 3A (CYP3A), for example, has been studied in this way. The maturation of CYP3A was modeled using the clearance of midazolam as its biological marker (20). Another successful example of systems pharmacology is pharmacogenomics, where variation in drug response has been mapped to single nuclear polymorphisms in drug metabolism genes, leading to clinical useful predictions (21).

Pharmacokinetics in pediatric critical illness - midazolam as CYP3A probe

Clinical studies in adults have reported reduced activity for CYP3A, CYP1A2, CYP2C9, CYP2C19 and CYP2D6 in patients with an acute infection or inflammatory disease (22-26). This cytokine-mediated decrease in drug metabolism can be up to 70%. Two studies in critically ill children have demonstrated a significant effect of inflammation on drug metabolism. In children with sepsis and organ failure the antipyrine clearance, as global marker of CYP activity, was two- and fourfold lower, respectively, than in non-septic ICU children (27). In addition, interleukin-6 (IL-6) was negatively correlated with antipyrine clearance, suggesting an important role of inflammation. In a cohort of 20 PICU patients, the presence of the systemic inflammatory response was associated with a 62% decrease in pantoprazole clearance, a CYP2C19 and CYP3A4 substrate (28). Supporting evidence was found from pharmacokinetic studies of midazolam. Average midazolam clearance in critically ill children was considerably lower than in healthy children of the same age (7 ml/kg/min vs. 12 ml/kg/min). We speculated that this large difference can be explained by inflammation (chapter 2).

To further study the interplay of developmental changes, inflammation-related and disease-related variation, a systems pharmacology approach was applied. The pharmacokinetics of midazolam, as a surrogate marker for CYP3A activity, and the influence of covariates such as age, inflammation, disease severity, genetics and drug interactions were prospectively studied (chapter 4). In addition to body weight, both inflammation (IL-6 and C-reactive protein (CRP)) and organ failure significantly affected midazolam clearance in these critically ill children: simulations show a 65% lower clearance at a CRP concentration of 300 mg/L compared to 10 mg/L. Also, three failing organs were associated with a 35% lower midazolam clearance as compared to one failing organ. Together, midazolam clearance can be up to 77% lower in the presence of both increased CRP and multi-organ failure. This effect is most likely due to IL-6 mediated downregulation of CYP3A activity, possibly heightened by reduced hepatic blood flow.

The complex mechanism of inflammation-mediated downregulation of drug metabolism is hardly investigated yet and far from elucidated. For most CYP enzymes studied,

the decrease in CYP450 protein expression are preceded or accompanied by a decrease in mRNA, implicating transcription as a primary mechanism. However, there are multiple post-transcriptional effects as well, including regulation of catalytic activity and destabilization of proteins (19, 29).
The mediators include multiple proinflammatory cytokines (IL-6 and TNF-α), eicosanoids, and histamine, which also regulate acute phase proteins (e.g. CRP). Animal and preclinical human hepatocyte models have described cytokine-induced changes in CYP since the 1980s, but the translation to the clinical setting is challenging and the ability to predict changes following inflammation has been limited. This may be due to the high cytokine concentrations used in the models. Furthermore, the clinical effects of multiple pro- and anti-inflammatory cytokine changes have not been fully assessed. Even in sepsis, a leading cause of mortality, the complexity of the inflammatory response, considered as a 'cytokine storm', makes it difficult to predict outcome or develop therapies by blocking the inflammatory cascades (30, 31).
Of all cytokines and CYPs investigated, both in models and in humans the strongest relation was found between IL-6 and CYP3A4 activity. This link is supported by clinical studies of the IL-6 inhibitor tocilizumab. Inhibition of IL-6 by tocilizumab seems to reverse the IL-6 mediated CYP3A downregulation in adult rheumatoid arthritis patients (32). Our results also support a regulatory role of IL-6, in view of the substantially decreased midazolam clearance, as marker of CYP3A, with increasing IL-6 levels in critically ill children. Other cytokines (e.g. IL1a, IL1b, IL2, IL4, IL8, IL10 and TNF-α) were not related to midazolam clearance (chapter 4). Nonetheless, IL-6 levels may also increase during an acute exercise-induced inflammatory reaction (33), making IL-6 a less specific marker.
It is not known yet whether inflammation also affects other CYP isozymes to this extent, such as CYP2C9 and CYP2D6, and whether this impact is also present in non-critically ill children with inflammatory conditions such as cancer and autoimmune disease.

In addition to inflammation, our study showed that organ failure affects midazolam clearance in critically ill children. The impact of organ failure is logically dependent on the organ type and the relative involvement of a specific organ in a drug's metabolism and clearance. Hepatic, renal and respiratory failure may all affect a drug's disposition in a complex interactive manner. For example, the mechanism by which liver disease impacts on drug clearance is determined by the extraction ratio of the drug. Hepatic drug clearance will depend on the rate of delivery of drug to the liver (determined by the hepatic blood flow) and on the efficiency of drug removal from the blood (the extraction ratio). As midazolam has a low to intermediate extraction ratio, changes in hepatic clearance are predominantly dependent on drug metabolism, but some impact of liver flow cannot be excluded (34, 35). Variation in liver flow in critically ill patients may result from changes in cardiac output subsequent to cardiac failure or restricted filling of the

right ventricle because of elevated intrathoracic pressure due to mechanical ventilation. The impact of acute liver failure on drug metabolism is more difficult to predict because it does not correlate well with the measured indices of liver function or damage (e.g. clotting factors, transaminases, bilirubin, albumin) (36). Therefore, drug metabolism can be altered in patients with apparently normal liver function.

