Analgosedatives in the pediatric intensive care

More than sleep alone?

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Analgosedatives in the PICU – more than sleep alone?

Analgosedatie op de kinder IC – meer dan alleen slapen?

Proefschrift

Ter verkrijging van de graad van doctor aan de
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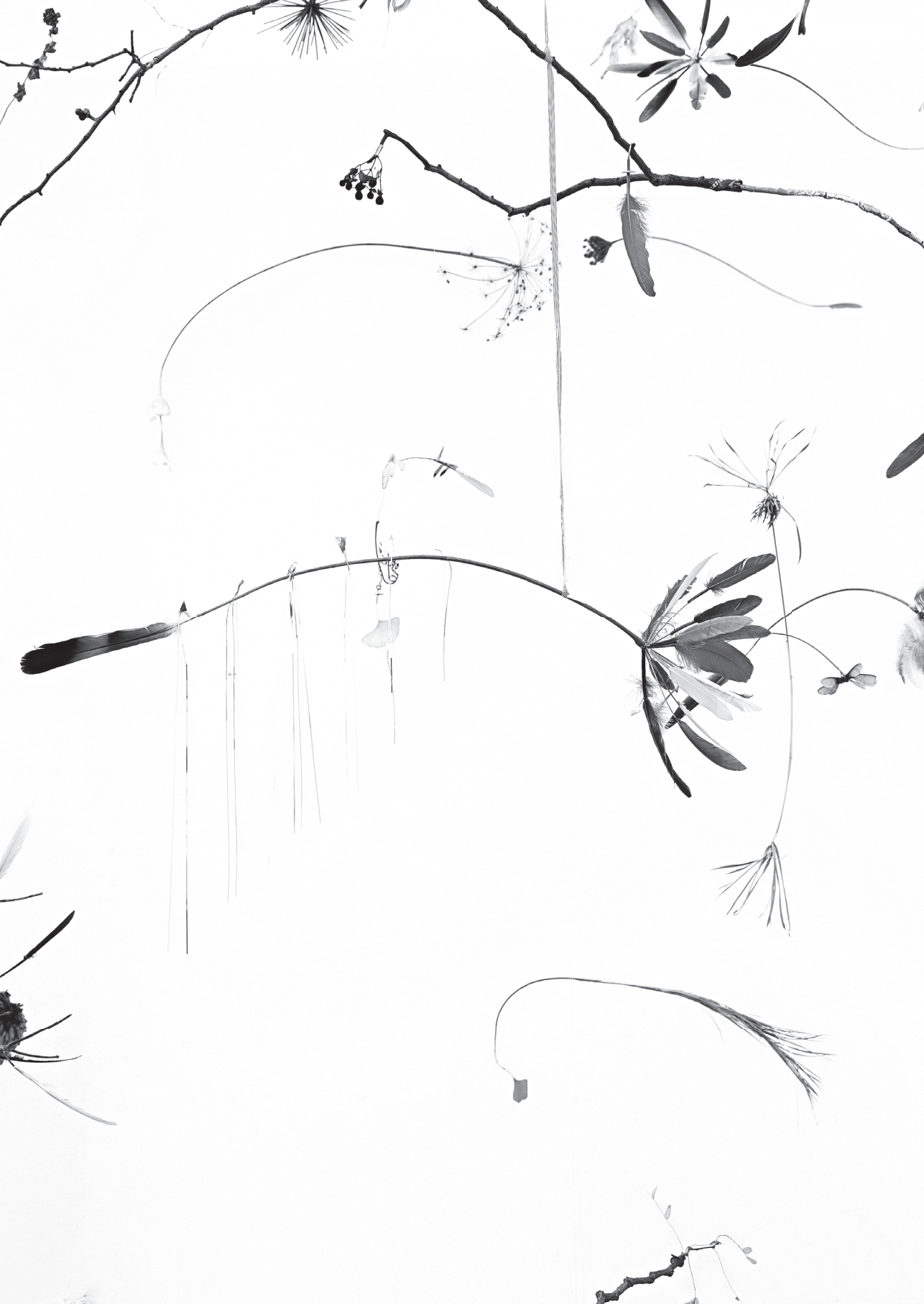
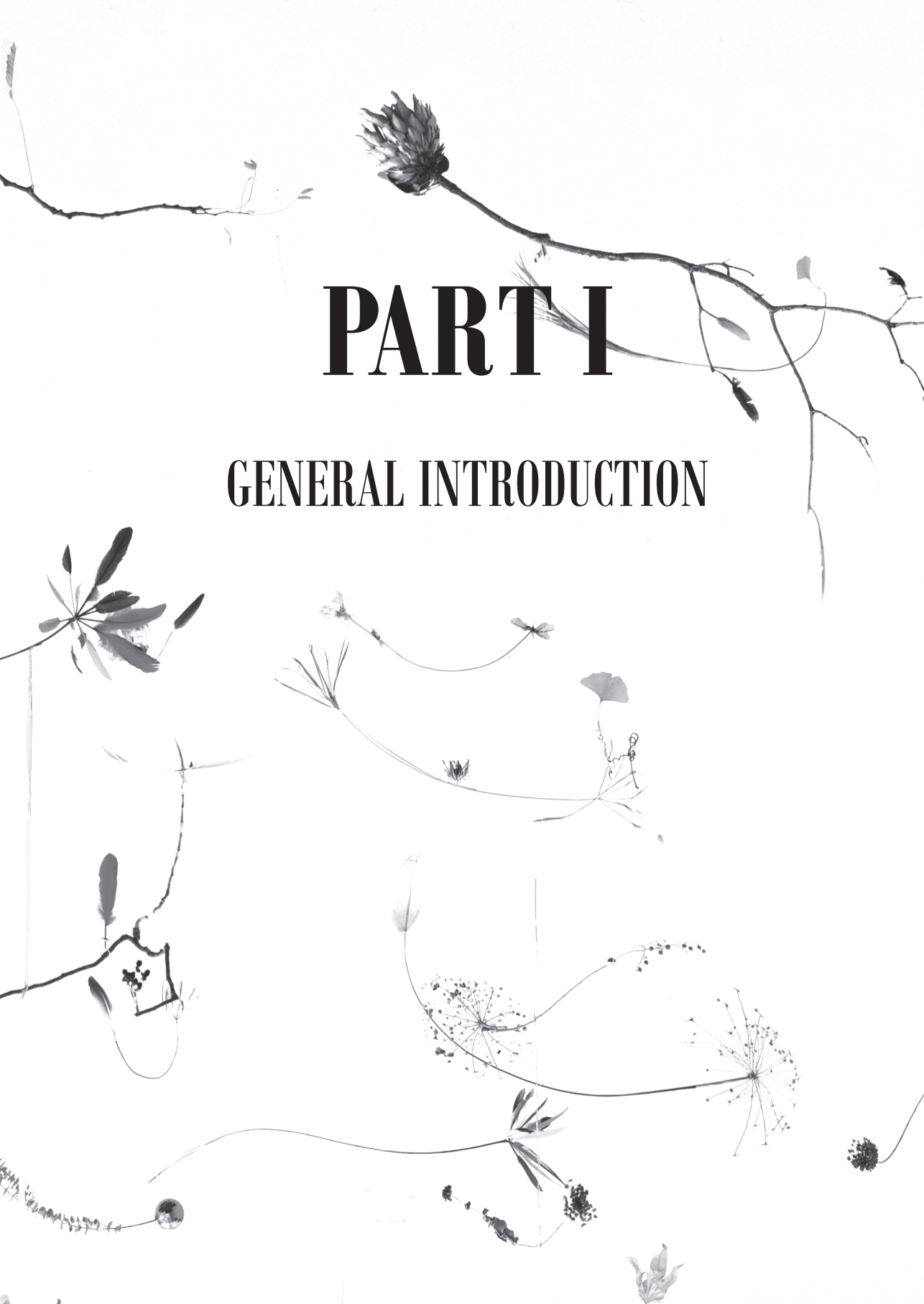
Analgosedation in the PICU
– more than sleep alone?
Analgosédation aux Soins intensifs pédiatriques_au delà du sommeil

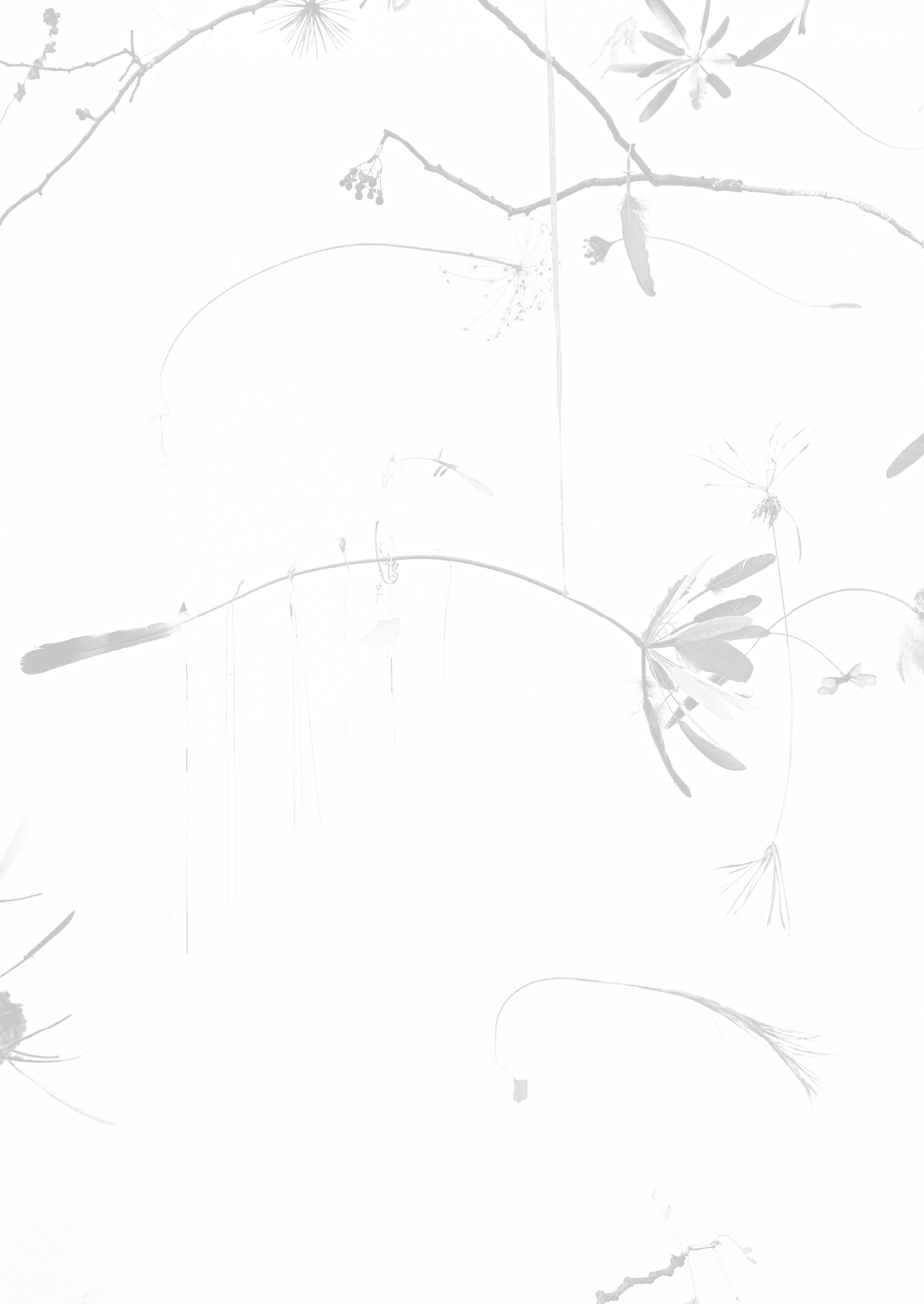
Niina Kleiber





PART I

GENERAL INTRODUCTION



Chapter 1

General introduction

Up to 70% of drugs administered to children in the pediatric intensive care unit (PICU) are used unlicensed or off-label (1, 2). This means, without regulatory review of information about safety and efficacy and without appropriate dosages or formulations (3). As many drugs administered to children have not been systematically studied in the pediatric population, the dosing is often derived from adult dosing (4). This practice is not without risk, however, as children cannot be considered "small adults". The absorption, distribution, metabolism and elimination of drugs as well as the drug response are maturing with age, and therefore the ontogeny of pharmacokinetic (PK) and pharmacodynamic (PD) processes needs to be taken into account to rationalize dosing in children (5–8). The relative lack of knowledge on drug disposition and effect in children can lead to treatment failure (9) and adverse events as serious as fatalities (10, 11). In the PICU, the effect of critical illness on PK and PD added to the effect of age further complicates the rational choice of drug and dosing. Therefore, research on drugs in the PICU is of paramount importance.

Drug studies in the pediatric ICU: pharmacokinetic, pharmacodynamic and ethical aspects

PK/PD

Critical illness has a major impact on all pharmacokinetic processes and on pharmacodynamics (12), and one of the processes altered by critical illness is the oral absorption (13, 14). The volume of distribution is influenced by patient-related factors like change in albumin or total body water. Liver and kidney failure, which are prevalent among critically ill patients, alter drug clearance (15, 16). Inflammation may also affect clearance by down- or upregulating drug metabolizing enzymes and transporters (17,18). Acute illness involves specific treatments such as continuous venous-venous hemofiltration (19), extracorporeal membrane oxygenation (ECMO) (20) and hypothermia (21–24), which also affect PK and PD.

ETHICS

To rationalize choice of drug, route of administration and dosing, research on drugs used in the PICU is of paramount importance but is hampered by practical, ethical, and scientific challenges. Classic pharmacokinetic studies are not ethically feasible as they imply administration of a non-therapeutic drug followed by extensive blood sampling. Therefore alternative study designs have been developed, such as opportunistic PK studies that use concentrations of a drug administered per standard of care, thus doing away with the administration of a study drug (25, 26). These studies are FDA approved (27). Other studies measure drug concentrations in blood collected during routine blood sampling or in leftover samples from routine analysis, thereby eliminating the burden of blood sampling for research purposes (26). These sparse sampling data, obtained at

any moment during treatment, necessitate the use of a versatile method for the analysis, such as population pharmacokinetics (28, 29). Population pharmacokinetics also allows determining the influence of patient characteristics on PK and PD, permitting to design dosing guidelines tailored to the individual patient's characteristics. This method is proven useful to study particular populations including critically ill and to investigate the influence of the interplay between age, disease severity and ECMO.

Moreover, alternative forms of the consent-seeking process have been developed taking into account the acute and unpredictable reality of the PICU where time constraints and parental stress are barriers to this process.

PK and PD of analgosedation in the PICU

Analgesics and sedatives are among the most commonly used drugs in the PICU (3). They are administered to alleviate any pain and stress related to the child's disease and treatment. Ideally, the child should be asleep but easily arousable (30). Reaching this ideal level of sedation implies a good knowledge of PK and PD of analgosedatives in a variety of different situations. Research on analgesics and sedatives in the PICU is improving but there is still a long way to go before the choice of the best agent and dose can be tailored to individual demographic, clinical and concomitant treatment characteristics.

Pharmacokinetics of analgosedation in the PICU

As pointed out above, the PK can be affected by several factors including interventions such as ECMO and hypothermia, but also, for example, altered oral absorption due to the critical illness. Thus, the existing PK data of analgosedatives may not always be applicable to each individual critically ill child, and each specific situation also merits further study.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is one of the situations in which clinicians are challenged to determine optimal drug dosing. Patients on ECMO require optimal analgosedation but the optimal dosing is hard to establish because the PK of medications may be altered by the ECMO system (20). Many drugs have never been studied in patients on ECMO, and one of these medications is clonidine, a central α-2-agonist with both sedative and analgesic properties (31, 32). As ex vivo studies on ECMO have shown that the speed and extent of drug adsorption correlate with lipophilicity (33) and amount of protein bound (34), the moderate lipophilicity (log $P = 1.6$) (35) and slight protein binding (20–40%) (36) of clonidine suggest the potential of significant adsorption.

Oral bioavailability

Although in general drugs to critically ill children are administered intravenously, oral administration is not uncommon in the PICU, and this has been documented in 15% of ventilated and 27% of non-ventilated patients (37). Still very little is known about oral drug absorption in critically ill children, who are likely to have altered gastrointestinal function and thereby altered oral drug absorption. The oral bioavailability of paracetamol, for example, has not been studied in paediatrics in general, let alone in critically ill children– and yet it is one of the most commonly used drugs in the PICU (3).

Oral bioavailability is best estimated by oral and intravenous administrations in the same patient. While this is traditionally done with crossover studies, in pediatrics these studies are advised against for ethical and practical reasons (38). Moreover, measurements at different time points – days apart – do not provide an accurate estimation of bioavailability in critically ill children, whose clearance, volume of distribution and bioavailability keep changing during the course of disease (39–41). Microtracer studies can overcome these limitations as oral and intravenous doses of the same drug are given simultaneously and can be distinguished from one another by labelling one of the doses.

Pharmacodynamics of analgosedation in the PICU

The main goal of analgosedative therapy is to optimize comfort while minimizing adverse events. The intended level of sedation may vary according to the goal, e.g. light sedation to keep the child comfortable and reduce the risk of as unintended removal of tubes and lines, or deeper sedation to guarantee hemodynamic stability, e.g. post cardiac surgery or in pulmonary hypertension. Interestingly, the effects of deep sedation on these outcomes have not received much attention in clinical trials. Additionally, apart from neuropsychological outcomes, adverse events are also understudied.

Depth of sedation after heart surgery

After heart surgery, patients may develop low cardiac output syndrome as a result of the decrease in cardiac output (43, 44). Sedation in this situation was traditionally aimed at lowering the metabolic demand and ensuring hemodynamic stability (45). But accumulating data suggest that profound sedation may be detrimental. It has been associated with longer durations of mechanical ventilation and ICU stay (46), extubation failure (47), increased risk of tolerance and withdrawal (48, 49), delayed recovery (50, 51) and detrimental neurodevelopment outcome on the longer term (52). Therefore there is much to be said for limiting sedative use after heart surgery, although the effect of this strategy on hemodynamic stability needs to be studied.

Hemodynamic consequences of clonidine use in the PICU

The use of clonidine, which has both analgesic and sedative properties, is increasing in the PICU (31,32, 53, 54). Enthusiasm for this agent is driven by concerns about the neurotoxic effects of benzodiazepines (55, 56) and by the absence of clinically significant respiratory depression with α2- agonists (57). On the other side, its potential adverse hemodynamic effects discourage its use, particularly in case of hemodynamic instability (32). Indeed, clonidine can induce hypotension and bradycardia mainly by inhibiting cardiac and vascular sympathetic activities (57) this may negatively affect cardiac output. Compared to dexmedetomidine, another α2-agonists with similar safety profile, studies on clonidine's hemodynamic effect in the PICU are few, preventing its use in the critically ill child.

In summary, a rational choice of drugs, dosing and route of administration of sedatives and analgesics for the critically ill child is so far hindered by the absence of data accounting for the diversity of the clinical situations encountered in the PICU. Innovative approaches including population and microdosing PK studies, alternative informed consent methods, and attention to the interplay between critical illness and pharmacodynamics outcomes are highly needed.

AIMS AND OULINE OF THIS THESIS

1) To review existing knowledge on PK, PD and ethical challenges in critically ill children, with a focus on analgosedatives.
2) To study complex PICU pharmacokinetics using as examples:
   a) The pharmacokinetics of clonidine in ECMO patients
   b) Oral bioavailability of paracetamol in critically ill patients
3) To study hemodynamic efficacy and safety outcomes of analgosedatives
   a) Is hemodynamic stability similar in tailored sedation versus pre-emptive sedation after heart surgery in young infants?
   b) What is the impact of clonidine on hemodynamic stability in neonates after heart surgery and in a general mixed PICU population?