Another consideration is the effect of renal failure on hepatic drug metabolism. Kidney disease does not only alter the renal elimination of drugs and metabolites, but also the non-renal disposition of metabolized drugs. Chronic kidney disease, but also acute kidney injury, which is common in critically ill children (37), may impact hepatic drug metabolism (38, 39). In critically ill adults with renal failure a reduced hepatic clearance of metamizol, a highly metabolized drug, was shown (40). Also, midazolam clearance was significantly lower in critically ill adults with acute kidney injury (41). Although the underlying mechanism is not well-characterized, accumulated uremic toxins and inflammatory cytokines (IL-6) may modulate drug metabolizing enzymes either directly or by inhibiting gene expression (38, 39). In our cohort of critically ill children, creatinine levels, as marker of kidney function, were not significantly associated with midazolam clearance (chapter 4), but children with increased creatinine levels were few. Furthermore, urinary NGAL and KIM-1, recently emerged biomarkers, may be more accurate than creatinine for the early detection of acute kidney injury (42).

In addition to age and disease, genetic variation in CYP3A4/5 activity may contribute to variation in midazolam clearance. We could, however, not identify a significant effect of genetic polymorphisms of CYP3A4 and CYP3A5 on midazolam clearance (chapter 4). There was a non-significant trend towards lower clearance in patients with CYP3A4*22, lacking true significance possibly due to the low prevalence of this SNP in our cohort. Patients in our population who express the CYP3A5*1 allele, i.e. who have functional CYP3A5 activity, did not have a higher midazolam clearance. We also could not confirm that functional CYP3A5 compensates for inflammation mediated CYP3A4 suppression, as previously suggested (41), but sample size was small.

We did not study the impact of treatment modalities on the pharmacokinetics of midazolam in critically ill children. Cardiopulmonary bypass, extracorporeal membrane oxygenation, dialysis and hypothermia may impact on drug disposition and response. For example, volume of distribution is often increased in ECMO-patients and clearance is altered either way (13). Hypothermia leads to changes in volume of distribution due to redistribution of blood flow and lower clearance due to lower drug metabolizing enzyme activity (14, 15).

Since midazolam is a validated probe for determining CYP3A activity *in vivo*, the results of our pharmacokinetic study can serve as a proof of principle. The 'system-specific' information of the influence of inflammation and organ failure on midazolam clearance in critically ill children can be used to predict variation in the clearance of other drugs metabolized by the same enzyme (43). As CYP3A is responsible for the metabolism of more than half of all clinically used drugs, this approach is promising. However, future studies need to confirm whether the effect of critical illness also holds for other CYP3A metabolized drugs and, next, for other CYP enzymes and their substrates.

The next question that arises is if reduced clearance and potential higher plasma levels will also result in increased effect and risk of toxicity. Drug receptor activity may also be subject to critical illness related changes and hence cause altered sensitivity to the drug's effect. For example, in rheumatoid arthritis patients, more active inflammation (increased IL-6 levels) was associated with decreased verapamil clearance and higher verapamil plasma levels. However, despite higher plasma levels, these patients showed significantly weaker dromotropic response (22), thereby protecting them from toxicity. In a pilot study we found that decreased midazolam clearance in critically ill children was seemingly unrelated to lower dose requirements as a surrogate pharmacodynamic marker (chapter 3). However, this study included only 21 patients and dose requirements may not be a good pharmacodynamic endpoint, especially since some sicker patients were more deeply sedated for clinical reasons and may have received higher midazolam doses. Pharmacokinetic-pharmacodynamic modeling may be a better approach, using the COMFORT-behavior scale as validated pharmacodynamic endpoint. To achieve predictable efficacy and safety in all critically ill children, the next steps will be to study variability in pharmacodynamics, to explore the pharmacokinetic-pharmacodynamic relationship in critical illness across the pediatric age range, and more specifically, the effect of inflammation and organ failure on pharmacodynamics.

Conclusions and recommendations:

1. In addition to body weight, inflammation and organ failure significantly affect midazolam clearance in critically ill children.
2. Most likely, this effect is due to IL-6 mediated downregulation of CYP3A activity, which may be emphasized by reduced hepatic blood flow.
3. The effect of acute kidney injury in relation to hepatic drug metabolism should be elucidated.
4. One of the future goals is to examine if extrapolation of the inflammation-related changes in the clearance of the CYP3A substrate midazolam to other CYP3A substrates is valuable.

5. The effect of inflammation should be studied in children with other inflammatory conditions, such as cancer and autoimmune diseases, and for other individual CYP enzymes.
6. The effect of critical illness in relation to the pharmacokinetic-pharmacodynamic relationship of CYP3A drugs needs to be studied.
7. A system approach, studying the 'system-specific' parameters in critically ill children constitutes an innovative approach to the study of pharmacokinetics and pharmacodynamics in this special patient population.

Pharmacodynamics in pediatric critical illness – midazolam as sedative

Midazolam is one of the most widely used drugs in pediatric intensive care for sedation. Adequate sedation has been described as the level of sedation at which patients are asleep but easily arousable (44). Although it is recommended to individually titrate sedatives, adequate sedation is often not obtained in clinical practice. In a systematic review critically ill children were optimally sedated in 57.6%, undersedated in 10.6% and oversedated in 31.8% of the assessments (chapter 5).

There are several possible reasons for the oversedation observed in clinical practice. First, deeper sedation levels are perceived as acceptable or considered clinically needed due to underlying disease. Also, there may be a tendency to sedate children more deeply at night. Adherence to systematic assessment of sedation and associated change in sedation medication might be lower during night shift. Second, there may be a role for pharmacokinetic and pharmacodynamic factors that influence sedative response in critically ill children. In addition to the factors described in the section above, kidney failure can contribute to a prolongation of effect, due to accumulation of the metabolite 1-OH-midazolam-glucuronide, as described in adults (45). Also, pharmacodynamic changes may occur as a result of illness. In critically ill adults, severity of illness particularly influenced the pharmacodynamics and to a minor degree the pharmacokinetics of propofol. Patients who were sicker were more likely to have a deeper level of sedation, and these patients need downward titration of propofol (46).

Inadequate sedation may have a detrimental impact. Undersedation may lead to increased distress and adverse events such as unintentional extubation or displacement of catheters. Oversedation may delay recovery, as greater sedatives consumption is associated with longer duration of ventilation as well as extubation failure in children (47). Oversedation also induces tolerance and withdrawal syndrome (48, 49). All these factors may lead to a longer PICU stay.

In view of the negative consequences of prolonged, deep sedation a shift from deep to light sedation was recommended in adults (50). An important first step was the introduction of protocolized sedation, targeting patient-specific sedation levels. In adults,

protocolized sedation has been associated with improved outcomes (e.g., shorter duration of mechanical ventilation and a shorter length of ICU stay) in a variety of ICU populations (51-56). In children, the benefits of protocolized sedation are less clear. A recent, large randomized controlled trial in mechanically ventilated children comparing protocolized sedation with usual care did not show improved clinical outcome in the protocolized sedation arm (57).

Another approach to avoid the negative effects of oversedation, and especially the adverse effects of continuous benzodiazepine use, may be daily sedation interruption (DSI). Clinical trials in adults have shown that DSI can reduce the duration of mechanical ventilation, hospital stay and amount of sedatives administered without compromising patient comfort or safety (58). Several later studies have confirmed this beneficial effect (59), whereas other studies, in different settings, showed no benefit (60, 61).
In critically ill children, a pilot study showed that DSI is feasible, but this study was not sufficiently powered to detect differences in clinical outcome (62). In a study from India comparing DSI with continuous sedation in children, DSI led to improved clinical outcomes, including shorter durations of mechanical ventilation and PICU stay (63). Patient characteristics in this study differed widely from those usually seen in the Western setting, e.g. a high incidence of neurotrauma, longer mean duration of mechanical ventilation, and more sedatives and neuromuscular blockers administered. The ability to extrapolate the results of this study to PICU practice in the Western world has therefore been questioned (64).
In our study, DSI combined with protocolized sedation did not improve clinical outcomes such as duration of mechanical ventilation, length of stay, or the amounts of sedative drugs administered, but rather was associated with a higher 30-day mortality (chapter 7). In addition, this approach did not seem to have an effect on short-term health-related quality of life for critically ill children (chapter 8). The effect of protocolized sedation itself on the clinical endpoints might have outweighed the effect of DSI, as also demonstrated in adults (60).
The higher mortality in the first 30 days in the DSI group compared to the control group was totally unexpected. An independent data and safety monitoring board could not identify a causal relationship between the study intervention and cause of death for the individual patients and the long time interval between active participation in the study and death for most patients renders causality unlikely. In addition, overall mortality in our total patient cohort was not higher than the reported ICU mortality in the Netherlands. Also, in previously published DSI studies, mortality was never increased (65). Therefore, it is highly unlikely that there is a relationship with DSI. We concluded that DSI is not the sedation strategy of choice in critically ill children provided protocolized sedation is implemented in the pediatric intensive care.

Several steps can be taken to further improve sedation management in critically ill children. For one, the use of non-benzodiazepine medications in critically ill children must be studied. As especially the continuous administration of benzodiazepines, such as midazolam, is associated with prolonged mechanical ventilation (66), the use of alternative medications that cause minimal respiratory depression, e.g. clonidine or dexmedetomidine, could improve outcome. Clonidine and dexmedetomidine are centrally acting α2-agonists. Clonidine has been shown a viable alternative to midazolam in critically ill children, without substantial safety issues (67). However, whether the use of clonidine improves clinical effectiveness is not yet known, a study is currently undertaken (NCT02509237). For dexmedetomidine, some retrospective studies have shown favorable results in critically ill children, although adverse events such as hypotension, bradycardia and withdrawal syndrome are not excluded (68-70). Overall, the evidence is weak and randomized controlled trials are needed to examine if these medications are better alternatives.