Part II Chapter 2 delineates the impact of critical illness and its treatment modalities on drug pharmacokinetics and pharmacodynamics. Chapters 3 and 4 review the ethical challenges of drug research in critically ill children. The recent progresses in sampling methods, data analysis and outcome measurement tools are described that minimize risk and burden for the children. Furthermore, alternative forms of consent that may be suited to the reality of the PICU are suggested. Chapter 5 describes the current knowledge on PK and PD of analgosedatives in the critically ill.

Part III Chapter 6 describes the first population PK study of clonidine on ECMO and proposes new dosing guidelines for children on ECMO. Chapter 7 presents the first determination of paracetamol bioavailability in a PICU population in an innovative microtracer bioavailability population pharmacokinetic study.

Part IV Chapter 8 presents a study in infants after major heart surgery comparing the effect on hemodynamic stability of pre-emptive sedation with that of sedation tailored to the patient's clinical condition. Chapter 9 describes the hemodynamic effect of clonidine in a neonatal population after heart surgery. Chapter 10 presents a study on the hemodynamic effect of clonidine and the consequences of bradycardia and its risk factors in a large mixed PICU population.

Part V Summarizes and discusses the main findings and conclusions of this thesis and gives recommendations for future research.

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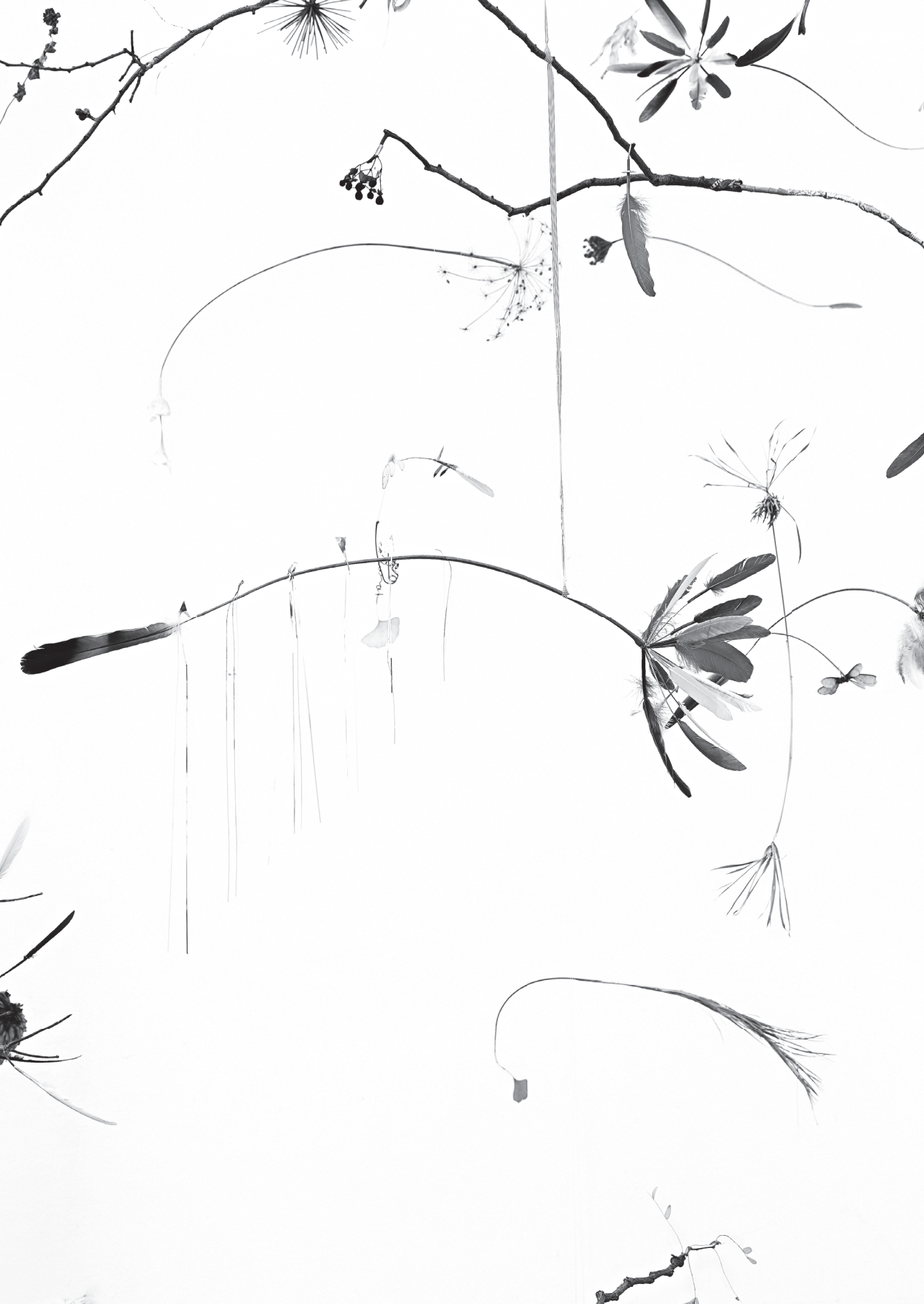
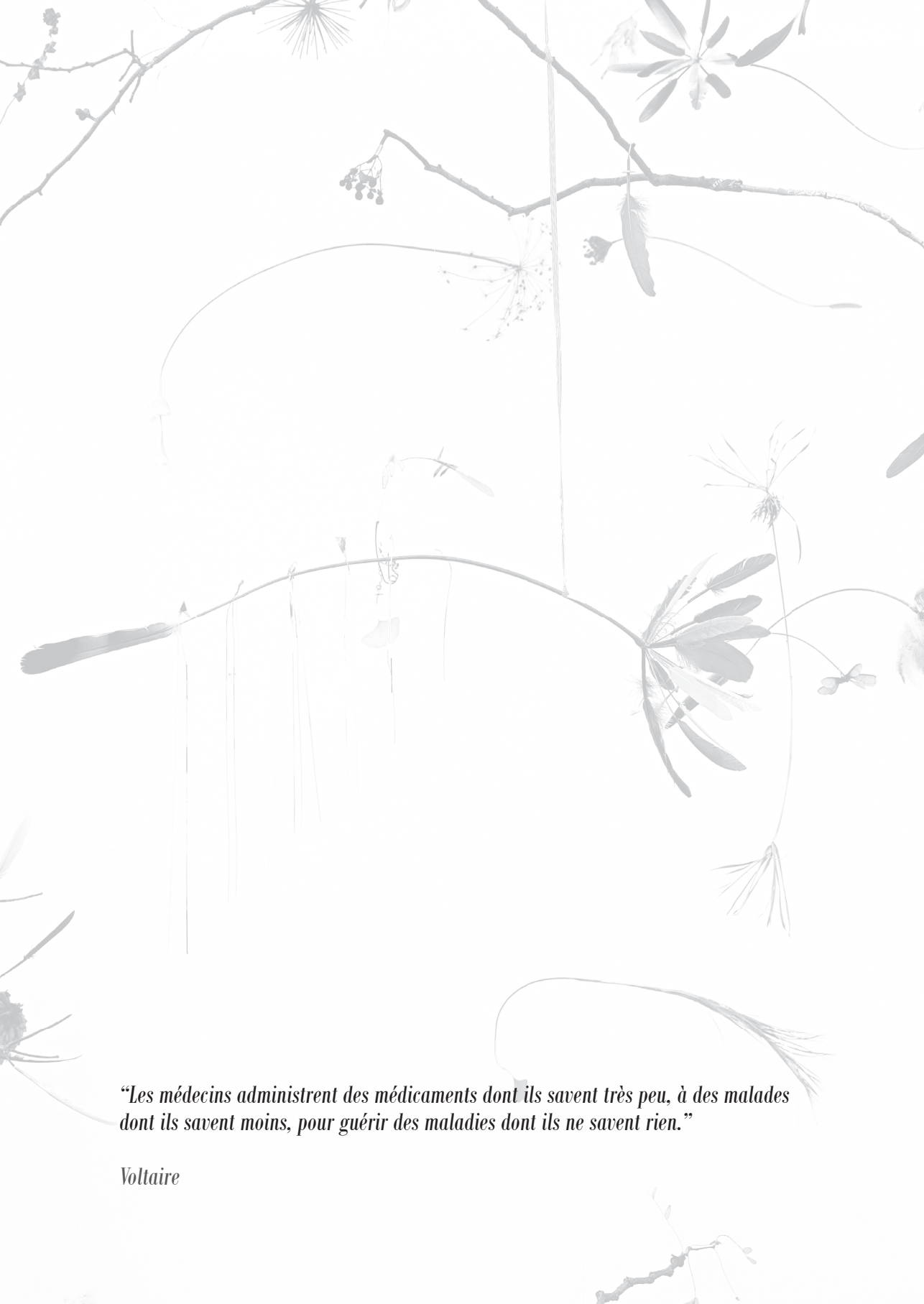


PART II

DRUG STUDIES IN THE PICU: PK, PD AND GENERAL ASPECTS



“Les médecins administrent des médicaments dont ils savent très peu, à des malades dont ils savent moins, pour guérir des maladies dont ils ne savent rien.”

Voltaire

Chapter 2

Drugs and pharmacology in the pediatric intensive care

N. KLEIBER
A. WIGNELL
S.N. DE WILDT

SHARLAND TURNER BARKER (ED) NEONATAL AND PAEDIATRIC PRESCRIBING [PROVISIONAL TITLE].
PHARMACEUTICAL PRESS, LONDON (IN PRESS)

INTRODUCTION

Drug dosing in the critically ill child is a real challenge. In addition to the age-related variation in volume of distribution, drug metabolism and renal excretion, we must take into account the effect of acute illness and its treatment modalities, which can impact on every step of drug pharmacokinetics (PK) and pharmacodynamics (PD). Our current knowledge does not allow for setting dosing guidelines accounting for the diversity of situations typically found in the intensive care unit (ICU). The aim of this chapter is to reduce the risk of improper dosing by delineating general principles governing PK-PD in the critically ill child and describing the main continuous medications used.

PK-PD IN THE CRITICALLY ILL CHILD

PK-PD changes in critically ill children can be due to either intrinsic factors related to the patient's condition or treatment modalities (e.g. ECMO, hypothermia, CVVH). They are summarised in figure 1.

Intrinsic factors related to the patient

Intrinsic factors related to the patient's condition can alter pharmacology in numerous ways:

Absorption

Intestinal absorption

Is dependent on the drug's chemical properties, gastric and intestinal motility and amount of blood flow to the gastro-intestinal tract.

Many conditions can impact on absorption:

- Ileus or decreased intestinal motility often present with shock, sepsis and various gastro-intestinal conditions and may result in delayed absorption and thereby delayed effect (1).
- Malabsorption and gastroenteritis may increase or decrease the extent of absorption and thereby systemic concentrations
- Low cardiac output: blood flow to the gut decreases and gut oedema impairs absorption (2) resulting in lower systemic concentrations of the parent drug.
- Inflammation: through regulation in drug metabolism and transporter activity, which influences gut absorption of drugs (3-5).

Therefore, in the unstable patient and in situations where there is doubt about the quality of absorption, IV formulations should be favoured (6).

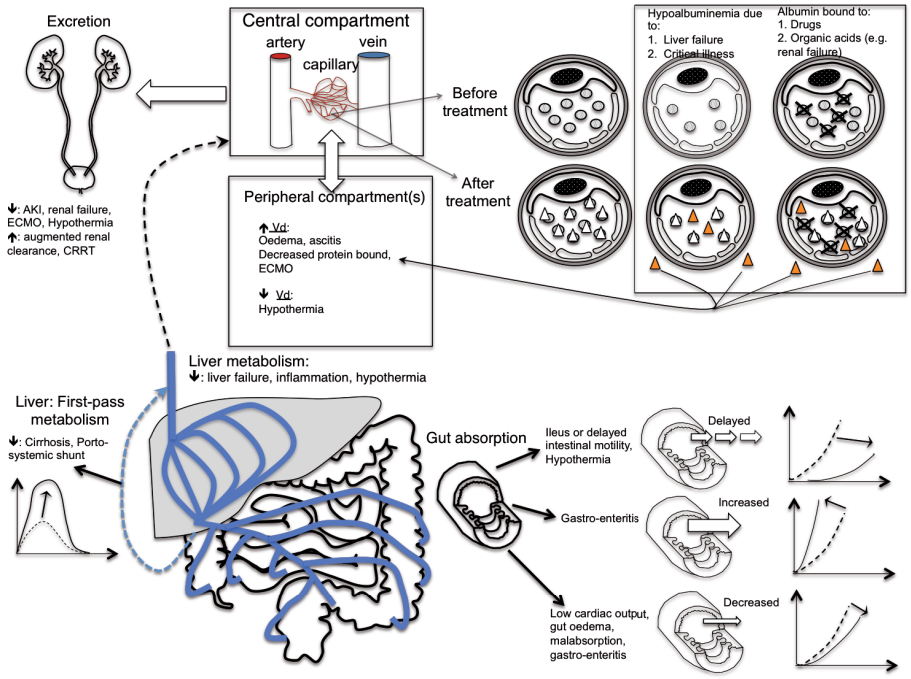


Figure 1: Illustration of the effect of critical illness on drugs pharmacokinetics. Changes in absorption are illustrated by the effect of illness on gut absorption (lower right) and first by-pass metabolism (lower left). Volume of distribution (Vd) is affected by albumin bound (upper right) and features of illness and treatment modalities (listed in the square representing peripheral compartment). The liver is the main organ of drug metabolism; and kidneys (upper left) are the main excretory organ. Changes are represented by an arrow (↑: increase : ↓ decrease) and a graphical representation of drug concentration over time with a dashed line representing PK in a healthy patient and the solid line representing the change induced by critical illness.

First-pass metabolism

In patients with cirrhosis, when the liver is bypassed by extensive porto-systemic shunts, the drugs that undergo extensive first pass metabolism may have significantly increased oral bioavailability leading to a risk of overdose (e.g. propranolol, morphine) (1, 7).

Distribution

The main factors affecting distribution in the critically ill are:

Albumin

A decrease in the amount of unbound albumin leads to:

- An increase in the free concentration of the drug: if the drug is active its effect can be enhanced because more free drug is available for receptor binding (e.g. phenytoin)

- An increased apparent volume of distribution (Vd): the drugs usually bound to albumin disperse into the tissue and decrease the relative concentration in blood for the same total amount.

This situation is typically found in the following situations:
(1) Renal failure, where organic acids compete with the liaison of albumin with drugs (8).
(2) Hypoalbuminemia, which often is seen in critical illness or liver failure (6, 7).
(3) Polypharmacy, as drugs may compete for albumin binding sites.

Change in total body water
Oedema and ascites were found to increase the Vd of hydrophilic drugs (e.g.: aminoglycosides), which distribute in the total body water (1, 8, 9).

Change in blood flow
Normally, it takes around 30 seconds for the blood to flow from a peripheral vein to the arterial circulation. When heart function is severely impaired, cardiovascular stability is fragile and distribution in the circulatory system can be significantly delayed. This warrants careful titration of cardiodepressant drugs (i.e. virtually all analgesic sedative drugs) as sudden collapse may occur if insufficient time is allowed for distribution.

Metabolism
The liver is the main organ of drug metabolism. Drug metabolites are generally inactive but can also be as active or sometimes even more potent than the parent drug (midazolam, morphine).

The mechanism by which liver disease impacts on drug clearance is determined by the extraction ratio (fraction of drug extracted by the liver):
- High clearance "flow limited"drugs: For the drugs that are almost completely extracted (extraction ratio around 1) (e.g. propofol), a decrease in liver blood flow leads to a decrease in metabolism.
- Low clearance "capacity limited" drugs: For drugs only partially extracted (extraction ration << 1) a decrease in liver metabolic capacity is the main determinant of the amount of drug metabolised.

The impact of acute liver failure on drug metabolism is difficult to predict because it does not correlate with the measured indices of liver function (transaminases, bilirubin, albumin) (7).

Systemic inflammation also impacts on liver metabolism (5, 10). Proinflammatory cytokines induce downregulation of the expression of most CYP450 enzymes resulting in a

decreased clearance and increased plasma levels of their substrates with risk of adverse effects (e.g: midazolam, theophylline).

Excretion

Glomerular filtration is the main pathway of drug elimination by the kidneys. This explains why creatinine clearance (CrCl) is currently used to guide dosage of drugs that are renally excreted. In the absence of a practical marker of tubular function, glomerular filtration rate (GFR), which may serve as marker of tubular damage, is also used to guide dosing of drugs dependent on renal tubular function (morphine, cephalosporins)(8). Usually, doses need to be modified when GFR is < 30–40ml/min/1.73m2.

CrCl measurement in patients with low muscle mass warrants caution. As creatinine production is proportional to the muscle mass the measurement may overestimate GFR(11). Some drugs metabolized by the liver have active metabolites that accumulate in renal failure (e.g. one of morphine's metabolites, M-6-G, is more potent than morphine). In patients with decreased GFR, maintenance dosage can be adjusted by increasing the dosing interval or by decreasing the dose. Dosing guidelines are available (e.g http://www.kdp-baptist.louisville.edu/renalbook/) and seeking advise from clinical pharmacists is recommended.

In contrast, augmented renal clearance (supranormal GFR) is an increasingly recognised condition in PICU patients (12–14) which leads to increase drug clearance with risk of underdosing renally excreted drugs. Subtherapeutic levels of, for example, antimicrobial treatment may potentially have devastating consequences (15–17).

Extrinsic factors related to the treatment of the patient

A number of external treatment modalities, discussed below, can also affect PKPD in ICU.

ECMO

Distribution

For most drugs Vd increases (volume added and adsorption to the circuit). Lipophilic drugs (midazolam, fentanyl) are more adsorbed by the circuit than the more hydrophilic drugs (morphine, gentamicin, cefotaxime) and therefore their blood levels may be lower. Hence, at initiation of ECMO, an increase in drug requirement is expected. Thereafter, steady state levels are mainly affected by clearance and dose rate(18).

Change in PK depends also on the type of ECMO circuit and composition of the priming solution (19).

Clearance

In general, clearance in ECMO-patients is lower than in non-ECMO patients (0–50% decrease). Sedatives and analgesics are titrated to effect and require generally higher

doses (mostly at initiation of ECMO). Antibiotics are affected. Cautious dosing and close monitoring of highly toxic agents such as gentamcin is advised, but dose adjustments are not necessary for beta-lactams such as cefotaxime (20).

To date, there are no recommended dosing guidelines for medications on ECMO.

Hypothermia

Absorption

Hypothermia decreases the rate of absorption. This therapy is often used in patients with decreased intestinal motility (secondary to a cardiac arrest or asphyxia), adding to the unpredictability of oral absorption (21). Therefore, intravenous administration is more reliable in hypothermic patients.

Distribution

The volume of distribution changes due to redistribution of blood flow, and changes in blood pH and physicochemical properties of the drugs with hypothermia (change in protein binding). Vd can increase or decrease depending on the drug properties, with risk of under- and overdosing, respectively (22–24).

Metabolism

Decreased enzymatic rate at low temperature decreases clearance of drugs eliminated via hepatic metabolism (e.g.: morphine accumulation in neonates even with same infusion rates (25)). There will be a delay of action for pro-drugs (slowed transformation into active compounds) while active drugs may accumulate.

Excretion

Decreased liver metabolism and renal clearance leads to a risk of accumulation. Maintenance doses need to be decreased especially for non-clinically titrable drugs and low therapeutic index medications.

Pharmacodynamics

The EC50 can increase or decrease with cooling, depending on the drug. For example morphine's EC50 increases, which implies that higher drug levels will be needed for the same effect. The opposite happens for inotropic drugs, the effects of which may be increased. Consequently the changes in PK could match PD in particular situations (e.g.: a drug has increased levels, but these higher levels are actually needed to produce the same effect) (22).

During the rewarming phase following hypothermia, the PK-PD parameters should normalize and care must be taken to adapt medication dosing accordingly.

Cardio-pulmonary bypass (CPB) and combined effect of ECMO and hypothermia

CPB is used to preserve perfusion during heart surgery. It combines the use of an extracorporeal circuit – similar to ECMO – and hypothermia (which preserves organ function) but it is applied for a shorter period and rewarming is initiated within a few hours.

ECMO combined with hypothermia is mainly used for neuroprotection after cardiac arrest. In the absence of any adult/paediatric data, the changes can only be speculated on based on the CPB literature and the available knowledge on each modality separately (24, 26).

Distribution

When either bypass or ECMO is combined with hypothermia, we have to account for opposite effects on Vd. Initiation of bypass or ECMO causes Vd to increase (notably in the case of lipophilic drugs), due to the added circuit and adsorption by the circuit. Hypothermia decreases Vd, but only to a limited degree compared to the increase secondary to ECMO.

Metabolism and excretion

In both cases, bypass combined with hypothermia, and ECMO combined with hypothermia, drug clearance will be lower.

Haemofiltration, which is commonly used on ECMO or bypass, affects elimination: the smaller size (< 500Da), hydrosoluble and poorly protein bound drugs will be significantly eliminated while the drugs that are not filtered will be concentrated (24, 27).

Continuous renal replacement therapy (CRRT)

Continuous haemofiltration is based on the principle of hydrostatic pressure to drive fluid through a filter. The filtered plasma is called ultrafiltrate. Continuous hemodialysis uses passive diffusion through a membrane for substrate removal. The dialysed plasma is called dialysate. Haemodiafiltration uses both principles.

CRRT has a major impact on drug clearance (28). Current dosing guidelines in paediatric patients on CRRT are mostly derived from adult studies(29).

An easy way to get an idea about the expected amount of drug that will be removed by CRRT (28, 30) is to evaluate:

Volume of Distribution

The higher the Vd the less likely a drug will be cleared by CRRT because it is mainly concentrated in extravascular compartments unavailable for RRT. Drugs with a Vd exceeding 0.7L/kg that are more lipophilic and concentrated in adipose tissues are less likely to be cleared. For example, CRRT is not effective for e.g. digoxin (Vd of 7.3L/kg) poisoning.

Sieving coefficient (Sc)

This coefficient represents the degree to which a particular membrane allows the passage of a solute. It is measured by the ratio of solute concentration in the ultrafiltrate to the solute concentration in the plasma (Sc = 1 means that 100% of solute will be removed; Sc = 0 means that the solute is not removed at all).

The major determinants of the Sc of a drug are:

- *Degree of protein binding*:
  Sc can be estimated by: Sc = 1-protein binding. It gives a quick estimate of the expected amount of drug removal.
- *Drug-membrane interactions*: The passage through the membrane is determined by:
  - size of the membrane pores: these allow molecules up to a certain size to pass through (usually 20 kDa)
  - charge of the molecule

Amount of ultrafiltrate or dialysate

This is prescribed by the clinician and is the principal determinant of drug removal.

General principles

Despite recent advances in the understanding of PKPD in the PICU, our knowledge is not sufficient to allow adequate titration of drugs. Dosing guidelines that incorporate the complexity of critical illness are unlikely to be achieved in the near future. In the meantime, the above principles should help the PICU clinician to develop a critical view when prescribing.

Between these areas of uncertainty, some general principles apply:

1) Drugs that can be titrated to effect (e.g. sedatives and inotropes) can be dosed clinically.
   Knowledge of their properties in a particular situation guides the choice of the right agent (for example morphine is less adsorbed than fentanyl in children on ECMO and therefore should be favoured) or the timely titration of the dose (decrease sedation in hypothermia).
2) Especially in critical illness with organ involvement, care must be taken to avoid every unnecessary medication. Favouring medication that is not inactivated by the liver or just metabolised through a single step decreases the potential for adverse reactions.
3) Frequent monitoring of serum levels of medication with a narrow therapeutic index (aminophylline, anticonvulsants, cardiac glycosides…) or medication with potentially severe consequences of underdosing (aminoglycosides,…) is recommended

when the clinical condition changes or after use of particular treatment modalities (ECMO, hypothermia,…)

4) Favour IV formulation if there is uncertainty about absorption.

CONTINUOUS MEDICATION USED IN PICU

Continuous medication allows easy titration and stable plasma levels. It takes 3–5 half-lives for a drug to reach steady-state, and for it to be largely cleared from the body. Hence, when the half-life is short, quick titration to the effective concentration is reached (inotropes, some antihypertensives). When the half-life is long a loading dose may be needed to reach therapeutic plasma level more quickly (e.g. milrinone, morphine, midazolam).

Cardio- and vasoactive drugs

Cardio- and vasoactive drugs are commonly used in the PICU for treatment of low cardiac output syndrome (LCOS) from sepsis, cardiogenic shock or its prevention after cardiac surgery. Conventional inotropic agents (adrenaline, noradrenaline, dopamine and dobutamine) stimulate different adrenergic receptors and therefore differ in their positive inotropic effect (β1 receptor effect of increased contractility), peripheral vasoconstrictive (α receptor effect) or vasodilatory properties (β2 receptor). Newer agents include milrinone, an inhibitor of phosphodiesterase type 3, and levosimendan, a calcium sensitizer agent that increases troponin C sensitivity to calcium (31, 32).The choice of medication is dictated by the patient's haemodynamics and physician's individual preferences. For example, in warm septic shock, vasodilation will be countered by noradrenaline while in cold shock adrenaline or dopamine will be preferred (33). Table 1 summarizes effects of cardio- and vasoactive drugs derived from adult studies. Milrinone has been shown to decrease the occurrence of LCOS diagnosed clinically (34). The lack of studies comparing the effectiveness of different agent for preventing of LCOS leads to a large difference in practice (35, 36). For prevention and treatment of LCOS, vasodilating agent are frequently added to cardioactive drugs to reduce afterload on the myocardium once BP has been restored toward normal range. Arteriolar and venodilator agents lacking inotropic negative effect are recommended (e.g. SNP, phentolamine).

Antihypertensive agents with inotropic negative properties (e.g. nicardipine and esmolol) are used for the treatment of hypertension with preserved heart function (37, 38).

Table 1: Effects of cardio- and vasoactive drugs derived from adult studies. The doses of dopamine and adrenaline inducing more vasoconstriction are approximate and should be correlated to the overall clinical picture.

2 useful formulas to keep in mind when titrating cardio- and vasoactive drugs

BP ≅ CO * SVR => good BP doesn't always reflect good CO

CO = HR * Stroke volume => but time for filling is needed to ensure Stroke volume

Agent		Receptor	HR	Inotropy	SVR	
Dopamine	<10mcg/kg/min	β > α	↑	↑↑	↑	
	>10mcg/kg/min	α > β	↑	=	↑↑	CO can decrease
Dobutamine		β	↑↑	↑↑	↓	More arythmias
Adrenaline	< ≈ 0.2 mcg/kg/min	β > α	↑	↑↑	↑	
	> ≈ 0.2 mcg/kg/min	α > β	↑		↑↑	CO can decrease
Noradrenaline		α >>β	↑	↑	↑↑↑	Good choice in vasoplegic patient
Milrinone		PDE-3 inhibitor	=	↑↑	↓	Vasodilation can cause decrease in BP. Caution if borderline BP.
Levosimendan		Calcium sensitizer	=	↑↑	↓	

Abbreviations: BP: blood pressure; CO: cardiac output; HR: heart rate; SVR: systemic vascular resistance

Sedatives and analgesics

Analgesics are targeted to relieve pain while sedatives serve to calm the patient in the stressful environment of the PICU and allow care (mechanical ventilation, usual nursing care,…).

Pain relief is most commonly achieved with continuous infusion of opiates (fentanyl or morphine); sedation with benzodiazepines (midazolam, lorazepam). Both agents induce respiratory depression. Alpha-agonists (clonidine and dexmedetomidine) have both sedative and analgesic properties and induce bradycardia instead of respiratory depression. Propofol has sedative and hypnotic properties, and a strong cardio-depressant effect hampering its use in the hemodynamically unstable child. It has a very short recovery time on discontinuation and facilitates weaning of long acting sedatives around the time of extubation. Its use is contraindicated in the official drug label for children < 16y due the risk of lethal propofol infusion syndrome. Despite these warnings, its

unique properties motivates some clinicians to use it even in small children and adverse effects may not be as common as feared (39).

The optimum level of sedation leading to better clinical outcomes is yet to be determined. Oversedation increases the risk of tolerance, withdrawal and delirium and prolongs duration of intubation (37). Despite this evidence, achieving the goal of optimal sedation remains a challenge and a tendency toward oversedation has been described in the PICU setting (40). A way of avoiding oversedation is to proceed to daily sedation interruption (41). Another way of decreasing medications that depress ventilation is to use alternative medications like paracetamol (42), clonidine (43) or dexmedetomidine. Virtually all available sedatives and analgesic medications are neurotoxic in animal models. Human studies are still scarce (44) and conflicing. Morphine administration in neonates has been reported to be without adverse long-term effects in a cohort of preterm newborns followed up at 8–9 years of age (45), while it has been shown to predict adverse neuropsychological outcome in meningococcal septic shock survivors (46). Improvement of neurological outcome is a significant concern in PICU, and analgesics and sedatives certainly play a significant role which requires further research.

CONCLUSION

Understanding of pediatric pharmacology in critical illness has grown enormously over recent years. This chapter has given an overview of this complex field. However, our current insight is still insufficient to allow targeted PK-PD optimization with simultaneous minimization of adverse effects in the critically ill. Population approaches of PK/PD modeling are promising (47). PKPD models taking into account the complexity and rapidly evolving critical disease states and treatment modalities are the ultimate goal, to facilitate dose individualization and optimizing clinical outcomes.

List of the most commonly used continuous drugs in the PICU

	Mechanism of action / site of action	**Relevant pharmacokinetic characteristics**	**Contraindications / Toxicity ((48, 49)and TDM if relevant) Important/common drug interactions**
Morphine	μ receptor agonist	Liver metabolism into M3G and M6G (the latter is more potent than morphine) they are excreted by kidneys => may accumulate with renal failure. Morphine clearance decreased with postnatal age < 10 days(48, 49). Not ideal for painful procedures: peak of action 20 minutes.	Can cause respiratory depression
Fentanyl	μ receptor agonist Synthetic opioid, 100 times more potent than morphine Anaesthetic agent	Metabolized by the liver by CYP450 3A4 into inactive metabolites. Compared to morphine: easier titration in renal failure (no active metabolite). Quick peak of action: ideal for short painful procedures. Context sensitive half-life: the longer the infusion, the longer the time taken to clear.	Can cause respiratory depression Can cause chest wall rigidity +/- associated laryngospasm inducing ineffective ventilation, desaturation (treatment options: naloxone, neuromuscular blocking agent, intubation)
Remifentanyl	μ receptor agonist Compared to fentanyl: equipotent, quicker onset of action Anaesthetic agent	Metabolized by plasma esterases. Elimination is independent of hepatic metabolism or renal excretion. Short offset even after long infusion.	Can cause respiratory depression
Midazolam	GABA receptor agonist Anxiolytic and amnesic agent	Extensive hepatic metabolism by CYP 3A=> primary metabolite 1-OH midazolam is equipotent to midazolam The 1-OH midazolam-glucuronide (weak sedative effect) accumulates with renal failure. Large Vd and low Sc therefore, no dosing adjustment is expected on CRRT.	Can cause respiratory depression Avoid bolus of midazolam in hemodynamically compromised patient (hypotension) Many interactions with CYP3A4 inducing or inhibiting agents: careful titration to effect
Clonidine	α-adrenergic receptor sedative and analgesic properties specificity for α-2 receptors: α-2:α-1 = 200:1	Increased half-life with renal failure Half-life: Neonates:18h (50) / Children: 9h (51) / Healthy adult: 12–26h / Adult with renal disease: 41h	Bradyaryhtmia No clinically significant respiratory depression (52)

List of the most commonly used continuous drugs in the PICU (continued)

	Mechanism of action / site of action	**Relevant pharmacokinetic characteristics**	**Contraindications / Toxicity ((48, 49)and TDM if relevant) Important/common drug interactions**
Dexmedetomidin e	α-adrenergic receptor sedative and analgesic properties more specific than clonidine for α-2 receptors (α-2: α-1 = 1600:1)	Liver metabolism Neonatal clearance: 40% of adult value, At 1 year: 85% of adult clearance ½ life: 2,4 h (children) (53)	Bradyarythmia No clinically significant respiratory depression (52)
Propofol	Alkylphenol with sedative and hypnotic properties, not well defined mechanism of action	Rapid onset and short duration of sedation on discontinuation and facilitates weaning of long acting sedative around the time of extubation and neurologic evaluation of patient with traumatic brain injury. Unaffected by renal and hepatic dysfunction. FDA recommends maximum rate of 4mg/kg/h for max urs	Contraindicated in hemodynamically unstable child: can cause profound hypotension and collapse. Risk of propofol infusion syndrome (PRIS) (clinical and biological signs: metabolic acidosis, increased liver, lipemia, rhabdomyolysis,…) that can be fatal. Any suspicion of PRIS should lead to an immediate interruption of propofol infusion but despite discontinuation, death can ensue (54).
Sodium nitroprusside	Nitric oxide liberation during rapid metabolic breakdown => peripheral vasodilator No negative inotropic effect: safe with decreased heart function or after cardiac surgery	Very easy titration: abrupt discontinuation or downward titration if hypotension with very quick response on BP 1. Converted into cyanide in blood and tissues 2. Liver: cyanide converted to thiocyanate (risk of cyanide accumulation in liver failure) 3. Thiocyanate renally excreted (risk of accumulation in renal failure)	Signs of cyanite toxicity: cellular dysoxia from mitochondrial dysfunction: lactic acidosis with high mixed venous saturation, hypotension, tachycardia, shock, coma, death. Measure cyanide level if liver dysfunction. Signs of thiocyanate toxicity: confusion, psychosis, coma, death. Level are advised if infusion > 3days or renal impairement.(38).
Esmolol	β- blocker with β1 selectivity / site of action: AV, SA node	Very quick onset of action Easy titration (38) Higher rate of clearance in neonates compared to older children No accumulation with liver or renal failure (metabolised in blood by esterase)(55) Some formulations contain ethanol and propylene glycol	Contraindication: Sinus bradycardia, heart block, uncompensated heart failure (negative inotropic effect) Caution: reactive airway disease

List of the most commonly used continuous drugs in the PICU (continued)

	Mechanism of action / site of action	**Relevant pharmacokinetic characteristics**	**Contraindications / Toxicity ((48, 49)and TDM if relevant) Important/common drug interactions**
Nicardipine	Slow Calcium channel blocker => decreased myocardial and vascular smooth muscle cell Calcium concentration => less Calcium available for contractility => vasodilation => decreased BP	Extensive hepatic metabolism by CYP 450 isoenzyme (CYP 3A4) => Many interactions (with CYP3A inducers or inhibitors)	If cardiac failure, be aware of negative inotropic effect. Contraindicated if significant obstruction of systemic circulation (e.g: coarctation of the aorta)(55)
Labetalol	Antagonist of α1 and β-adrenergic Receptor	Long half-life (3–3h) Titration should be slow. Metabolised by hepatic glucuronidation(55).	Contraindicated in cardiac failure due to negative inotropic effect Risk of bronchospasm in asthmatic patient
Hydralazine	Direct arteriolar vasodilator with unknown precise mechanism. Combined positive inotropic and chronotropic stimulation of the heart => increased cardiac output Particularly useful in children with underlying hypertension on multiple medication	Extensive first pass effect with oral administration: 10-30% of oral bioavailability depending on acetylator status. Onset of action: 10 minutes	Contraindication: dissecting aortic aneurysms, mitral valve rheumatic disease (increase of stroke volume can worsen dissection or regurgitation), significant coronary artery disease (risk of ischemia). Adverse effect with long term use: Drug-induced lupus like syndrome. Concomitant use of MAO inhibitors may cause profound hypotension.
Phenoxybenzamine, Phentolamine	Systemic vasodilators by α -adrenergic blockade. Used in catecholamine-induced hypertension (e.g pheochromocytoma) or for afterload reduction after cardiac surgery. Phentolamine: competitive reversible antagonist Phenoxybenzamine: irreversible	Once α –blockade is achieved, if needed β-blockade can be done to counteract tachycardia(37).	Suspect overdosage if signs of sympathic nervous system blockade: vomiting, marked tachycardia, hypotension shock. Treatment of overdose: Noradrenaline. NB: Adrenaline contraindicated (because α-receptors are blocked and adrenaline will cause selective β-adrenergic stimulation and will further increase hypotension)(55).