Drug 'cycling' or 'rotation' may be another approach to decrease the adverse effects of continuous sedation (71). This strategy is aimed at preventing tachyphylaxis and tolerance by cycling drug combinations. For example, an opioid and benzodiazepine regimen can be changed to ketamine and promethazine, followed by clonidine and chloral hydrate, all on a weekly basis. However, evidence supporting the beneficial effects of cycling is lacking.

In adults, a strategy of no sedation is suggested to further improve clinical outcome. No sedation during mechanical ventilation resulted in a lower number of days on ventilation and a shorter ICU stay, compared to DSI (72). Interestingly, delirium was more frequent in the no sedation strategy. As yet, a strategy of no sedation may not be recommended for critically ill children. Often unable to comprehend in what situation they are when they are awake for a longer period, they may show more distress than adults, with possibly higher risk of adverse events such as unintentional extubation.

The role of sedatives on short- and long term neurological outcome needs to be clarified. There is emerging evidence that sedatives, and especially midazolam, are a risk factor for development of delirium in adults (73). Delirium is a manifestation of acute brain dysfunction and is an important independent predictor of negative clinical outcomes in adult ICU patients, including increased mortality and long-term cognitive impairment with a dementia-like state (74, 75). For critically ill children, risk factors for delirium are probably the same, but long-term consequences are unknown (76). Furthermore, the role of sedatives and analgesics on long term neurological outcome needs to be elucidated. Virtually all available sedatives and analgesic medications are neurotoxic

in animal models (77). Human studies are still scarce (78) and conflicting. Morphine administration at neonatal age was not associated with adverse long-term effects in a cohort of preterm newborns at 8-9 years of age (79, 80) and in a cohort of neonatal extracorporeal membrane oxygenation survivors at school-age (81). In contrast, opioid administration was associated with adverse neuropsychological outcome in meningococcal septic shock survivors (82).

Although sedation studies have focused primarily on brain-related outcomes, other organ systems, such as the kidneys, may also be affected. A no sedation strategy in mechanically ventilated adult patients decreased the incidence of acute kidney injury (83). A decrease in the microcirculation within the kidneys following sedation could partly explain this finding. Although methodological limitations preclude firm conclusions regarding mechanisms underlying this association, this study generates the hypothesis that sedation may harm organs other than the brain during critical illness (84).
Sedatives may also affect the immune system, as studies suggest that sedatives have anti-inflammatory effects and may increase susceptibility to infection (85). For example, both midazolam and propofol impair multiple aspects of the innate immune response, for example by reducing macrophage chemotaxis and phagocytosis, suppressing nitric oxide production and limiting production of interferon, tumor necrosis factor and various interleukins (85). The possible exception is the α2-agonist class of drugs (e.g. dexmedetomidine), which may improve immune function and outcomes, including mortality in sepsis (85). Human studies are limited, but supportive of immunomodulatory effects of sedatives with a possible increased risk of infections (86, 87). Clinical studies are needed to determine whether these data are relevant in the clinical setting and if consideration of the immune effects may play a role in sedative selection in the far future.

Conclusions and recommendations

1. Sedation in PICU is often suboptimal and oversedation is common.
2. There is no beneficial effect of daily sedation interruption in addition to protocolized sedation for critically ill children.
3. Other sedative regimes, like drug cycling, and other sedatives, like clonidine and dexmedetomidine, may add to optimal sedation and need further study in well-designed multicenter clinical trials.
4. The influence of sedatives on short- and long term neurological outcome, as well as potentially systemic effects, need to be clarified.

Although widely prescribed, the safety and efficacy of drugs administered to critically ill children is hardly studied in this population. In addition to age-related maturation of drug-metabolizing enzymes and renal function, critical illness (inflammation and

organ failure) severely affects the clearance of (CYP3A metabolized) drugs. This may lead to an increased risk of drug toxicity or therapy failure, but further exploration of the pharmacokinetic-pharmacodynamic relationship in critical illness is necessary. Until then, physicians should '*be awake*' and consider the influence of critical illness on drug therapy and, if possible, use therapeutic drug monitoring in patients with unexplained symptoms potentially related to drug toxicity or therapy failure.