List of the most commonly used continuous drugs in the PICU (continued)

	Mechanism of action / site of action	**Relevant pharmacokinetic characteristics**	**Contraindications / Toxicity ((48, 49)and TDM if relevant) Important/common drug interactions**
Dopamine	α1, α2, β1 >β2 adrenergic receptors agonist, dopaminergic receptors increased contractility, increased BP. Precursor of noradrenaline	Precursor of noradrenaline Very easy titration Short half life	At high doses may lower cardiac output by marked vasoconstriction
Dobutamine	β1 > β2, α1 adrenergic receptors agonist leading to increased contractility, HR, vasodilation	Very easy titration Short half life Tachycardia not uncommon.	Can decrease BP by vasodilation (56)
Adrenaline	α1, β1, β2 adrenergic receptors agonist Multiple indications: In bolus: cardiac arrest, extremely low BP or symptomatic bradycardia, anaphylactic reaction. Infusion: shock, bronchospasm (if no more selective β2 agonist available)	Very easy titration Short half life	At high doses may lower cardiac output by marked vasoconstriction Can increase lactates at high dose (can be misinterpreted as anaerobic metabolism due to shock) (56)
Noradrenaline	α >> β1 adrenergic receptors agonist Ideal drug for warm shock	Very easy titration Short half life	Vasoconstriction can increase BP without affecting cardiac output or decrease CO (31)
Milrinone	Phosphodiesterase inhibitor class 3 Lusitropic properties: improvement in diastolic function (and properties listed in table 1)	Excreted unchanged: accumulation with renal failure. Relatively long half-life (slow titration and bolus dose may be needed to quickly reach steady state)(55)	Can cause hypotension by decrease in vascular resistance. Do not give if borderline BP(56)
Levosimendan	Calcium sensitizing drug: interacts with troponin C and increases its sensitivity to calcium => increased efficiency of contractile apparatus of myocytes	Hepatic metabolism(8) Infusion given over several hours. Loading can be given at the beginning of infusion but can lead to significant vasodilation and hypotension. Effect last for many days	Can cause hypotension by decrease in vascular resistance. Do not give if borderline BP (31)

Abbreviations: AV: atrio-ventricular; BP: blood pressure; CO: cardiac output; CRRT: continuous renal replacement therapy M3G morphine-3-glucuronide; HR: heart rate; M6G: morphine-6-glucuronide; SA node: sinus node; TDM: therapeutic drug monitoring

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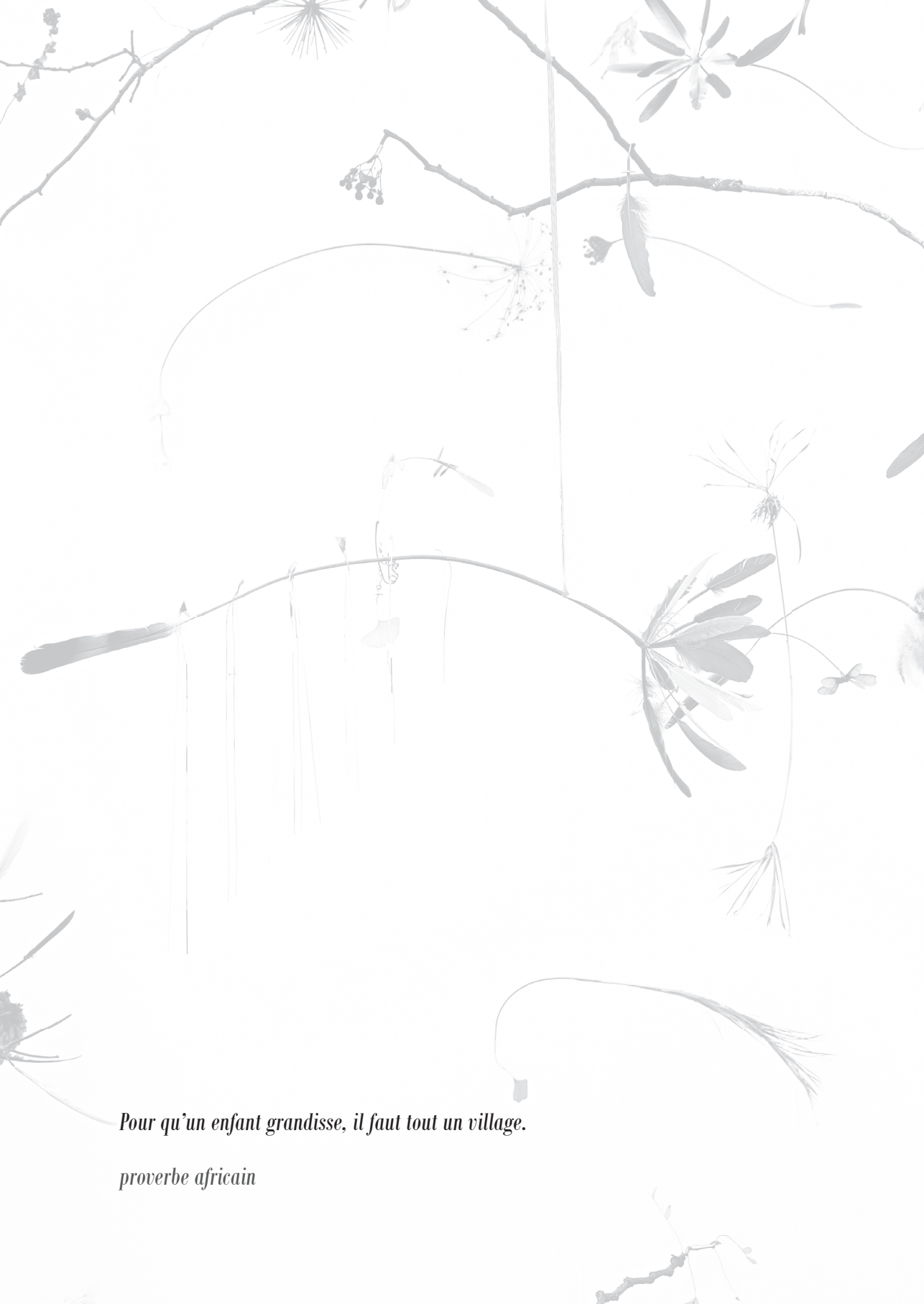

Pour qu'un enfant grandisse, il faut tout un village.

proverbe africain

Chapter 3

Ethics of Drug Research in the Pediatric Intensive Care Unit

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ABSTRACT

Critical illness and treatment modalities change pharmacokinetics and pharmacodynamics of medications used in critically ill children, in addition to age-related changes in drug disposition and effect. Hence, to ensure effective and safe drug therapy, research in this population is urgently needed. However, conducting research in the vulnerable population of the pediatric intensive care unit (PICU) presents with ethical challenges. This article addresses the main ethical issues specific to drug research in these critically ill children and proposes several solutions.

The extraordinary environment of the PICU raises specific challenges to the design and conduct of research with the ability to generate useful results. The need of proxy-consent of parents (or legal guardians) and the stress-inducing physical environment may threaten informed consent. The informed consent process is challenging because emergency research reduces or even eliminates the time to seek consent. Moreover, parental anxiety may impede adequate understanding and generate misconceptions. Alternative forms of consent have been developed taking into account the unpredictable reality of the acute critical care environment

As with any research in children, the burden and risk should be minimized. Recent developments in sample collection and analysis as well pharmacokinetic analysis should be considered in the design of studies.

Despite the difficulties inherent to drug research in critically ill children, methods are available to conduct ethically sound research resulting in relevant and generalizable data. This should motivate the PICU community to commit to drug research to ultimately provide the right drug at the right dose for every individual child.

Key points

- Drug research in the pediatric intensive care unit is highly important for the advancement of pediatric medicine, but is a precarious enterprise due to the vulnerability of the research population.
- The informed consent process for research in the pediatric intensive care unit comes with ethical and practical challenges due to the stress-inducing environment, time constraints, lack of capacity of minors to decide about trial participation, and the role of parental (or other proxies') consent.
- Innovative research methods might help minimize burden and risk for children participating in drug research in the intensive care unit.

1. INTRODUCTION

1.1 Protection of minors vs. advancement of knowledge

Drug research in children balances between the advancement of knowledge – and consequently improvement in clinical care – and protection of this vulnerable population susceptible to harm and exploitation. Children are relatively incapable of protecting their own interests and therefore need additional protection as recognized in many international ethical and legal documents concerning research with humans [1–4]. Specific provisions for minors, for example relating to the informed consent process and the acceptability of burden and risks have recently been reviewed by our group [5]. These provisions pose challenges to research in children. Failing to conduct clinical trials in minors turns children into « *therapeutic orphans* » because the level of protection is not balanced with the need of generating knowledge to improve care [6].

1.2 The need for drug research in children

We need to be aware that every medication used in clinical practice that has not been studied in clinical trials can be considered an experiment. Clinical drug trials in children are essential because data on effectiveness and safety often cannot reliably be derived from data in adults. Major changes in pharmacokinetics (PK) and pharmacodynamics (PD) occur with increasing age due to changes in body composition, ontogeny of drug metabolism and transport and renal function [7]. The relative lack of knowledge on drug disposition can lead to treatment failure [8, 9] and adverse events as serious as fatalities [10, 11]. It is known that extrapolation from adult data has caused harm in the past. For example, a lack of knowledge on ontogeny of enzymes responsible for conjugation caused grey baby syndrome in neonates treated with doses of chloramphenicol derived from adult studies [12, 13]. Similarly, drug choice and dosing for patients in the pediatric intensive care unit (PICU) cannot always be derived from research in the general pediatric population because PK/PD is influenced by critical illness [e.g. inflammation [14], liver and renal failure [15–17]) and its treatment modalities (e.g. extra corporeal membrane oxygenation (ECMO) [18], hypothermia [19], continuous renal replacement therapy [20].

Some drugs (such as vasoactive and sedative drugs) are almost exclusively used in critically ill children, and therefore can only be researched in these patients. However, a large proportion of drugs used in pediatric practice has not been systematically tested in the pediatric population. To stimulate pediatric drug research the Best Pharmaceuticals for Children Act [21] and a similar directive in Europe [22] offered incentives to pharmaceutical companies to generate data in children. Regrettably, fewer than 50% of these studies and 26% of those focusing on safety were published in peer-reviewed journals. Moreover, studies on safe and efficient drugs were more likely to be published than studies resulting in negative labelling change [23], putting children at risk of inefficient or unsafe prescrip-

tions. Although these stimulating measures generated some useful safety and prescribing information in children, they did not result in the expected reduction of off-label use [24, 25]. Estimates of off-label use in the pediatric population still range from 10–65% [26]. In the PICU, even up to 70% of drugs are unlicensed or off-label [27, 28], which reflects the lack of knowledge on drug efficacy and safety in the PICU population [29].

1.3 Challenges of drug research in the PICU

The previous section has made clear that drug research in the PICU is essential. But research in this population of critically ill children is precarious and raises specific ethical challenges. These challenges may be specific to culture and legislation of each individual country; this article focuses mainly on research in high income countries. The ethical dilemma of conducting research in the PICU is recognized by pediatric intensivists themselves; in a survey of 415 pediatric intensivists, over 95% found randomized controlled trials (RCTs) on potentially life-saving therapies ethically acceptable, but at the same time almost all were in ethical conflict with these studies [30]. The specific challenges faced by researchers in the PICU are, first, the extraordinary physical environment of the PICU that presents challenges to the design and conduct of research and its ability to generate useful results. Second, the children themselves may be too young to consent or incapable of it due to acute illness and sedation. Then, parents or surrogates are responsible for the decision to involve their child in research, with consequences for the informed consent process, notably under the stressful conditions of the admission. Last, patients in the PICU already undergo many painful and invasive procedures as part of clinical care. Therefore, additional burden must be minimized.

Improving care of the critically ill child implies generating reliable knowledge with research widely endorsed by caregivers and families. This article addresses the main ethical issues specific to drug research in the PICU and proposes several solutions.

2. OPTIMAL STUDY DESIGN AND CONDUCT

2.1 Introduction

Research subjects included in research of poor quality are exposed to risk and burden without benefit, neither for themselves nor for others. Therefore only methodologically sound research that can generate new results should be proposed to possible research subjects. This requirement was already laid down in the Nuremberg Code in 1949[2], and consequently in all other important ethical and legal documents concerned with research with humans (for example [1, 3, 4]). The specific study population, recruitment method, outcomes measures, use of rescue medication and protocol adherence can influence the validity of research in the critically ill child and consequently influence the usefulness of the generated results (Table 1).

Table 1. Challenges to quality of clinical drug studies in critically ill children

Theme	Challenge	Impact on results of trial
Study population	Heterogeneous, small patient populations and relative lack of multi-center research networks	Risk of inconclusive trials due to limited sample size
Recruitment	Risk of selective recruitment: the sickest patient may not be enrolled	Risk of bias and reduced generalizability
Outcome measure	Selection of clinical relevant outcome measures may be jeopardized by small sample sizes	Outcome may be clinically irrelevant
Rescue medication	Allowing rescue medication with the study drug in placebo arm, as not doing so may be perceived as unethical	True efficacy of study drug cannot be determined
Protocol adherence	Protocol violations due to ethical conflicts e.g. when a child's condition deteriorates and physician is biased towards the, potential life-saving, study intervention	May severely impact the validity of study results

2.2 Study population

Children in the PICU represent a wide age range and a broad case mix of underlying diseases and ICU diagnoses. Moreover, the acutely ill child receives many drugs simultaneously and combinations differ between centers. Therefore, while studying a single drug, the interactions with co-medications and type of underlying diagnosis and care may interfere with outcomes. More than 80% of randomized controlled trials (RCT) are single-centered [31]. This reduces generalizability of the results from these trials. Data sharing and collaboration in larger international PICU research networks could overcome this limitation. Examples of pediatric critical care networks are the Canadian Critical Care Trials Group (Pediatric Interest Group) and the NICHD Collaborative Pediatric Critical Care Research Network. Europe and the other continents are lagging behind: to our knowledge international PICU networks are non-existent to date.

2.3 Recruitment

An underestimated limitation to the generalizability of PICU trial outcomes could be the difficulty with recruitment. One third of RCTs in the PICU is terminated before the needed sample size is achieved, often due to recruitment problems [31]. One of the reasons for recruitment problems could be reluctance to approach potential research subjects, also known as 'gate-keeping', which attitude may be due to the clinicians' fear of excessive patient burden [32]. This usually means that the sickest patients are less likely to be included in research. To our knowledge, the study by Menon et. al. is the only addressing barriers to the recruitment process in the PICU. This was an observational trial implying an ACTH stimulation test, blood sampling on an existing line and recruitment within 26 hours of admission. Almost 50% of 1707 eligible research subjects were

not approached due to unavailability of legal guardians, language issues, lack of agreement of treating physician and prior enrolment in another study [33]. Thus, we need to be aware of possible selection bias and its effects on generalizability of research results in the PICU. One solution to recruitment issues could be co-enrolment of patients in multiple studies [34]. Research shows that participation rates do not decline when parents are asked to have their child participate in two studies simultaneously. This is only possible, however, if it does neither effect study outcome (e.g. simultaneous inclusion in two RCTs with potential influence on outcome of the studies) nor increases patient burden and risk to unacceptable levels (e.g. additive blood sampling volume increases above safety margins).

2.4 Outcome measures

Appropriate outcome measures in PICU research are another challenge. It is 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 of many studies (median of 49 patients) [31]. While the majority of trials report laboratory or physiological primary outcomes, mortality was the primary outcome measure in 2% of trials [31]. Data from a recent feasibility trial of clonidine for sedation suggest that at least 190 patients are needed to show a 1.5 day difference in days of ventilation and many more to show relevant differences for other outcomes such as length of PICU and hospital stay [35]. Laboratory or physiological outcomes should be clinically relevant, otherwise the research cannot result in improvement of patient outcome [36]. Relevant outcome measures and validated assessment tools are therefore essential. The latter is not always the case. For example, Vet et al. showed that two thirds of the many different sedation scores used in studies on ventilated children receiving a continuous infusion of sedatives were not validated for PICU patients [37]. Regarding the effect of a medication, it must be kept in mind that adverse effects may not become apparent until years after PICU stay. A major concern in this regard is the possible effect of sedative and analgesic medication on longer-term neurological outcome [38]. Enrolling former PICU patient in follow-up programs can broaden our knowledge on long-term outcomes. This should be encouraged, as currently very few units provide care and research beyond the ICU stay.

2.5 Rescue medication

The use of rescue medication in a randomized trial for a potential life-saving intervention with a placebo group presents additional ethical and scientific challenges [39]. Full equipoise regarding the efficacy of the study drug contrasts with the clinician's perceived need to administer the study drug as a rescue therapy despite the inclusion of the patient in the placebo group. When rescue therapy is allowed, only 'early' versus 'late' effects can be determined when analyzing data on an intention to treat basis. More chil-

dren are needed to show a beneficial effect of the drug. As a consequence, overall more children will receive placebo and be at risk for a negative outcome, including death, provided the study drug is really effective. Holubkov et al. [39] present an interesting hypothetical study, i.e. steroids for pediatric septic shock, and use sample size simulations to illustrate this challenge. A solution to avoid misuse of rescue medication is to educate physicians, nurses and other staff involved in the care of research participants on the rationale and clinical equipoise in research.

2.6 Protocol adherence

Protocol adherence may be jeopardized if the treating physician is biased towards the study drug and may decide to violate the study protocol when a patient's situation is deteriorating. In the survey of Morris et al., discussed above, a large majority of physicians admitted that they may be biased toward the study arm on the basis of published data from uncontrolled studies [30]. Moreover, two thirds indicated that they do not fully adhere to the study protocol when the patient's condition deteriorates and parents ask for the study drug. There was a strong correlation between the occurrence of an ethical conflict and the likelihood of protocol violations, compassionate use of the study drug or alterations to the protocol. These violations are an important risk factor for bias in these studies and consequently may affect the validity of the findings. A way of avoiding protocol violation is to inform everyone involved in the care of the research subjects about the rationale for the study, the existing equipoise motivating its conduct and the potential benefits of the study.

3. INFORMED CONSENT PROCESS IN THE PICU

3.1 Informed consent in research

Informed consent is one of the ethical cornerstones of performing research with human subjects. It represents the implementation of the ethical principle of respect for persons. Respect means that persons are treated as autonomous agents, and that persons with diminished autonomy have a right to protection [3]. Informed consent has been incorporated in all ethical and legal guidelines concerned with research with humans (for example [1–4, 40, 41]). Five elements are distinguished, which are all essential for a valid consent: transmission of information; understanding of this information; no coercion by others; competence; and actual consent [42]. These requirements cannot always be met for children in the PICU as they may be too young, to ill or too heavily sedated. In these cases their parents (or legal guardian) need to consent for them, which process is known as proxy-consent [43].

3.2 Factors influencing informed (proxy) consent in the PICU

A qualitatively good consent process prepares future research subjects for the trial, is free and informed. In the PICU, quality of consent is threatened by several factors.

Anxiety

The stressful PICU environment has great impact on parents and children. Many parents of acutely ill children suffer from acute and post-traumatic stress disorder and this often lasts for months after discharge [44, 45]. Practitioners asking consent for trials in emergency situations reported that some parents are unable to focus on anything else than the health of their child and will not be able to take any decision about research, whereas others will still be receptive [46]. The most important reason for refusal to consent as spontaneously provided by parents in the PICU is anxiety or 'being overwhelmed' [33, 47]. In contrast, in a study by Thomas et al. parents mentioned being anxious, but said that this did not influence their decision regarding research participation [48]. These parents provided useful suggestions. For example, tell parents about ongoing trials prior to PICU admission if possible (e.g. in the case of planned surgery) and do not approach parents when their child is in the operating room, but before *or* after surgery [48].

Burden of research

In a large study by Hulst et al., 421 parents who declined informed consent to a nutritional assessment study implying additional procedures were asked for the reason. Two-thirds wanted to avoid additional burden to their child [49]. In two multicenter studies, Menon et. al. analyzed parents' reasons to decline informed consent. The one study was an observational study involving blood sampling, the other concerned different kinds of PICU research. In both studies, the burden of blood sampling was a major reason for declining participation [47, 33]. A small qualitative interview study was conducted by Thomas et al. among parents who accepted or declined consent in an undefined PICU trial. The interviews identified added pain, discomfort and additional diagnostic testing as factors discouraging participation [48]. Overall, it would seem that limiting the burden of research procedures is essential to increase participation. This is further elaborated on in section 4.

Illness severity

Interestingly, severity of illness does not seem to influence consent rates in the PICU. Two studies done in the PICU could not identify a difference in severity of illness between children of consenting and non-consenting parents [49, 33]. Still it should be borne in mind that the life-threatening nature of illness in the ICU can make parents more susceptible to the idea that the trial might convey a therapeutic benefit, when this is very unlikely [50].

Understanding

Parents reach a good understanding of their child's health condition within 24 hours after admission in PICU [51] but this need not be true for research participation. Studies in the neonatal intensive care unit (NICU) suggest that the conditions for a valid consent are often unmet [52, 53]. Understanding and recalling of information is difficult for parents in the hospital situation [54] and they also overestimate their understanding [55]. Written information and posters are identified by parents in the PICU as useful information tools in the informed consent process [48, 56].

3.3 Alternative forms of informed consent

The life-threatening and acute nature of illness in the PICU puts great pressure on the validity and process of informed consent. It is not always possible to achieve written informed consent before start of the study in emergency settings. Alternative consent processes should balance the respect for the decision of future research participants and the benefit trial participation might bring them. Two different alternative consent processes are available to deal with these time constraints: a waiver of consent or deferred consent.

Waiver of consent

A waiver of consent, also known as exemption from informed consent, means that no consent is required for inclusion of research participants in research. It is sometimes allowed for studies in life-threatening conditions for which available treatments are unproven or unsatisfactory and the study intervention needs to be applied urgently to be effective. The conditions under which a waiver (or) is acceptable vary between countries. For example in the USA, additional requirements are community consultation and public disclosure [57]. They favor dialogue with the community, which is informed about the project beforehand and its results afterwards [58]. Raymond et al. describe an efficient way of in-hospital community consultation for a trial of vasopressin added to adrenaline in cardiac arrest in the PICU. All parents were informed about the trial through posters, written information, a website and the research team, and were offered the possibility to opt-out of the study. 80% of parents were aware of the trial and knew how to opt out. The authors suggested this approach could increase recruitment while preserving freedom of choice [56].