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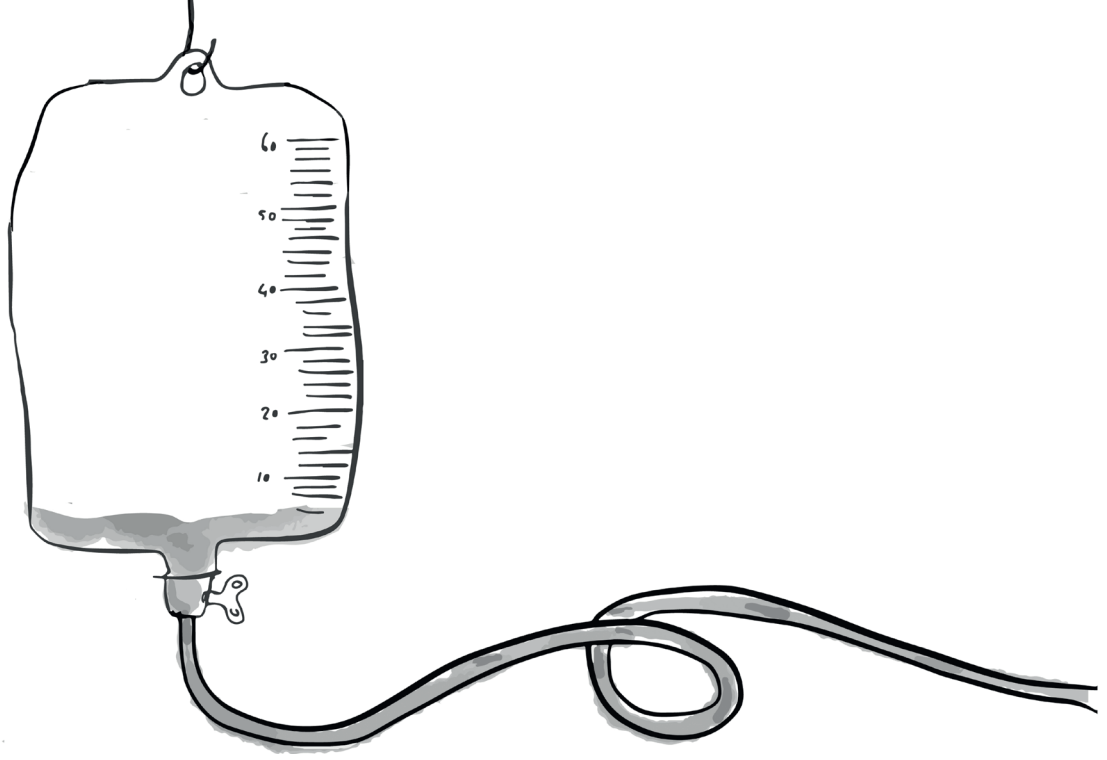
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Chapter 10

Summary

Samenvatting

SUMMARY

On average, a critically ill child admitted to a pediatric intensive care unit receives tendifferent drugs. The safety and efficacy of most of these drugs have hardly been studied in this population and yet they are widely prescribed. Dose recommendations are often empirical, based on body weight and an extrapolated adult dose. In view of the mostly non-linear developmental changes in young children as well as the physiological differences between adults and children, empirical dosing can lead to over- or underdosing.
Drug dosing in critically ill children poses an extra challenge. In addition to the age-related maturation of drug-metabolizing enzymes and renal function, acute illness and its treatment modalities may also impact drug disposition and response. More evidence-based dosing regimens can be derived only if the effect of factors such as inflammation, disease state and genetics on pharmacokinetics as well as pharmacodynamics is known.
The aims of this thesis were:

1. To study the influence of critical illness (inflammation and disease state) in children on midazolam pharmacokinetics, as a surrogate measure of CYP3A activity.
2. To study the safety and efficacy of daily sedation interruption in critically ill children.

Pharmacokinetics in pediatric critical illness - midazolam as CYP3A probe

Previous studies on the effect of inflammation on drug metabolism and drug effect are discussed in **chapter 2**. This review showed that *in vitro*, animal and few human studies have reported alterations in drug metabolism and the pharmacokinetics of drugs in the presence of inflammation. Two studies in critically ill children demonstrated a significant effect of inflammation on drug metabolism, with a decrease in drug clearance of up to 75%. Pharmacokinetic studies of midazolam showed that average midazolam clearance is considerably lower in critically ill children compared with healthy children of the same age. It is speculated that this large difference can be explained by inflammation-mediated downregulation of CYP3A metabolism, which largely determine midazolam clearance. Little is known on the clinical implications of these changes for drug dosing, and pharmacodynamic data in children are lacking.

The pilot study described in **chapter 3** suggests that severity of organ failure in critically ill children, as reflected by the Pediatric Logistic Organ Dysfunction (PELOD) score, affects the clearance of midazolam, most likely as a result of reduced activity of CYP3A. This severity is not related, however, to decreased dose requirements of midazolam as a surrogate pharmacodynamic marker.
These observations prompted the study presented in **chapter 4**, a prospective population pharmacokinetic study on the effect of critical illness in 83 children. We found that, in addition to body weight, both inflammation, as reflected by C-reactive protein or

interleukin-6, and organ failure significantly affected midazolam clearance. Simulations show that a C-reactive protein of 300 mg/L in comparison to 10 mg/L is associated with a 65% lower clearance and that three failing organs is associated with a 35% lower clearance compared to one failing organ. The combination of increased C-reactive protein and multiple failing organs can even lead to up to 77% lower midazolam clearance. Most likely this effect is due to inflammation-mediated downregulation of CYP3A activity, which may be amplified by critical illness related reduced hepatic blood flow. These observations are of concern as they suggest that critically ill children are at increased risk for toxicity by CYP3A metabolized drugs given at normal doses.