Deferred consent

Another way of dealing with the acute nature of decisions in emergency research, but still taking into consideration parental decision, is the use of deferred consent. This form of consent implies that patients are recruited without consent and that after enrollment consent is asked for use of already collected information and ongoing participation. Just like a waiver of consent, deferred consent is an alternative in emergency situations

where obtaining prior informed consent is not possible and postponing the intervention would potentially harm the child. The conditions under which deferred consent is acceptable vary between countries, too. An example of conditions can be found in the upcoming new EU regulation on clinical trials [40].

Research suggests that parents favour deferred consent over waived consent and consider it an acceptable alternative to informed consent for emergency situations [59, 60]. In a study by Woolfall et al. parents suggested it would be advisable for the researchers to seek advice from the bedside nurse to establish the moment when the child's condition was stable and then ask consent [60]. Practitioners with experience in asking deferred consent were generally positive about parental acceptance of this method of consent. They highlighted the importance of explaining the purpose of its use [46]. A systematic review on waiver of informed consent in pediatric resuscitation trials concluded there is a general endorsement of research in life-threatening situations, but that parental preferences for waiving of consent or deferred consent vary depending on the approach and population [61]. Opinions of children about being enrolled in studies with a waiver of consent or deferred consent have not yet been addressed in research.

Interpretation of approval of alternative forms of consent by researchers and Institutional Review Board (IRB) members may differ. It has been shown that IRB members may be less prone to accept alternative forms of consent than are researchers [62]. This may be a barrier to conduct trials with alternative forms of consent. Documenting parental acceptance of deferred consent process could provide insight into its acceptability.

Questions still remain on how to handle consent when a child dies before deferred consent from parents or proxies is asked. Problems arise with use and storage of the collected data. Excluding data from deceased patients (for whom no deferred consent was obtained) may impair validity of the results [63, 64]. Still, although seeking deferred proxy-consent for a deceased child can burden parents, the majority of parents wishes to be informed [59]. Bereaved parents said it was important to adapt to their needs on a case-by-case basis and to allow time after the child's death [60].

Combined forms of consent

The waiver of consent and deferred consent methods are justified only in life-threatening situations where postponing trial inclusion would harm to the research subject.

If the required conditions should not be met, full informed consent needs to be given prior to inclusion. Practitioners have suggested that an approach taking the reality of parents into account would be ideal [46]. Combining different forms of consent could be a useful way of adapting to the unpredictability of acute care environment. The FEAST trial, which studied the effect of fluid resuscitation on mortality, is an example of such a combination [65]. Informed consent was asked only if the child was stable enough and

the parents not too distressed. Otherwise, verbal assent was sought prior to inclusion and full written consent after child's stabilization.

3.4 Improvements to the informed consent process

It would be worthwhile to study alternative consent approaches in pediatric intensive care, taking into account that approaches in different situations cannot be uniform. Although we should be wary about adding burden to parents (which an informed consent conversation and decision can be), parents must be given the opportunity to make a decision. The approaches to obtaining informed consent in different situations cannot be uniform. The solutions to practical problems may never be a permit for exploitation and harm of the vulnerable population at the PICU.

Getting informed consent is not a one time achievement: informed consent is a continuous process, especially in the PICU. After improvements in health or decrease of sedation, children can regain the capacity to consent or assent; and they are entitled to do so after reaching legal age of consent. They should then be informed about the study they were involved in and their assent or consent should be sought when feasible – usually when the acute phase of the disease is over or after transfer to the ward. It is advisable to consider this re-consent process in the design of the study because the research team needs to plan for the resources needed to allow this important follow-up. There are no studies on this re-consent process in critically ill children.

To our knowledge the amount of empirical research on preferences and motivations of parents and children to participate in drug research in the PICU is small. These preferences have been assessed more extensively in other pediatric populations, but data from the PICU are lacking.It would be relevant to study factors that shape the decision to consent or dissent to drug research in the PICU– for example with a focus on altruism, hope and loyalty. Having this information would enable us to better tailor the process of recruitment and informed consent to the needs of the parents (or legal guardians) and children.

4. BURDEN AND RISK OF DRUG RESEARCH

4.1 Burden and risk in pediatric research

According to the principle of proportionality, risk and burden of research participation should be balanced against the possible benefit of the trial. The principle of subsidiarity entails that research can only take place if there are no other less burdensome and less risky methods of generating the same results. In other words: burden and risk for the research participant need to be minimized, irrespective of the possible benefits of the trial for the individual or society. These principles of proportionality and subsidiarity underlie important ethical guidelines concerning research with humans [1–4] Children

are vulnerable and therefore need additional protection against the risks and burdens of research participation. Recent progress in drug research can decrease burden and risk for children participating in research in the PICU. Some of these new techniques are illustrated in the following section.

4.2 METHODS TO DECREASE BURDEN AND RISK BY USE OF NEW TECHNIQUES

PK studies traditionally implied collecting many 1–2ml blood samples from a patient at scheduled intervals upto 12 times in 24 hours, which means a considerable burden to research subjects. Recent progress in sampling methods, data analysis and outcome measurement tools can decrease this burden while rational evidence-based drug regimens can still be derived. As an example, a solution to oversedation with morphine, which is often observed in neonates was found using a three-step approach. First, PK data were collected during two RCTs [66, 67]. Second, the data were analyzed with population PK, and it was found that same dosing guidelines of morphine resulted in much higher plasma concentrations in neonates than older infants [68]. Third, a new dosing guideline was created on the basis of this finding, and validated [69]. The following section details how limited blood sampling schedules, novel drug concentration assays and data analysis methods can decrease burden and risk.

Opportunistic or sparse blood sampling methods

PICU patients usually have an arterial or venous central line from which blood can be drawn. To avoid accessing lines just for research purposes, sampling for research purposes can be combined with regular blood work. In the absence of a line, samples can by collected during routine heel pricks [70]. Opportunistic studies determine levels of the drug received as part of the patient's treatment and no study drug is given [71]. Another strategy is to measure drug concentration in blood left over from routine analysis [70, 71].Population pharmacokinetics make use of randomly collected and limited blood samples per patient. Maximum allowed amounts of blood for research purposes vary between hospitals and countries, but generally the maximum is set at 3–5% of total blood volume within 24 hours and 5–10% of total blood volume over 8 weeks [72].

Low Volume Drug Assays

High performance liquid (LC-MS) or gas (GC-MS) chromatography allows simultaneous analyses of many low concentration substances in small plasma volumes (10–100 µL) or left-overs [70, 73]. This is of particular interest for studies in neonates and small children, whose total blood volume is small [71]. New emerging technologies such as

digital microfluidics will further decrease the sample volume needed [74, 75] [76] and may represent the future of PK studies. If combined with sampling using micro needles sharp enough to minimize nerve contact [77] these technologies will further decrease the burden and risk of clinical drug trials in children.

Dried Matrix Spots

Dried matrix spot analysis requires no more than a minimal volume (5–30µL) of biological fluids (urine, plasma, blood) on blotting paper, allowing for easy and cost-effective sample processing, storage and shipping [71, 78]. These samples can be used in PK studies [79, 78, 80] and pharmacogenetic tests [81, 82]. Dried blood spots obtained during routine newborn screening can be for genetic (DNA) [82] and epigenetic (DNA methylation) [83] analysis until 30 years later if stored at -20°C, as is routinely done in some countries.

PK-PD modelling tools

Population PK-PD analysis using non-linear mixed effect models allows using samples derived from different dosing regimens with random timing and only few samples per patient to estimate PK parameters and the PK-PD relationship and to optimize dosing recommendations [84]. Sparse sampling is a strategy by which just 2–3 samples per individual allow deriving PK parameters from a group of 25–100 infants [85]. This enables studies in which the patient already receives the drug for clinical reasons and even the use of left-over material from regular blood work. Population PK calculates both the inter- and intra-individual variability. The effects of different covariates like age and weight are tested by delineating their effects on inter-individual variability. Particularly relevant to PICU patients, the effect of disease and its treatment can be taken into account (e.g. renal function, inflammation, ECMO) [86]. PK-PD parameters in particular populations, such as patients on ECMO [87], can be estimated . A next step is to validate the obtained PK data and the dosing guidelines derived from these data in a prospective trial performing the same sample analysis. In an efficient new dosing regimen, inter-individual variability should be greatly reduced and dose-effect relationships should remain unchanged or improve. Regrettably, this validation is rarely performed [71, 85].

Microdosing studies

Microdosing is an elegant new method to minimize burden and risk in PK-studies in children [88]. It uses a sub therapeutic, extremely low dose of drug, known as a microdose (e.g. 1/100th of therapeutic dose) [89, 90].

Microdosing is ideal for non-therapeutic pharmacokinetic studies in critically ill children because therapeutic or adverse effects will not occur. Microdosing also enables knowledge gain on drug metabolism or excretion, using probe drugs for these specific

pathways. Radioactive labeling allows detection of the extremely low dose [91] and carries very minimal risk, because the level of radioactivity is well below international cut-offs for radiation safety. It cannot be excluded, however, that parents and health care providers perceive this differently, and it is recommended therefore to underline in the informed consent process the minimal risks of microdosing.

5. CONCLUSION

Drug research in the PICU is essential because there is a great need of evidence-based dosing guidelines. Conducting drug research in critically ill children is a precarious enterprise because of the vulnerability of the research population and the specific circumstances in the PICU – which present specific ethical challenges. Examples of these challenges are presented in table 2.

Characteristics of the specific study population, recruitment issues, challenging outcome measures, use of rescue medication and sub-optimal protocol adherence stand in the way of obtaining useful results. Gatekeeping does not only limit recruitment but is

Table 2 Examples of ethical challenges of clinical drug trials in critically ill children

Example of drug trial*	**Ethical challenge****
RCT with daily sedation interruption [92]	Risk of "gate-keeping' during recruitment and non-adherence to protocol during study for fear of accidental extubation or line removal
RCT with corticosteroids for pediatric septic shock [39]	Potential life-saving medication: rescue medication in placebo arm may reduce validity of trial
RCT with vasopressin add-on for cardiopulmonary resuscitation [93]	Emergency treatment leaves no time for informed consent: when are deferred consent or waiver for consent acceptable?
Pharmacokinetic study with drug already prescribed to patient [70]	No potential benefit to patient. Multiple catheter accesses may increase risk of infection. Blood sample volume may compromise health, especially in small children
Dose-finding study for new drug, e.g. imatinib for pulmonary arterial hypertension	Risk of off-label prescription without any trial, ethical barriers may be perceived too high to perform a 'non-therapeutic trial'
Microdosing pharmacokinetic study with radio-active labeled drug [94]	No potential benefit to patient despite safe radiation dose: 'gate-keeping' by physicians and/or nursing staff out of fear for radiation-related negative outcomes. And possible misunderstanding of minimal risks by parents.

* Examples are illustrative and based on trials and experiences of researchers in the PICU.
** Ethical challenges are examples that researchers could face when performing these kind of studies, but are of course not limited to these examples.

also an underestimated source of bias especially with acutely ill children. Collaboration of intensive care units is bound to improve quality of research and to increase the likelihood of producing generalizable data.

Informed consent for research in the PICU implies almost invariably proxy-consent by the parents or legal guardians. Documenting informed consent does not imply, however, that parents know what they signed for. Indirect evidence shows that informed consent may not be achieved in the stressful situation of the PICU due to parental anxiety and misunderstanding. The informed consent process does not stop when the consent is signed, but is rather a continuous process. Continuous dialogue between researchers and parents is the only way to do justice to the unpredictable and changing reality of the PICU. «One size fits all» is not always possible for structuring informed consent in the PICU therefore alternative approaches to consent need to be developed and evaluated.

Drug research carries burdens and risks for the subjects and it is only logical that we should prevent or minimize these, especially in the vulnerable population in the PICU. New technics allow us to generate evidencewith decreased burden and risk to the research subject and deserve to be widely used and systematically evaluated. The different types of studies (e.g. dose-finding studies, PK studies, RCTs) each present specific challenges. Dealing effectively with these challenges is an essential step towards evidence for dosing and drug choice in pediatric intensive care practice.

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We must be free not because we claim freedom,
but because we practice it.

William Faulkner

Chapter 4

Trial Recruitment in the Pediatric Intensive Care: Ask Consent Before You Start?!

KLEIBER N
TROMP K
TIBBOEL D
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CRIT CARE MED. 2016 MAY;44(5):E309-10

To the Editor:

We read with great interest the paper of Ventura and colleagues on their randomized controlled trial (RCT) comparing the effect of first-line inotropic drug (dopamine versus epinephrine) on mortality in severe sepsis in children (1). Such trials are essential to generate evidence-based management guidelines to reduce mortality from this disease. The combined effect of higher prevalence and mortality rate of sepsis in Brazil compared to more economically developed countries allowed achieving a major challenge in pediatric intensive care (PICU) research: randomize enough patients in a timely manner to study a robust outcome.

We are nevertheless quite surprised by the high recruitment and informed consent rates reported: they were able to approach *all* eligible patients and 96.4% of the parents gave informed consent. These figures differ a lot from our own experience and rates reported in other emergency trials. Previous research shows that up to one third of RCTs in the PICU are terminated before the needed sample size is achieved, often due to recruitment problems (2). Therefore, we would be very grateful if the authors could provide us information to help understand these surprising numbers. Approaching parents and getting informed consent for research participation in emergency situations is challenging (3). The stress-inducing physical environment, illness severity of the child and possible time constraints influence recruitment and consent rates and challenge the validity of the obtained consent (4). For example, an important reason for refusal to consent in the PICU is parental feelings of 'being overwhelmed'(4).

Ventura et al. asked informed consent within 3 hours of admission. Was dedicated research personnel available 24/7, as septic patients present at all times of the day? This 3 hours period leaves little time for parents to receive information, process it and take an informed and consensual decision, while timely start of the intervention is of crucial importance.

We wonder if the authors considered using an alternative design for obtaining informed consent from the parents. We would like to make the suggestion of deferred consent in this situation. This form of consent implies that patients are recruited without consent and consent is asked after enrolment for use of already collected information and ongoing participation. Research suggests that parents generally support this form of consent (5).

Another way of adapting to the time-constraints could be to use a continuous consent (or two-step consent): only most relevant information is given to seek consent for inclusion in emergency setting but this short consent is followed by a deeper informed consent conversation that gives an additional opportunity to parents to withdraw (3). Did the authors feel that their obtained consent was valid under the difficult circumstances? Was an alternative form of consent considered?

To conclude, we encourage other researchers in emergency trials to provide detailed information on the recruitment and consent process in their papers and discuss the rationale for the chosen method. Learning from each other's experiences may contribute to a lower failure rate than currently in pediatric emergency trials.

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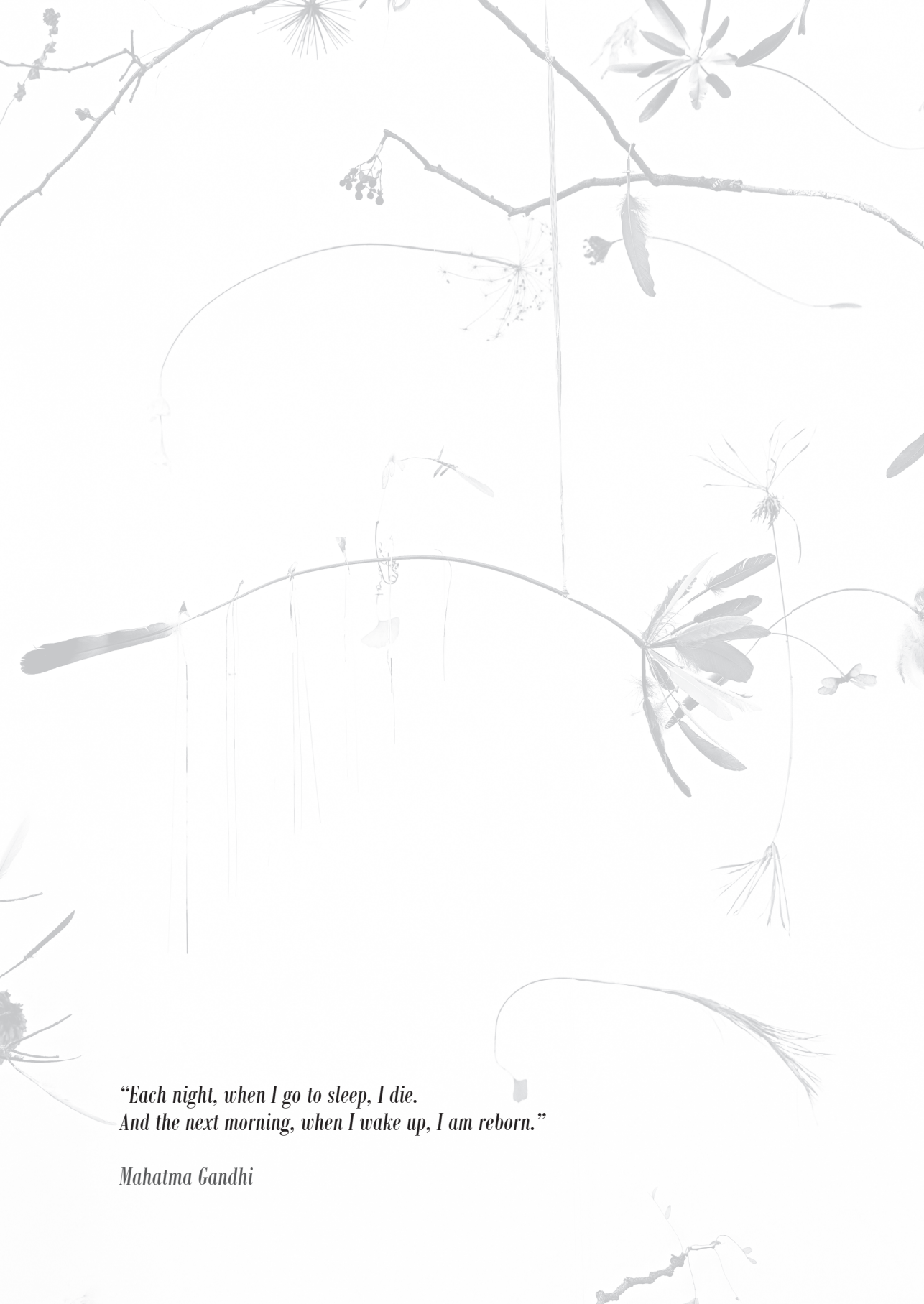

"Each night, when I go to sleep, I die.
And the next morning, when I wake up, I am reborn."

Mahatma Gandhi

Chapter 5

Sedation in critically ill children with respiratory failure

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ABSTRACT

This article discusses the rationale of sedation in respiratory failure, sedation goals, how to assess the need for sedation as well as effectiveness of interventions in critically ill children, with validated observational sedation scales.

The drugs and non-pharmacological approaches used for optimal sedation in ventilated children are reviewed, and specifically the rationale for drug selection, including short- and long-term efficacy and safety aspects of the selected drugs. The specific pharmacokinetic and pharmacodynamic aspects of sedative drugs in the critically ill child and consequences for dosing are presented. Furthermore, we discuss different sedation strategies and their adverse events, such as iatrogenic withdrawal syndrome and delirium. These principles can guide clinicians in the choice of sedative drugs in pediatric respiratory failure.

INTRODUCTION

Critically ill children who are mechanically ventilated often require sedative and/or analgesic drugs to diminish anxiety or pain and ensure comfort. Moreover, adequate sedation facilitates synchronization with mechanical ventilation and enables invasive procedures to be performed. Adequate sedation has been described as the level of sedation at which patients are asleep but easily arousable (1). In pediatric intensive care unit (PICU) practice this means that a child is conscious, breathes in synergy with the ventilator, and is tolerant of or compliant with other therapeutic procedures. However, the optimal level of sedation varies for each patient, depending on the type and severity of underlying disease and the need for certain therapeutic, invasive procedures.

To achieve the optimal level of sedation in individual patients, doses of sedatives are preferably titrated to effect based on observational sedation scales validated for the population in question. Nonetheless, it can be difficult to reach optimal sedation, because of variability in plasma drug levels and response, as well as in the patient's clinical state. 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 (2). Part of this effect may be due to muscle weakness consequent to immobility (3). Oversedation also induces tolerance and withdrawal syndrome (4, 5). Undersedation, on the other hand, may cause distress and adverse events such as unintentional extubation or displacement of catheters, may lead to adverse memories (posttraumatic-stress syndrome) and increased need for nursing requirements. All this may lead to a longer PICU stay.

This article addresses how to assess the need for sedation, including relevant sedation scales, pharmacokinetic and pharmacodynamic considerations of analgosedative drugs, sedation strategies and long-term adverse effects of sedation, to guide clinicians to optimal sedation practice in pediatric respiratory failure. Moreover, we aim to elucidate the information gaps in current knowledge and propose future research directions.

Sedation assessment

In order to provide adequate sedation, the level of sedation in critically ill children should be regularly assessed and documented. Furthermore, sedation assessment is needed to both determine the efficacy of sedatives and related interventions and to facilitate inter-institutional comparisons. Thus, the use of formal sedation assessment is recommended using a validated sedation scoring scale. Several behavioral assessment tools are described. The Ramsay and the Richmond Agitation Sedation Scale (RASS) are frequently used in critically ill children, but are only validated for adult ICU patients (6–8). The COMFORT scale (9, 10), the COMFORT behavior scale (11, 12) and the State

Table 1. Characteristics of the COMFORT (behavior) scale and the State Behavior Scale

Instrument	Parameter measured	Population (age)	Exclusion criteria	Observation items	Score range	Validation		
					Item / Total	Reliability	Validity	Cutoff points
COMFORT scale (9, 10)	Distress	37 (newborn to 17 yrs)	Seriously compromised neurological status[a], Profound mental retardation, Recent multiple trauma, Altered muscle ton or contractures, Severe acute pain	Heart rate, Mean arterial pressure, Alertness, Calmness, Respiratory response, Movement, Muscle tone, Facial expression,	Numerical Item: 1 to 5 Total: 8 to 40	$r = 0.84$; $p < 0.01$ (n = 50 paired obs)	COMFORT vs. VAS $r = 0.75$; $p < 0.01$	OS ≤ 16 AS 17–79 US ≥ 30
COMFORT behavior scale (12)	Distress / sedation	78 (0 to 16 yrs)	Children with severe mental retardation, Children with severe hypotonia, Patients receiving neuromuscular blockade	Alertness, Calmness/agitation Respiratory response or crying Physical movement, Muscle tone, Facial tension	Numerical Item: 1 to 5 Total: 6 to 30	Kappa = 0.77–7.0 (n = 40 paired obs) ICC = 0.99	COMFORT behavior vs. NISS (Kruskal-Wallis, $p < 0.001$)	OS ≤ 10 AS 11–12 US ≥ 23
State Behavior Scale (13)	Sedation/ agitation level	91 (6 wks to 6 yrs)	Patients receiving neuromuscular blockade, Postoperative patients, Patients assessed to be in pain, Unstable patients, Patients at risk for opioid withdrawal	Respiratory drive, Coughing, Best response to stimuli, Attentiveness to care provider, Tolerance to care, Consolability, Movement after consoled	Bipolar numeric Item: -3 to +1 Total: -21 to 7	Kappa = 0.44–4.76 (n = 198 paired obs) ICC = 0.79	SBS vs. NRS ($F = 75.8$, $p < 0.001$)	Not done

PICU, pediatric intensive care unit; VAS, visual analogue scale; NISS, nurse interpretation sedation score ; SBS, State Behavior Scale; NRS, numeric rating scale; kappa, linearly weighted Cohen's kappa; r, Pearson product correlation coefficient; yrs, years; wks, weeks; obs, observations; OS, Oversedation; AS, Adequate sedation; US, undersedation; ICC, intraclass correlation coefficient;

Behavioral Scale (SBS) (13) are validated scores for PICU patients. The characteristics and psychometric properties of these scales are presented in Table 1.

The COMFORT scale was originally described in and validated for measuring discomfort in ventilated pediatric patients. This observational scale consists of two physiological items - Heart rate and Arterial blood pressure - and six behavioral items - Alertness, Calmness/Agitation, Respiratory response, Physical movement, Muscle tension and Facial tension. Because the physiologic variables are affected by inotropic and other drugs often used in pediatric intensive care, it was questioned whether their use contributes to the overall assessment of sedation in the individual patient. Therefore, the COMFORT scale was adapted in the COMFORT behavior scale, which does not include the two physiological items. Many psychometric properties of this scale have been tested (14–16). As well-sedated children do not always show unambiguous behavior, it was more realistic to define score ranges rather than cutoff points. Score range 6–10 was defined as oversedation; score range 23–30 as undersedation. Score range 11–22 was defined as a grey area in which a second assessment, for example the Nurse Interpretation of Sedation Score (NISS), is recommended for clinical purposes (12, 17).

The SBS appraises seven behavioral dimensions; 'Respiratory drive/ response to ventilation', 'Coughing', 'Best response to stimulation', 'Attentiveness to care provider', 'Tolerance to care', 'Consolability' and 'Movement after consoled'. The score range from -3 to +3 and a score of 0 describes a patient who is alert and calm. Psychometric properties of this scale are good.

General considerations of pharmacokinetics and pharmacodynamics in critically ill children

The pharmacokinetic (PK) properties of a drug include the processes of absorption, distribution, metabolism and excretion, while the pharmacodynamic (PD) properties comprise the actual responses to the administered drug and therefore may represent both efficacy and safety. In addition to the age-related variation in PK, critical illness and its treatment modalities impact PK and PD. These factors are summarized in Figure 1. Intrinsic factors related to the patient's clinical condition include shifts in body fluid (altering volume of distribution), inflammation (altering drug transport and metabolism, clearance), and liver, renal and heart failure (altering absorption, distribution, drug metabolism and excretion). Extrinsic factors include treatment modalities such as extra-corporeal membrane oxygenation (ECMO), hypothermia, and continuous renal replacement therapy (18). Volume of distribution is often increased and clearance is altered either way in ECMO-patients (19). Hypothermia leads to changes in volume of distribution due to redistribution of blood flow and a decreased clearance due to a decreased drug metabolizing enzyme activity (20, 21).

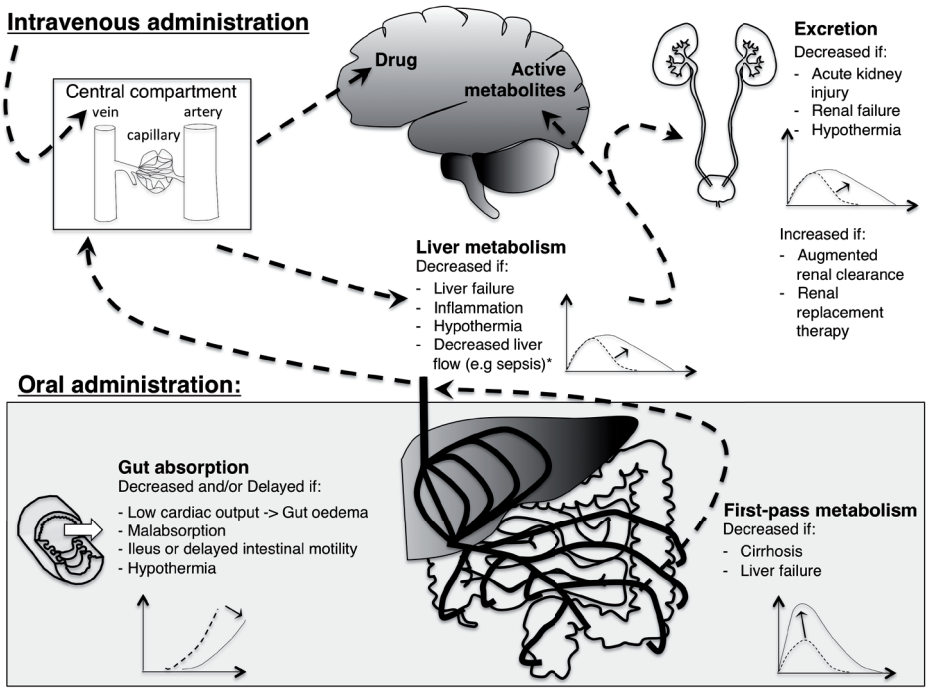

Figure 1. Illustration of the effect of critical illness on pharmacokinetics of analgosedative drugs
With intravenous administration (upper left), drugs are injected directly into the central compartment: bioavailability is complete. With oral administration (lower left), gut absorption and first by-pass metabolism limit bioavailability. Analgosedative drugs are metabolized by the liver into more water-soluble metabolites that are excreted by the kidneys. Some analgosedatives have active metabolites (e.g morphine and midazolam) that may accumulate with decreased renal function.
A graphical representation of drug concentration over time depicts pharmacokinetics changes induced by critical illness: the dashed line represents the curve of a healthy individual while the solid line shows the change induced by critical illness.
* Liver flow affects clearance of drugs with a high hepatic extraction ratio (e.g. propofol)

Furthermore, critical illness itself may be of influence on the effect of sedation. For instance, a critically ill child who is less reactive due to its underlying illness (e.g. sepsis) will respond differently to a sedative drug than a relatively healthy child who receives sedation for the acceptance of a tube after airway reconstruction.

Although the impact of separate aspects of critical illness on drug disposition is increasingly recognized, only few factors are actually taken into account in current dosing such as dosing adjustments with renal failure. For sedative drugs, this underscores the importance of dosing and titrating the drugs to effect.

Commonly used agents (Table 2)

An ideal sedative drug exhibits anxiolysis, amnesia and analgesia qualities, should be easily titrated to effect, and without any adverse effects. However, none of the existing drugs does meet all these qualities. Therefore, medications are commonly co-administered to compensate for any shortcomings and to achieve an optimal effect.

In PICU, benzodiazepines and opioids are frequently used agents. Despite the widespread use of sedatives in PICU, high-quality data supporting appropriate dosing and safety are lacking (22). Many commonly used sedatives and analgesics in the PICU (e.g lorazepam, dexmedetomidine, fentanyl) are still used off-label, which means that their efficacy and safety have not been adequately proven (23). A rational choice for a particular agent is based on the desired effect of the drug the interaction of the patient's disease and the side-effects of the drug. These systemic effects can be adverse effects (e.g. propofol is avoided in patients with unstable hemodynamics due to its cardiodepressive properties (24)) or desired effects (ketamine is a bronchodilator used in asthma (25)). Ideally the choice for a particular agent should include its long-term effect on neurodevelopment. Most commonly used sedative and analgesics are neurotoxic in animals (26–28), which has caused uncertainty for their long-term safety in humans. Reassuringly, these animal data have not been confirmed in human studies. No adverse long-term effects of morphine administration at neonatal age were reported (29, 30). Moreover, short duration sevoflurane anaesthesia in infancy does not appear to increase the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake-regional anaesthesia (31).

Benzodiazepines

Benzodiazepines (midazolam, and to a lesser extent lorazepam) are the most commonly used sedatives and the sedative of choice in many pediatric intensive cares (32). 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 (33). The amnesic effects of midazolam probably play an important role in the low levels of unpleasant experiences recalled by survivors of PICU treated with this agent (34).

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 (35). A reduction of CYP3A activity as a result of inflammation, organ failure (36) or concomitant administration of other therapeutic drugs (drug-drug interactions) (37) may account for the failure of critically ill children to metabolise midazolam. In patients with renal failure prolonged sedative effects may be caused by the accumulation of the active metabolite, 1-OH midazolam-glucuronide (38).

Although most commonly used, midazolam is certainly not an ideal sedative agent. Adverse events associated with its use are tolerance, dependence and withdrawal, but also paradoxical hyperactivity (4, 5). In adults, continuous benzodiazepine use is associated with prolonged mechanical ventilation and length of ICU stay (39). Also, hypotension may occur and is most likely with bolus administration, particularly in neonates, in the setting of hypovolemia or concomitant use of morphine (40).

Lorazepam is a long-acting benzodiazepine used orally and intravenously. The use of intravenous lorazepam is limited by the fact that it is dissolved in propylene glycol, which can accumulate to produce metabolic acidosis and renal dysfunction (41, 42). For weaning, oral lorazepam is a good alternative for midazolam, because of its long half-live.

Opioids

Although opioids are analgesic drugs, they have sedative effects. Some PICUs use morphine as a first line sedative while others favour sedatives (mainly benzodiazepine) in the absence of suspected pain (43). Morphine provides sedation as well as analgesia and can be used as a single agent for analgesia and sedation.

As morphine clearance is substantially reduced in neonates less than 10 days of age, 1/3 to 1/2 of dosing in older children is needed to reach the same plasma levels as in older children. For analgesia this dose reduction is related to adequate analgesia, but sedation data are lacking (44). Morphine has a relatively long duration of action of around two hours when administered as a single dose intravenously (peak analgesic effect after 20 minutes). Morphine is characterized by hepatic metabolism (glucuronidation) and renal excretion with intermediate volume of distribution. Therefore, its effects can be prolonged in patients with renal impairment. The impact of liver failure seems mild or moderate at best (45). Morphine stimulates the release of histamine and inhibits compensatory sympathetic responses, leading to vasodilation and consequently hypotension, particularly following bolus administration (46). The opioid fentanyl has powerful analgesic properties and provides some sedation, as demonstrated in a randomized controlled trial comparing continuous fentanyl and remifentanil in postoperative orthopedic children (47). No studies are available for the use of fentanyl for long-term sedation in PICU. An important, but rare adverse effect is fentanyl-induced chest wall rigidity causing respiratory compromise, generally occurring after a large fentanyl bolus administration (48).

Alpha-agonists

Clonidine and dexmedetomidine are central α-2 agonists with sedative and analgesic properties (49) increasingly used as first line sedatives or as adjunct to other sedatives. Enthusiasm for these agents is driven by the absence of clinically significant respiratory

depression (49, 50), which is an advantage in the spontaneously breathing patient or when extubation is planned (51). Moreover, they do not show neurotoxicity in animals (52), have opioid and benzodiazepine sparing properties (53, 54) and may decrease the incidence of withdrawal and delirium (55). A RCT comparing continuous intravenous clonidine and midazolam in 129 ventilated children (30 days-15 years) showed a similar sedative effect (56). Sedation under dexmedetomidine may more closely resemble natural sleep than sedation under benzodiazepines, although these theoretical advantages have not yet been demonstrated to improve patients' perception of sleep in adult ICU (57, 58). For children, the use of dexmedetomidine is still off-label; it is approved for continuous sedative infusion in adults for 24 hours.

The main adverse effect of alpha agonists is bradycardia/arythmia and hypotension (49, 59), but these effects are rarely of clinical significance (54, 56). Data in children with severe hemodynamic compromise is insufficient to recommend their use in this particular population. To date, no study compared dexmedetomidine to clonidine in the PICU.

Propofol

Propofol has sedative and hypnotic properties. It involves GABA receptor activation (60) although its mechanism of action is not fully understood. Due to its strong cardio-depressant effect (24) its use should be avoided in the hemodynamically unstable patient. Long-term infusions in the PICU are contraindicated in the official drug label for children < 16 years due the risk of lethal propofol infusion syndrome (PRIS). Any suspicion of PRIS (clinical and biological signs: metabolic acidosis, increased liver enzymes, lipemia, rhabdomyolysis, renal and cardiac failure) should lead to an immediate interruption of propofol infusion but despite discontinuation, death can ensue (61). Propofol infusion rate and duration, the presence of traumatic brain injury and fever are factors associated with mortality in PRIS (62). The use of propofol should be limited; when used maximum infusion rate must not exceed 4 mg/kg/h with a maximum duration of 24 hours (62).

Propofol's very short half-live offers an advantage around the time of extubation (mainly in agitated patients): it allows weaning from the longer acting sedative inducing respiratory depression, control sedation during the time of extubation and ensure a quick recovery after. Therefore, in this special case, a short-term infusion of propofol can be considered.

Ketamine

Ketamine is an NMDA receptor antagonist (63) with cataleptic, amnestic and analgesic properties. It maintains hemodynamics (64, 65) by inducing release of endogenous catecholamine (65). However, in patients with hemodynamic compromise and chronic illness or stress who have depleted catecholamine stores, it can decrease myocardial contractility and even induce collapse (66, 67). Ketamine is used in the PICU as a co-analgesic

with opioids for pain control (low dose, around 0.1 mg/kg/h) (68) and occasionally when usual sedative agents fail to provide adequate sedation (high dose, 1–3 mg/kg/h). Due to its bronchodilatory properties, it is the first line analgosedative in status asthmaticus (25, 69). A very common adverse effect of ketamine is the occurrence of hallucinations, and therefore low dose of benzodiazepines should be co-administered. Early work hints at its potential to elevate intracranial pressure (70) and many physicians still avoid its use in traumatic brain injury despite more recent work not showing this effect (71).

Antihistamines

Promethazine, alimemazine and diphenhydramine are first generation antihistamines with anti-dopaminergic and anticholinergic drug actions. These drugs may produce significant sedation as well as quiescence. A combination of oral chloral hydrate and promethazine was more effective than midazolam infusion for maintenance sedation in critically ill children, but less than half the patients in each study arm reached target sedation during study period (72). No other studies are available, and therefore, evidence to use antihistamines for (long-term) sedation in PICU is low.

Barbiturates

Pentobarbital and thiopental are primarily used for therapy resistant status epilepticus, but its use as sedative in therapy resistant agitation has also been reported (73, 74). Barbiturates are highly lipid-soluble. Given by infusion it accumulates in adipose tissue whence it diffuses slowly back to the blood after infusion cessation. This, coupled with a long half-life (5–10 h), is responsible for the persistence of sedation after infusion cessation. Barbiturates are also associated with high rates of adverse events, including hypotension, depression of cardiac contractility, severe skin and mucous reactions (Stevens Johnson syndrome and Toxic Epidermal Necrolysis) and neurologic sequelae (73). Life-threatening hypokalemia and rebound hyperkalemia has been observed after cessation of thiopentone coma for intracranial hypertension. As this has not been observed with other underlying diseases or with pentobarbital, its cause is likely due to an association between the underlying clinical symptoms and thiopentone (75).