Pharmacodynamics in pediatric critical illness – midazolam as sedative

The provision of adequate sedation to critically ill children is an important aspect of care in the pediatric intensive care unit. To achieve optimal sedation in individual patients, doses of sedatives are titrated to effect. However, this endpoint if often not obtained. The systematic review presented in **chapter 5** showed that critically ill children are undersedated in 10.6% of the assessments and oversedated in 31.8% of the assessments.

Both under- and oversedation may have negative effects. Oversedation delays recovery, as greater sedatives consumption is associated with longer duration of ventilation as well as extubation failure. Oversedation also induces tolerance and withdrawal syndrome. Undersedation, on the other hand, may lead to increased distress and adverse events such as unintentional extubation or displacement of catheters. This may also lead to a longer ICU stay. With the risks of oversedation and the difficulties of reaching adequate sedation in mind, the question was raised whether daily sedation interruption in critically ill children might be beneficial. **Chapter 6** describes the study protocol of a multicenter randomized controlled trial to compare daily sedation interruption plus protocolized sedation to protocolized sedation only. The results of this study are presented in **chapters 7 and 8**. Daily interruption of sedation did not reduce the duration of mechanical ventilation, length of stay, or the amounts of sedative drugs administered, but was associated with a higher 30-day mortality. In addition, daily sedation interruption did not seem to have an effect on the children's short-term health-related quality of life. Therefore, we concluded that daily sedation interruption in critically ill children cannot be recommended.

In **chapter 9** the results of our studies are discussed and recommendations for future research are given. We conclude that besides body weight, inflammation and organ failure significantly affect midazolam clearance in critically ill children and that they are at an increased risk of drug toxicity or therapy failure when receiving CYP3A substrate drugs. Future studies need to confirm whether the effect of critical illness can also be applied

to other CYP3A metabolized drugs and, next, to other CYP enzymes and their substrates. Also, the effect of critical illness in relation to the pharmacokinetic-pharmacodynamic relationship of CYP3A drugs needs to be studied. We also conclude that there is no short term or long term beneficial effect of daily sedation interruption in addition to protocolized sedation for critically ill children.

SAMENVATTING

Een ernstig ziek kind dat op een intensive care afdeling ligt, krijgt gemiddeld tien verschillende medicijnen toegediend. Ondanks het veelvuldig gebruik, is de werkzaamheid en veiligheid van deze medicijnen bij kinderen vaak niet goed onderzocht. Doseeradviezen zijn doorgaans empirisch, waarbij de dosering voor het kind is afgeleid van de dosering voor volwassenen. Hierbij wordt geen rekening gehouden met de groei en ontwikkeling van het kind en de fysiologische verschillen tussen kinderen en volwassenen. Deze methode kan daarom leiden tot over- of onderdosering van geneesmiddelen. Het bepalen van de juiste dosering voor ernstig zieke kinderen is een extra uitdaging. Naast de leeftijdsafhankelijke veranderingen in geneesmiddelmetabolisme en nierfunctie, hebben de ziekte zelf en de gegeven therapie ook invloed op de farmacokinetiek en werking van een geneesmiddel. Over het effect van factoren als inflammatie en ziekte op de farmacokinetiek en farmacodynamiek is nog weinig bekend. Meer kennis daarvan is nodig om tot een juiste dosering bij ernstig zieke kinderen te komen.
In dit proefschrift hebben we het volgende onderzocht:

1. het effect van inflammatie en ziekte op de farmacokinetiek van het slaapmedicijn midazolam, waarbij de omzetting van midazolam een surrogaat is voor de activiteit van het enzym CYP3A.
2. de veiligheid en effectiviteit van het dagelijks onderbreken van sedatie (slaapmedicatie) bij ernstig zieke kinderen.

Farmacokinetiek bij ernstig zieke kinderen – midazolam als CYP3A probe

Hoofdstuk 2 geeft een overzicht van de literatuur op het gebied van inflammatie en geneesmiddel metabolisme. Hieruit blijkt dat *in vitro*-, dier- en enkele studies in mensen een afname laten zien van de activiteit van metaboliserende enzymen en een veranderende farmacokinetiek ten tijde van inflammatie. Bij ernstig zieke kinderen zijn twee studies verricht die laten zien dat de klaring van een geneesmiddel tot 75% is afgenomen wanneer er sprake is van inflammatie. Farmacokinetiek studies van midazolam laten zien dat de gemiddelde midazolam klaring veel lager is bij ernstig zieke kinderen dan bij relatief gezonde kinderen van dezelfde leeftijd. Wij veronderstellen dat dit verschil wordt veroorzaakt door een afname van CYP3A metabolisme. Er is niet veel bekend over de klinische gevolgen hiervan en farmacodynamische studies ontbreken.

Het onderzoek beschreven in **hoofdstuk 3** laat zien dat bij ernstig zieke kinderen, de ernst van orgaanfalen, welke beschreven wordt met de Pediatric Logistic Organ Dysfunction (PELOD) score, invloed heeft op de klaring van midazolam. Meest waarschijnlijk komt dit door een afname van de activiteit van het enzym CYP3A. De ernst van orgaanfalen is echter niet gerelateerd aan een afname in de hoeveelheid midazolam die nodig was.