Neuro-muscular blockers

Analgesia and profound sedation have to be ensured before starting neuromuscular blockade. Neuromuscular blocking agents are associated to critical illness polyneuropathy and myopathy and therefore should be restricted to special circumstances, discontinued as soon as possible and used at the smallest possible dose (76, 77). The level of evidence supporting their prolonged use for particular indications is poor (76, 78). They are recommended if effective mechanical ventilation cannot be achieved despite profound sedation (e.g ARDS (77), severe asthma (25, 79)). They are often used in case of

Table 2. Drugs used for sedation in critically ill children and their PKPD considerations

					Dosing adjustment in organ impairment	
	Indications	**Dose**	**Elimination/ Metabolism**	**Effect of age on PK/PD**	**Liver ***	**Renal**
Benzodiazepine						
Midazolam	Sedation/amnesia	50–000 mcg/kg/h iv	Liver (CYP3A4/5) Active metabolite: 1-OH-midazolam and 1-OH-midazolam glucuronide	CYP3A4/5 activity is low at birth and reaches adult values in the first years of life (123)	Consider (124)	Yes, in severe renal failure (125)
Lorazepam	Sedation/amnesia	0.01–1.1 mg/kg/h iv	Liver (glucuronidation by multiple UGT2B enzymes) No active metabolite	UGT2B7 low at birth and increases with age (126)	Consider (127)	No (125)
α-2 agonist						
Dexmedetomidine	Sedation and analgesia	0.2–2.7 mcg/kg/h iv	Liver (glucuronidation and mainly CYP2A6) No active metabolite	Decreased clearance in children < 1 years of age (128)	Yes	No
Clonidine	Sedation and analgesia	0.5–5.5 mcg/kg/h iv	50% renal elimination / 50% liver metabolism (mainly CYP2D6) No active metabolite	Decreased clearance in neonates	Consider	Yes / not significant
Propofol	Sedation and hypnotic	1–1 mg/kg/h iv < 24 hrs duration	Rapid and extensive liver metabolism (mainly CYP2B6) No active metabolite	Preterm neonates and neonates in the first week of life at increased risk for accumulation (129)	Consider (130, 131)	No
S-ketamine	Analgesia and sedation	1–1 mg/kg/h (sedation)	Liver metabolism (demethylation and hydroxylation) Active metabolite: norketamine (around 3 times less potent than ketamine)	Appears similar to adults from one week onwards (132)	Hepatotoxic (133)	No
Pentobarbital	Sedation	1–1 mg/kg/h iv	Liver (microsomal enzyme system) No active metabolite	Reduced clearance in neonates (134)	Consider (135)	No (136)

Table 2. Drugs used for sedation in critically ill children and their PKPD considerations (continued)

					Dosing adjustment in organ impairment	
	Indications	**Dose**	**Elimination/ Metabolism**	**Effect of age on PK/PD**	**Liver ***	**Renal**
Opioids						
Morphine	Analgesia with sedation	5–50 mcg/kg/h iv	Liver (glucuronidation by UGT2B7) Active metabolite: Morphine-6-glucuronide (more potent than morphine)	age-dependent increase in plasma clearance in children younger than 10 years of age (126)	Consider (137)	Initiate at lower dose and titrate slowly (138)
Fentanyl	Analgesia and sedation	1–10 mcg/kg/h iv	Liver (CYP3A4)	NA	Consider	Yes
Benzodiazepine						
Midazolam	Increased Vd and drug loss in vitro (139, 140)	Hypotension with bolus dosing (141) Fall in cardiac output (142)	Respiratory depression	++ (5, 84)		
Lorazepam	High drug loss in vitro (143)	Hypotension	Respiratory depression	++ (84)		
α-2 agonists						
Dexmedetomidine	No data	Bradycardia and hypotension rarely of clinical significance Bradyarrhytmia has been reported	No significant respiratory depression, useful for extubation of in spontaneously breathing patient	Rebound hypertension and possible withdrawal after prolonged infusion (weaning required or switch to oral clonidine) (144)		
Clonidine	No data			Rebound hypertension and withdrawal (weaning required)		
Propofol	High drug loss in vitro (19, 145) No in vivo study	Myocardial depressant	Respiratory depression Very quick emergence by stopping, useful during weaning of mechanical ventilation	Irritability, jitteriness and agitation on abrupt discontinuation after prolonged infusion (101)		

Table 2. Drugs used for sedation in critically ill children and their PKPD considerations (continued)

					Dosing adjustment in organ impairment	
	Indications	**Dose**	**Elimination/ Metabolism**	**Effect of age on PK/PD**	**Liver ***	**Renal**
Ketamine	No data	Usually preserved hemodynamic stability, but when endogenous stores of catecholamines have been depleted by stress or chronic illness ketamine can induce cardiovascular depression.	No respiratory depression 1st line sedative in asthma (Bronchodilator)	Delirium after prolonged use in adult. No data in PICU		
Barbiturate	Increased Vd (146)	Hypotension, depression of cardiac contractility	Respiratory depression	++ (73)		
Opioids						
Morphine	High drug loss in vitro (143, 147) Clearance and Vd changes during prolonged ECMO (148)	Histamine release leading to vasodilatation and hypotension, particularly following bolus dose	Respiratory depression Use with caution in asthmatic patients due to potential histamine release	++ (84)		
Fentanyl	High drug loss in vitro (140, 147)	Large bolus doses can cause hypotension	Respiratory depression	++ (84)		

all drugs that are significantly metabolized by the liver may need adjustment in fulminant acute liver failure, but not with mild increases of liver enzymes. Consider using only bolus doses and titrate to effect or use non-hepatically cleared drug like remifentanil.

severe cardio-vascular instability but their benefit may be limited because only modest decrease in energy consumption is achieved compared to profound sedation (80, 81). Other common uses are refractory pulmonary and intracranial hypertension (82).

Sedation strategies

Optimizing sedation in the critically ill is of major importance. In general, the current tendency is to lighten sedation in the intensive care to avoid delayed recovery with longer duration of ventilation (83), tolerance and withdrawal (5, 84). Despite the awareness of the adverse effects of oversedation, it remains common practice in the PICU (85). Sedation strategies play a key role to achieve adequate sedation.

Protocolized sedation

To optimize sedation in critically ill children, it is recommended to assess levels of sedation and to titrate sedatives and analgesics on the guidance of sedation protocols or algorithms. Implementing a sedation protocol allows targeting patient-specific sedation goals. In the adult intensive care, protocol implementation decreases days of mechanical ventilation and ICU stay (86). But more recently, adult studies failed to show these positive effects (87). These changes in results over time may be explained by the growing awareness of the deleterious effect of oversedation and general tendency to avoid it. In the PICU, the effect of protocolizing sedation is less clear, but studies are recent and avoidance of oversedation may already have entered the practice. Several non-randomized trials reported conflicting results on the impact of protocolized sedation on outcomes like length of PICU stay, duration of mechanical ventilation or the need for analgesia and sedation (88). Recently, in a large cluster randomized trial among children undergoing mechanical ventilation for acute respiratory failure, the use of a sedation protocol compared to usual sedation practice did not improve clinical outcome (89).

Daily sedation interruption

Another approach to potentially avoid the negative effects of oversedation, and especially the adverse effects of continuous benzodiazepine use, is daily sedation interruption (DSI). In adults, 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 (90). Several later studies have confirmed this beneficial effect (91), whereas other studies, in different settings, showed no benefit (92, 93).

In critically ill children, two pilot studies showed that DSI is feasible and safe, even in ECMO patients, but both studies were not designed to detect differences in clinical outcome (94, 95). Another study, comparing DSI with continuous sedation in children, DSI led to improved clinical outcomes, including shorter durations of mechanical ventilation and PICU stay (96). In a recent study comparing DSI + protocolized sedation to proto-

colized sedation only, no beneficial effect of daily sedation interruption was found (97). DSI did not reduce the duration of mechanical ventilation, length of stay, or the amounts of sedative drugs administered. There are important differences between these studies in study design (DSI and Standard of Care arm versus DSI + protocolized sedation and protocolized sedation arm), setting (India versus Europe), patient population (e.g. high incidence of neurotrauma versus respiratory infection) and ICU practices (e.g. longer mean duration of mechanical ventilation, more sedatives and neuromuscular blockers administered in the first study) (98). For the latter study (DSI+PS vs PS), the effect of protocolized sedation itself on the clinical endpoints might have outweighed the effect of DSI, as also demonstrated in adults (92).

Drug cycling

Some PICUs use drug 'cycling' or 'rotation' as a method of decreasing the adverse effects of continuous sedation (99). 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, to our knowledge, evidence supporting the beneficial effects of 'cycling' are lacking.

Adverse effects

Withdrawal

Prolonged administration of analgesics and sedatives in critically ill children may induce drug tolerance and physical dependency. Abrupt discontinuation or too rapid weaning of these drugs in physically dependent children may cause withdrawal syndrome. Symptoms of benzodiazepines- and opiates withdrawal can broadly be distinguished into three groups: 1) overstimulation of the central nervous system (e.g. agitation, tremors, anxiety, hallucinations), 2) autonomous dysregulation (e.g. sweating, fever, tachycardia and tachypnea), and 3) gastro-intestinal symptoms, which have only been described in opiate withdrawal (100). Withdrawal syndrome has been particularly reported after administration of opioids and benzodiazepines. The onset of withdrawal syndrome depends on the half-life of the drug and can be after 1 hour or up to several days after discontinuation of these drugs (101). Both longer duration of administration and high total doses of opioids and/or benzodiazepines are clearly related with the occurrence of withdrawal syndrome in critically ill children, and may therefore be considered risk factors (84, 100). Moreover, the exact biochemical mechanisms responsible for the development of withdrawal syndrome remain unclear. The reported prevalence of withdrawal syndrome in critically ill children who had received benzodiazepines and/or opioids for 5 or more days range from 17 to 57% (100, 102).

The development of pediatric scoring tools for withdrawal syndrome is a huge step forward. Two validated assessment tools for observing and identifying withdrawal syndrome after long-term use of benzodiazepines and opioids in PICU patients have been described. These are the Withdrawal Assessment Tool version-1 (WAT-1), and the Sophia Observation Withdrawal Symptoms-scale (SOS) (103–106). Table 3 provides details on symptoms and psychometric properties of the WAT-1 and SOS. The WAT-1 is an 11-item scale and scores of three or higher (on a scale of 0–12) indicates that the child is suspected for withdrawal. The SOS consists of 15 items and is based on the underlying empirical structure of co-occurrences of withdrawal symptoms that experts considered relevant. A SOS score of 4 or higher reflect a high probability of withdrawal.

Strategies to reduce the prevalence of withdrawal syndrome should begin by making active efforts to reduce doses of benzodiazepines and/or opioids during the whole ICU course, and thereby preventing oversedation. As discussed above, daily sedation interruption does not appear to add to protocolized sedation to reach this goal. Protocolized sedation targeting at conscious sedation appears at this time the best available approach.

A weaning strategy for gradual decreasing of opioid and/or benzodiazepine dosages once the patient is recovering may be effective to prevent withdrawal syndrome. Strategies include slowly tapering off the intravenous infusion rate over time, using an alternative route, e.g. enteral or subcutaneous, or transition to long acting drugs like methadone from morphine/fentanyl or lorazepam from midazolam. Disappointingly, little evidence is available on efficacy or safety of different weaning strategies. Weaning strategies ranging from 10 days to several months have been evaluated in observational (retrospective and prospective) studies (107–111). Two negative RCTs evaluated methadone weaning in 5 vs 10-days (112), and a high- vs low-dose methadone schedule in children (113). And while target drug levels for sedative and opioid dependence have been established for adults, they are lacking for children, as are pharmacokinetic data. Hence, we can not advise on the optimal weaning strategy or preferred drugs in pediatric ICU withdrawal.

Nevertheless, some suggestions to reduce withdrawal syndrome while avoiding unnecessary prolonged drug use can be made. First, awareness among clinicians on the risk factors for withdrawal symptoms may aid to prevent a too rapid reduction in drug doses. Moreover, it may lead to a faster switch from IV, short half life drugs to oral or subcutaneous, long half-life drugs. This may also facilitate faster ICU discharge. Second, regular monitoring of withdrawal symptoms with validated scales, will also help to faster diagnose and treat withdrawal as well monitoring of the effect of interventions.

Table 3. Symptoms and psychometric properties of the WAT-1 and SOS

			Structure		Psychometric evaluation		
Instrument	**Population**	**Observation items**	**Total items**	**Score-range**	**Reliability**	**Validity**	**Withdrawal cut-off scores**
Withdrawal Assessment Tool version 1 (WAT-1) (103, 104)	Children	Tremor Uncoordinated/repetitive movement Yawning or sneezing State [a] Loose /watery stools Vomiting / retching/ gagging Temperature > 37.8°C Sweating State [a] Startle to touch Time to gain calm state (SBS≤ 0)	11 Numerical	0–02	*Internal* [b]: PRINCALS, 4 factors *IRR* N = 30 paired observations ICC = 0.98 Cohen's kappa = 0.80	*Construct* Sen. = 0.87 Spec. = 0.88 r_s: 0.80 (between WAT-1 score and NRS-withdrawal) Peak WAT-1 scores for each subject correlated moderately with total cumulative opioid exposure (r = 0.23, *P* = .009), cumulative benzodiazepine preweaning (r = 0.30, *P* < .001) and total (r = 0.33, *P* < .001) exposure *Sensitivity to change* N = 51 episodes of withdrawal (in 21 pts) WAT-1 score; - before rescue therapy: 6 (4–8) - after after rescue therapy: 2 (1–3) (Wilcoxon signed rank test *P* < .001)	≥ 3
Sophia Observation withdrawal Symptoms-scale (SOS) (105, 106)	Children	Tachycardia Tachypnoea, Fever (≥ 38.5°) Sweating Agitation Anxiety Tremors Increased muscle tone Inconsolable crying Grimacing Sleeplessness Motor disturbance Hallucinations Vomiting Diarrhoea	15 Numerical	0–05	*Internal* [b]: MDS, 3 dimensions *IRR* N = 23 paired observations ICC = 0.97 Cohen's kappa = 0.73–3.0 (items)	*Construct* 85 experts *Construct* Sen. = 0.83 Spec. = 0.93 r_s: 0.51 95% CI 0.32–0.66, $p < 0.001$) cumulative doses of benzodiazepines r_s: 0.39 (95% CI 0.17–0.57, $p < 0.01$) cumulative doses of opioids *Sensitivity to change* N = 156 paired SOS assessments in 51 pts. Decrease SOS score: 1.47 (95% CI, –1.91 to –1.04) after rescue therapy.	≥ 4

Pediatric Delirium

Pediatric intensive care staff has become more alert to the occurrence of delirium in their patients – not least since studies showed an estimated incidence of 4 to 29% (114–116). The core diagnostic criteria for delirium are: a) disturbance of consciousness with reduced ability to focus, shift or maintain attention; b) change in cognition (such as memory deficit, disorientation, language disturbance) or development of a perceptual disturbance; c) the disturbance develops over a short period of time and tends to fluctuate during the course of the day. The pathogenesis of delirium is largely unknown. The sufferers may be hyperactive, hypoactive or show signs of both states. Typical for the hypoactive delirium are slowed or sparse speech, hypoactive or slowed motor activity as well as lethargy or also described as reduced awareness or apathy. A number of delirium symptoms overlap with those observed in other conditions, such as pain and withdrawal syndrome (100).

Adults and children largely show the same symptoms although hallucinations, cognitive changes and hypoactive delirium are difficult to diagnose in the very young, preverbal PICU population. For this reason, PD is underdiagnosed in this age group (114, 116). Another reason is that nurses and physicians may not specifically focus on the symptoms of PD. Still, it is also possible to assess PD in this vulnerable age group by carefully observing behavior (114, 117, 118). Diagnosing of PD in the PICU setting requires a reliable, validated and clinically useful bedside tool that may also serve for screening and guiding of treatment. This is an area in full development but several suitable instruments are already available: the pediatric Confusion Assessment Method for ICU (pCAM-ICU) (116); the Cornwell Assessment Pediatric Delirium tool (CAP-D) (115, 119), and the Sophia Observation withdrawal Symptoms-Pediatric Delirium scale (SOS-PD) (120). Haloperidol and risperidone are antipsychotics used for delirium in critically ill children and also adults. To date, studies showing benefit of antipsychotics to prevent or treat ICU delirium are lacking. Moreover, in a retrospective cohort of critically ill children, almost 10% of children showed severe adverse events associated with haloperidol treatment, including extrapyramidal syndrome (121). Hence, while ICU delirium has been associated with an increased risk of mortality, it is unclear if the benefits of antipsychotic treatment outweigh the risks. In the Netherlands, the Dutch Pediatric Drug Handbook (www.kinderformularium.nl) advices a low haloperidol starting dose to be carefully titrated to effect, while diligently monitoring potential side effects.

Non-pharmacological approach

Drug therapy is the most obvious treatment modality of distress, withdrawal syndrome and delirium in critically ill children. Increasingly, the importance of non-pharmacological interventions is recognized. Such interventions use a multi-component approach, which including repeated reorientation, early mobilization, noise reduction (use of ear plugs),

and a non-pharmacological sleep management. We suppose that these interventions could reduce distress and delirium, but evidence is limited. However, common sense suggests that these interventions (for example promoting orientation and day-night rhythm, and avoiding overstimulation by light and sounds) may be effective for children as well.

Another strategy is adaptation of the environment, like noise reduction. Noise is a major environmental factor to cause anxiety and sleep disturbance in critically ill patients (32). In a way, noise reduction could well be effective in decreasing anxiety. It would be worthwhile, therefore, to reduce noise in the PICU as much as possible. All in all, based on the limited evidence it is difficult to extrapolate the effectiveness from adults to children. However, common sense has it that most of the interventions, for example promoting orientation and day-night rhythm and avoiding overstimulation by light and sounds, may be suitable for children as well, so as to create a comfortably calm environment for child and parents. Adult data show a reduction in delirium rates with a multifaceted approach, not only including lighter sedation approaches, but also non-pharmacological changes as noise reduction and aids for patients to better orientate themselves (122).

Future research

Despite the widespread use of sedatives to facilitate mechanical ventilation in pediatric intensive care, evidence to guide clinical practice is remarkably scarce. Only few adequately powered, well-designed RCTs to study efficacy and safety of individual drugs or their combinations have been performed. Several roadblocks to the conduct of these trails have been identified and should be taken into account with the design of future studies.

Hence, robust study design including adequate power calculation, randomization procedures and blinding. (International) multi-center design is very likely needed to reach adequate sample size and high likelihood of generalizability. This adds complexity to the trial and asks a tremendous effort in training of local nurses, physicians and other study personnel. Validated sedation scales for the specific population, e.g. also taking into account age of patient and patient-controlled or nurse-controlled, must be used to assess sedation level in children.

Further, especially in critically ill children, 'gate keeping', i.e. not including the sickest patients for fear of overburdening patients and parents, presents an important challenge towards adequate recruitment. But, previous studies have shown that these challenges can be overcome and taking them into account, future research could focus on the following aspects of pediatric sedation in the ICU:

- Does protocolized sedation indeed improve clinical outcome? Preferably, short-term outcomes like as ventilator-free days, extubation readiness, withdrawal syndrome

and long-term outcomes, like neurodevelopmental outcome, occurrence of PTSD and quality of life should be evaluated. This should also be evaluated in RCTs aiming to study non-pharmacological and pharmacological interventions.

- What are optimal drug doses to be used in pharmacological trials? Can we target similar drug concentrations in all patients, or do different patients need different target concentrations, e.g. based on severity of disease, underlying disease? Before a RCT can start, pharmacokinetic data should be available, from the literature or from prospective observational studies to explore PK and PD of the future study drugs. Especially, data is missing to guide dosing during critical illness and associated treatment modalities (e.g CVVH, ECMO).
- Using a good understanding of the drug's PK and preferably target concentration, these data should be used to design RCT's comparing sedation regimens. Ideally, the pharmacokinetics of the sedative drugs are also studied in these trials to validate the dosing assumptions and better understand variability in response.
- Another underrated aspect of drug trials is the recording of adverse events. A prospective, well-designed approach to document adverse events, may also aid to balance efficacy and safety of the different sedation approaches and guide future treatment decisions.
- Industry-initiated trials follow strict regulatory guidelines for the performance of clinical trials, including adequate documentation of adverse events, according to good clinical practice guidelines with extensive monitoring. Traditionally this have been weaker in investigator-initiated trials, due to a lack of oversight and funds. Hence, consulting with experts in regulatory drug trials is important to safe-guard the quality and thereby also the safety of participants, as well as the generalizability of the results.