Deze bevindingen waren de aanleiding voor de studie beschreven in **hoofdstuk 4**. In dit hoofdstuk bespreken we een prospectieve populatie farmacokinetiek studie naar het effect van ernstige ziekte bij 83 kinderen. We vonden dat inflammatie (weerspiegeld door het ontstekingseiwit C-reactief proteïne of interleukine-6) en orgaanfalen, naast het lichaamsgewicht, de klaring van midazolam sterk beïnvloeden. Simulaties laten zien dat wanneer een kind een C-reactief proteïne van 300 mg/L heeft, dit geassocieerd is met een 65% lagere klaring in vergelijking met een C-reactief proteïne van 10 mg/L. Als een kind drie falende organen heeft, is dit geassocieerd met een 35% lagere klaring in vergelijking met één falend orgaan. De combinatie van een verhoogd C-reactief proteïne en meerdere falende organen kan leiden tot een 77% lagere midazolam klaring. Meest waarschijnlijk is dit het gevolg van een inflammatie-gemedieerde afname van CYP3A activiteit, welke versterkt wordt door een verminderde bloedstroom in de lever tijdens ernstige ziekte. Deze observaties zijn van belang, omdat ernstig zieke kinderen bij de nu gebruikte dosering mogelijk een verhoogd risico hebben op bijwerkingen van geneesmiddelen die door CYP3A gemetaboliseerd worden.

Farmacodynamiek bij ernstig zieke kinderen – midazolam als sedativum

Ernstig zieke kinderen die op een intensive care liggen, krijgen regelmatig kalmerende middelen (sedativa, zoals midazolam) om discomfort en onrust te voorkomen. Adequate sedatie is heel belangrijk. Om optimale sedatie te bereiken, wordt de dosering individueel aangepast en wordt gekeken naar het effect (diepte van sedatie). Desalniettemin wordt 'optimale sedatie' vaak niet bereikt. In **hoofdstuk 5** laten we zien dat in 10.6% van de observaties een kind onvoldoende gesedeerd is (ondersedatie) en in 31.8% van de observaties een kind te diep gesedeerd is (oversedatie).

Zowel over- als ondersedatie kan leiden tot complicaties. Oversedatie vertraagt het herstel; het geven van meer sedatie is geassocieerd met een langere beademingsduur. Oversedatie kan ook tolerantie en ontwenningsverschijnselen veroorzaken. Daarentegen kan ondersedatie leiden tot discomfort en ongewenste gebeurtenissen, zoals het uittrekken van een beademingsbuis, infuus of katheter met als mogelijk gevolg ook een langere ligduur op de intensive care. Met de risico's van oversedatie in gedachte, kwam de vraag op of het dagelijks onderbreken van sedatie bij ernstig zieke kinderen beter zou zijn.

In **hoofdstuk 6** beschrijven wij het onderzoeksprotocol voor een multicenter gerandomiseerd onderzoek waarin het dagelijks onderbreken van sedatie in combinatie met geprotocolleerde sedatie wordt vergeleken met geprotocolleerde sedatie alleen. De resultaten van dit onderzoek staan beschreven in **hoofdstuk 7 en 8**. Dagelijkse onderbreking van sedatie heeft niet geleid tot een kortere beademingsduur, ligduur op de intensive care of een afname in de hoeveelheid gegeven sedatie, maar was geassocieerd

met een verhoogde mortaliteit op 30 dagen. Hiernaast had het dagelijks onderbreken van sedatie geen effect op de kwaliteit van leven van de kinderen na twee maanden. Daarom bevelen wij het dagelijks onderbreken van sedatie bij ernstig zieke kinderen niet aan.

In **hoofdstuk 9** worden de resultaten van onze studies bediscussieerd en aanbevelingen gedaan voor toekomstig onderzoek. We concluderen dat inflammatie en orgaanfalen, naast lichaamsgewicht, van invloed zijn op de klaring van midazolam bij ernstig zieke kinderen. Hierdoor ontstaat een verhoogd risico op bijwerkingen of het falen van de therapie bij het geven van geneesmiddelen die via CYP3A worden gemetaboliseerd. Toekomstige onderzoeken moeten laten zien of het effect van ziekte ook geldt voor andere CYP3A-gemetaboliseerde medicijnen en, vervolgens, ook voor geneesmiddelen die via andere CYP enzymen worden omgezet. Ook moet onderzocht worden wat het effect van ziekte is op de farmacokinetiek-farmacodynamiek relatie.
We concluderen ook dat er geen gunstige korte en langere termijn effecten zijn van het dagelijks onderbreken van sedatie als toevoeging op geprotocolleerde sedatie bij ernstig zieke kinderen.

Appendices

Affiliations co-authors

About the author

List of publications

Portfolio

Dankwoord

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Erwin Ista, PhD	Intensive Care and Department of Pediatrics, Erasmus MC - Sophia Children's Hospital, Rotterdam
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ABOUT THE AUTHOR

Nienke Vet was born in Leiderdorp on September 27th, 1982. After graduating secondary school at Helen Parkhurst College in Almere in the year 2000, she started medical training at the Vrije Universiteit (VU) in Amsterdam. Her preference for pediatrics was soon apparent, which resulted in the choice for the graduation profile 'Kind en Jeugd'. As part of her scientific training she studied the reporting of child abuse in the VU Medical Centre and the results were published in the 'Nederlands Tijdschrift voor Geneeskunde'. In November 2006 she obtained her medical degree (cum laude) and took a position as a pediatric resident at the Diakonessenhuis in Utrecht. After 6 months she transferred to the Erasmus MC-Sophia Children's Hospital in Rotterdam. In 2008 she got the opportunity to start her PhD project under supervision of Prof.dr. M. de Hoog, Prof.dr. D. Tibboel and Dr. S.N. de Wildt at the department of Intensive Care of the Erasmus MC-Sophia Children's Hospital.

The project was performed in collaboration with 'Stichting Kinder Intensive Care' (SKIC) and funded by project grants from the Netherlands Organization for Health Research and Development, ZonMw (Priority Medicines for Children) and Erasmus MC (Cost-Effectiveness Research). During a two-month traineeship at the Leiden Academic Centre for Drug Research (LACDR) she gained more experience in population pharmacokinetic modelling.

In 2009 she was happy to receive a grant from ZonMw (AGIKO-stipendia), and combined her research with pediatrics training at the Erasmus MC-Sophia Children's Hospital (Prof. dr. M. de Hoog) and Sint Franciscus Gasthuis in Rotterdam (Dr. N.G. Hartwig). In 2012 she started a fellowship Clinical Pharmacology, which she expects to finish in 2016.

LIST OF PUBLICATIONS

Vet NJ, de Wildt SN, Verlaat CW, Mooij MG, Tibboel D, de Hoog M, Buysse CM, on behalf of SKIC. Short-term health-related quality of life of critically ill children following daily sedation interruption. *Provisionally accepted* Pediatr Crit Care Med

Vet NJ, Brussee JM, de Hoog M, Mooij MG, Verlaat CW, Jerchel IS, van Schaik RH Koch BC, Tibboel D, Knibbe CA, de Wildt SN, on behalf of SKIC. Inflammation and organ failure severely affect midazolam clearance in critically ill children. Am J Respir Crit Care Med. 2016.

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Verlaat CW, Heesen GP, **Vet NJ**, de Hoog M, van der Hoeven JG, Kox M, Pickkers P. Randomized controlled trial of daily interruption of sedatives in critically ill children. Paediatr Anaesth. 2014;24(2):151-6.

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Vet NJ, Canninga-van Dijk MR, de Waal WJ. Burn wounds in neonates caused by hot warming bottles. Ned Tijdschr Geneeskd. 2009;153(18):880-3.

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PHD PORTFOLIO

Name PhD student: Nienke Vet
PhD period: 2008-2016 (Agiko)
Erasmus MC Department: Intensive Care and Department of Pediatrics
Promotors: Prof. dr. M. de Hoog, Prof. dr. D. Tibboel
Copromotor: Dr. S.N. de Wildt

	Year	Workload (ECTS)
General courses		
BROK (Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers)	2009	1
Minicursus Methodologie van Patientgebonden Onderzoek	2009	0.3
Introduction to Clinical Research	2010	0.9
Biostatistics for Clinicians	2010	1
English Biomedical Writing and Communication	2010	4
Biostatistical Methods I: Basic Principles	2012	5.7
Specific courses		
LACDR Cursus Farmacokinetiek	2008	1
European Course: Evaluation of Medicinal Products in Children	2010	2
NIH 'Principles of Clinical Pharmacology'	2010 - 2011	2
Symposia and workshops		
Workshop Modeling and Simulation Approaches in Drug Discovery and Development	2009	0.3
Masterclass Analgesie, Sedatie en Delier op de Intensive Care	2010	0.3
Sophia Research Day	2009, 2013	0.6
TULIPS Jonge Onderzoekersdag	2014, 2015	0.6
(Inter)national Conferences		
ESDPPP Congress, Chamonix, France (poster presentation)	2009	1
111th Annual Meeting ASCPT, Atlanta, USA (oral presentation (Presidential Trainee Award) and poster presentation)	2010	2
Figon Dutch Medicines Days, annual meeting, Ede (poster presentation)	2010, 2012	1
EACPT Summer School on Education	2012	1

114th Annual Meeting ASCPT, Indianapolis, USA (poster presentation)	2013	1
24th Annual Meeting ESPNIC, Rotterdam (poster presentation)	2013	1
ESDPPP Congress, Belgrade, Servia (oral presentation)	2015	1
Congres Kindergeneeskunde NVK, Veldhoven	2011 - 2015	1
Teaching activities		
Teaching lecture 'polypharmacy' (3rd year medical students)	2014 - 2015	0.2
Other		
F1000 Associate Faculty Member (writing F1000 evaluations)	2009 - 2010	1
Pediatric Pharmacology Research Meetings (weekly) (oral presentations)	2009 - 2015	2
Clinical Pharmacology and Pharmacogenetics Meetings (weekly) (oral presentations)	2010 - 2015	1
Fellowship Clinical Pharmacology	2012 - 2016	
Working visit: Leiden Academic Centre for Drug Research (LACDR)	2014	8

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

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