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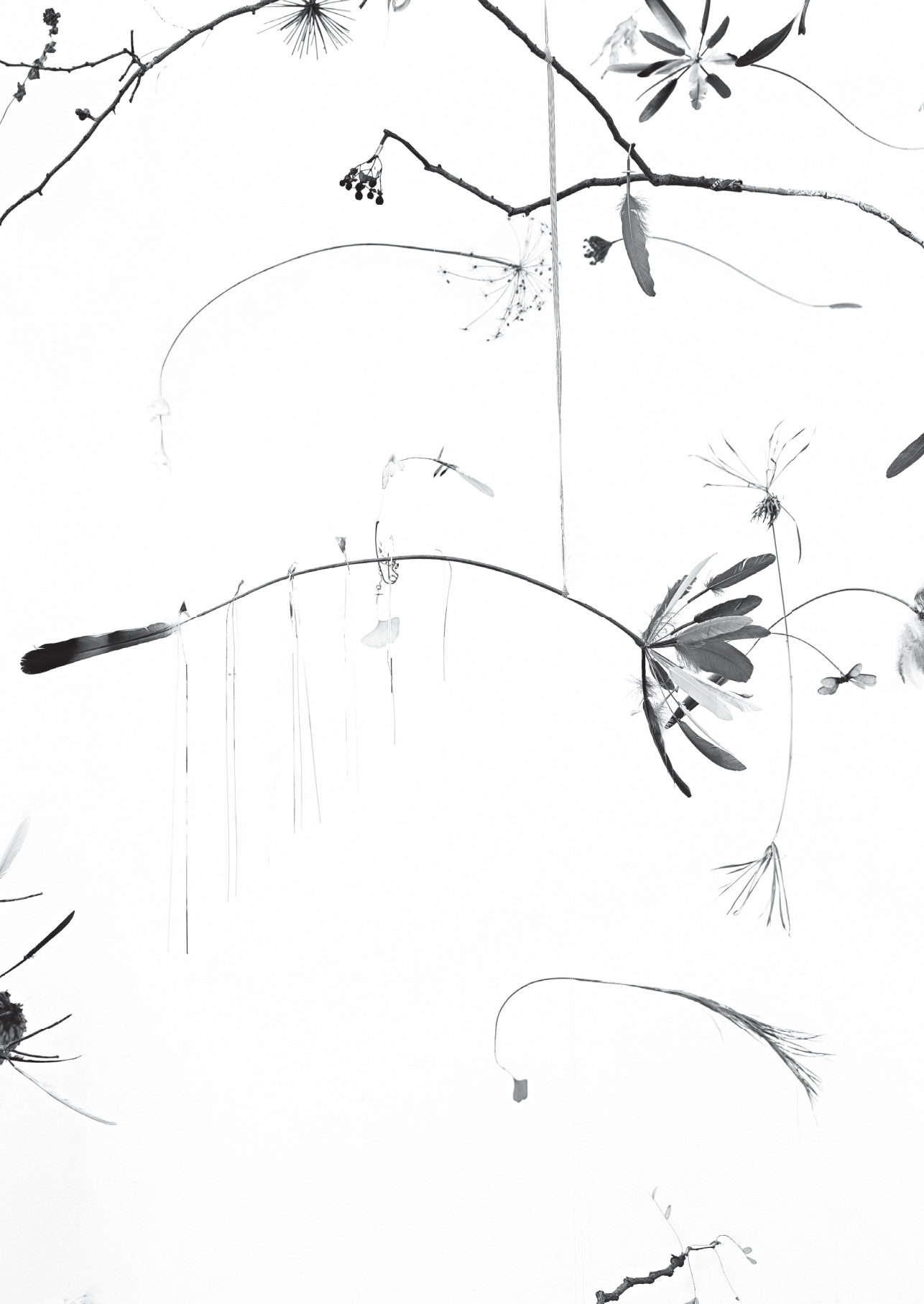
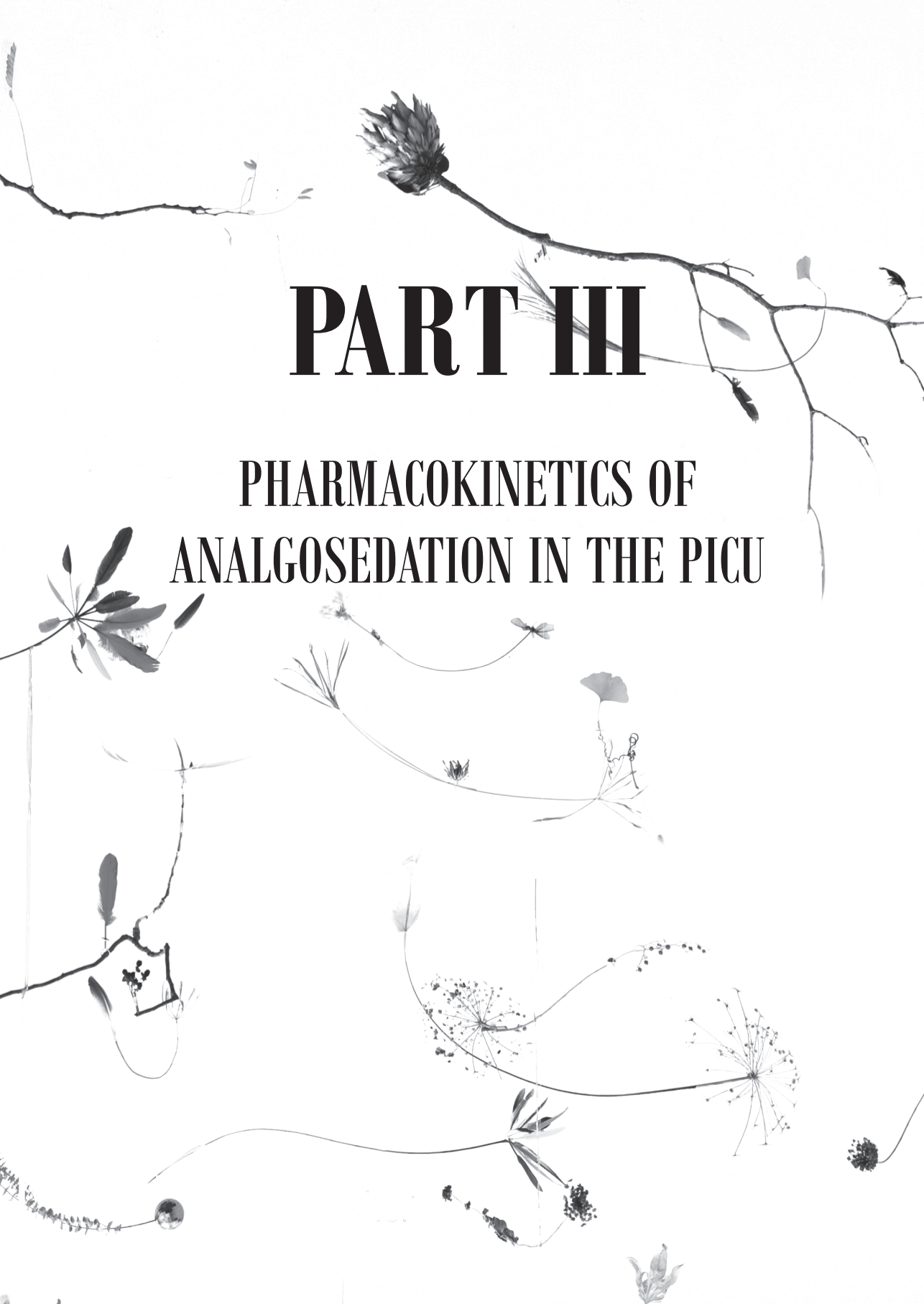
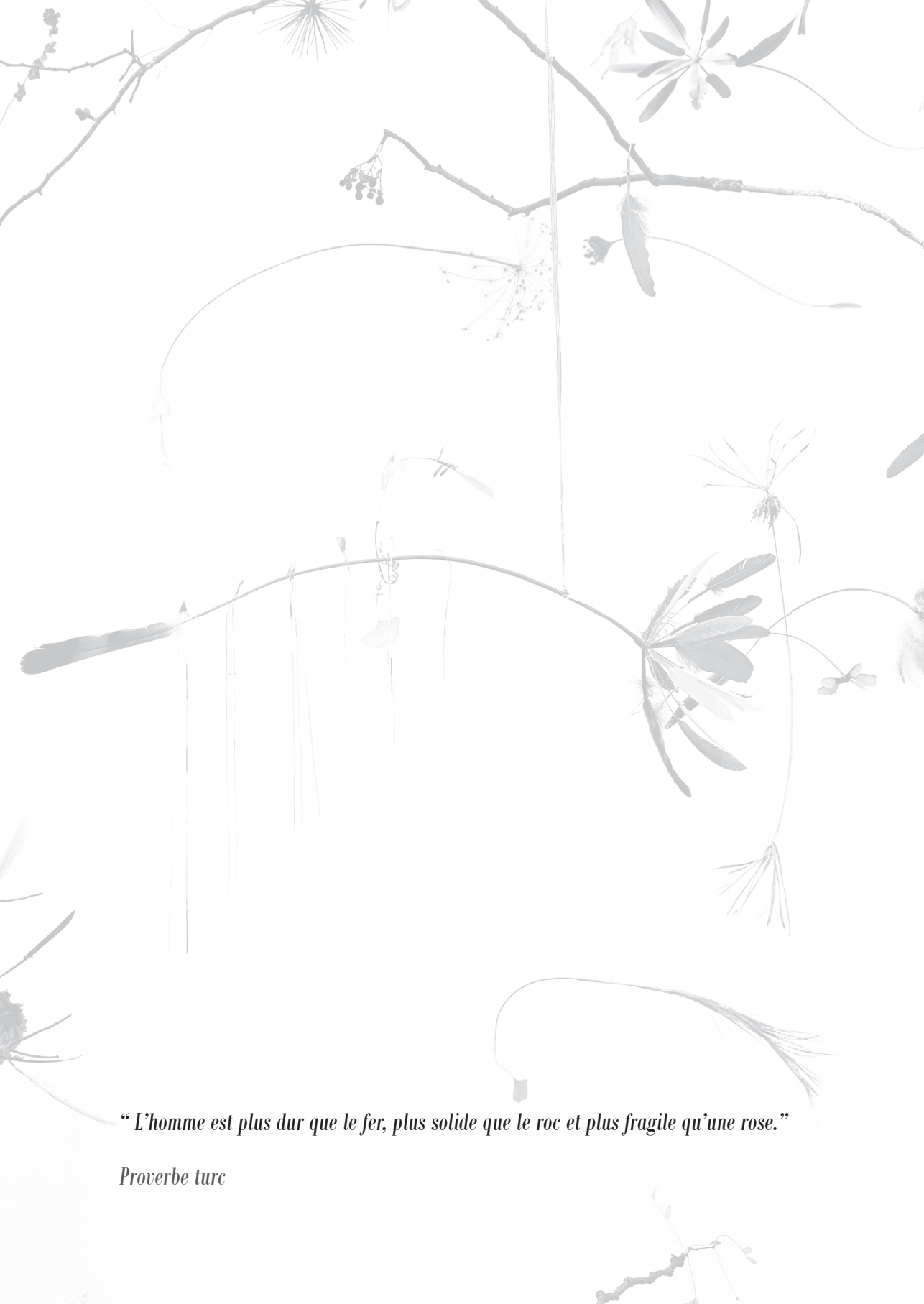




PART III

PHARMACOKINETICS OF ANALGOSEDATION IN THE PICU



“ L’homme est plus dur que le fer, plus solide que le roc et plus fragile qu’une rose.”

Proverbe turc

Chapter 6

Population pharmacokinetics of intravenous clonidine for sedation during pediatric extracorporeal membrane oxygenation (ECMO)

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STRUCTURED SUMMARY

Aims

Clonidine is used for sedation in the pediatric intensive care unit. Extracorporeal membrane oxygenation (ECMO) provides temporary support if respiratory and cardiac function is threatened. ECMO influences the pharmacokinetics of drugs. Clonidine during pediatric ECMO cannot be effectively titrated as PK data are lacking. The aim of this study is to describe clonidine PK in a particular ECMO system and propose dosing guidelines for children on this particular ECMO circuit.

Methods

All children below the age of 18 who received clonidine during ECMO were eligible. The pharmacokinetic analysis was conducted by non-linear mixed effect modeling (NONMEM) which enables to establish the separate influences of determinants on drug blood level and to provide individualized dosing.

Results

Twenty-two patients, median age 1 month (IQR 6.4) and weight at inclusion 4 kg (IQR 3.1) were included of whom 90% in addition to ECMO received pre-emptive continuous veno-venous hemofiltration to optimize fluid balance. The clonidine clearance rate was twofold that measured in patients not on ECMO. Clearance increased steeply with postnatal age: at days 6, 8 and 10, respectively 30%, 50% and 70% of the adult clearance rate was reached. The use of diuretics was associated with a lower clearance. The volume of distribution increased by 55% during ECMO support.

Conclusion

Our findings suggest that a higher dose of clonidine may be needed during ECMO. The PK parameters on ECMO and the dosing guidelines proposed hold the potential to improve sedation practices on ECMO but need to be repeated with different ECMO systems.

What is already known about this subject:

- Extracorporeal membrane oxygenation (ECMO) influences pharmacokinetics.
- Clonidine pharmacokinetics during ECMO has never been reported.

What this study adds:

- Clearance of clonidine during ECMO is twice higher compared to values in non-ECMO patients and volume of distribution increases by 55%.
- Clonidine may need dosing adjustment during ECMO.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique providing temporary respiratory and cardiac support when survival is compromised. To date, it has been mostly used to support children, and in particular neonates (1). The ECMO system pumps blood from a central venous site, which then flows through an oxygenator and is redirected to the patient. Two main types are distinguished. The veno-venous type (VV-ECMO) ensures only lung function; the blood is returned to the right atrium. The veno-arterial type (VA-ECMO) temporarily replaces both heart and lung function; the blood is ejected into the carotid to ensure organ perfusion. Furthermore, continuous veno-venous hemofiltration (CVVH) can be added to the ECMO circuit to optimize fluid balance and support renal function (2).

Patients on ECMO require optimal analgesia and sedation but effective dosing is hard to establish because the pharmacokinetics (PK) of commonly used medications is altered by the ECMO system (3). One of these medications is clonidine, a central α-2-agonist with both sedative and analgesic properties (4, 5). Enthusiasm for this agent is driven by concerns about the neurotoxic effects of most other sedatives noted in animal studies (6) and by the absence of clinically significant respiratory depression with central α-2 agonists (7).

PK data are needed to rationalize drug dosing during ECMO (8, 9) but these have not yet been established for clonidine. Population pharmacokinetic studies delineate the influence of various determinants on drug blood level (e.g. age, organ failure, inflammation, co-medication) and provide dosing guidelines adapted to a patient's individual characteristics. The aim of this study is to describe clonidine PK in a particular neonatal and pediatric ECMO and CVVH system and propose dosing guidelines for children on this particular ECMO circuit.

METHODS

Setting

The Erasmus MC - Sophia pediatric intensive care unit (PICU) is a level 3 ICU and provides ECMO support to on an average 30 patients per year. This pharmacokinetic study included neonates and children up to 18 years of age treated with veno-venous (VV-ECMO) and veno-arterial ECMO (VA-ECMO). It was approved by the Erasmus MC ethics review board considering that ECMO and administration of clonidine and other drugs are standard clinical care. Parental informed consent was obtained for blood sampling and PK analysis.

ECMO standard of care

The criteria for ECMO were: gestational age > 34 weeks, weight > 2 kg, mechanical ventilation < 7 days and an oxygenation index > 25. A clonidine infusion (0.1–1 mcg/kg/h) was added when continuous morphine and midazolam failed to achieve adequate sedation and then incremented stepwise to reach adequate sedation measured by the COMFORT-B scale, a validated pain and sedation scale for critically ill PICU patients (10). On the physician's discretion, clonidine boluses (1–2 mcg/kg) were given at start of the infusion or when the infusion rate was increased due to breakthrough distress.

The ECMO circuit was composed of cannulas (Medtronic®, Kerkrade, the Netherlands), polyvinyl chloride tubing (Bentley Bypass 70 tubing; Baxter, the Netherlands), a silicone rubber membrane oxygenator (Medtronic®; for neonatal system: 1.5m^2 Paediatric Extended Capacity Membrane Oxygenator; for pediatric system: 2.5m^2 I-2500–2A silicone Surgical Membrane Oxygenator) and a heat exchanger (Medtronic® Heat Exchanger Monitoring adapter and Luer-lock). The neonatal system was applied in children < 10–12 kg; the pediatric system in children with higher weight. Priming volume was 350 ml in the neonatal and 900 ml in the pediatric system. Ninety per cent of the patients were pre-emptively treated with continuous veno-venous hemofiltration (CVVH) while on ECMO (2). The filter (Multiflow 100; Hospal, Lyon, France) was placed parallel to the ECMO circuit, distal to the ECMO roller pump.

Blood sampling

Blood samples for PK analysis were collected concomitantly with routine blood sampling three times daily. In addition, blood was sampled, if possible, before, at the time of ECMO cannulation, 1 and 3 hours thereafter and after decannulation. Blood was sampled from the preoxygenator access point and collected in EDTA-decoagulation tubes.

Laboratory analysis

After centrifugation (5 minutes, 4000 x g), the supernatant serum was stored at -80°C until the assay was performed. Clonidine was analyzed using LC-MS/MS in the positive ionisation mode. To precipitate proteins, 50 µl tri-chloroacetic acid containing the internal standard clonidine-d4 was added to 20 µl of plasma. Samples were vortexed, stored at -20°C for 30 minutes, vortexed again and centrifuged (4 minutes at 2750 x g). For the determination of clonidine 5 µl of the sample solution was injected onto a Thermo Scientific Hypersil Gold (50 x 2.1 mm, 1.9 µm) column. A chromatographic gradient was applied using an acetonitrile and water mixture with a constant 5% addition of 1% ammonium formate / 2% formic acid in water. The flow was 600 µl/min. Clonidine was measured as $[M+H]^+$, using the mass transition 232.1/44.0 and Clonidine-d4 with mass transition 236.1 / 48.0. The method was validated over a range of 0.100 – 20.0 µg/L.

The accuracy ranged from 98.6% to 113.8% across the validated range, the intra-day precision was below 6.4% and the inter-day precisions was below 6.4%.

Clinical parameters

Demographic data (weight, date of birth, gender, gestational age where applicable) were retrieved from the electronic patient data management system. The most recently measured bodyweight prior to ECMO was used for drug dosing and PK analysis. In addition, the following data were retrieved: exact dose and time of clonidine infusion and boluses, laboratory parameters, indication for ECMO, ECMO type (VV or VA) and ECMO flows, CVVH flows (if applicable), urine output, fluid balance, use of diuretics and inotropic drugs, and body temperature. Concomitant medications included other analgesics and sedatives (morphine, midazolam, pentobarbital), vecuronium, antibiotics, inotropes and vasoactive drugs and diuretics (furosemide, bumetanide, spironolactone).

PK model development

The pharmacokinetic analysis was conducted with nonlinear mixed effect modeling software (NONMEM 7.2.0; Icon Development Solutions, Ellicott City, Maryland, USA). Nonlinear mixed effects modelling allows determination of fixed (typical values for PK parameters) and random parameters (inter- and intra- individual variability and residual variability). The first-order conditional estimation (FOCE) with interaction between inter-individual and residual random effect was used during the entire model development. R (version 3.1.2) (11) and Pirana (version 2.7.1) (12) were used to visualize the results and evaluate the output. The log-likelihood ratio test was the main tool for the selection between two hierarchical models, using the objective function value (OFV) produced by NONMEM. The OFV is a measurement of goodness of fit of the model and is proportional to minus two times the logarithm of the likelihood (-2 log likelihood) of the data. During basic model building and covariate analysis, a difference in objective function value (OFV) of more than 10.8 (corresponding to a *p*-value of 0.001 assuming a Chi-square distribution) was considered statistically significant when the models differed by one parameter. Goodness of fit plots and confidence interval in parameter estimates were also evaluated during basic model building and covariate analysis.

The population model was built in 3 steps:

1.) Structural model

One, two and three compartment models were evaluated. Between-subject variability in clearance (Cl) and volume of distribution (V) were evaluated with exponential models:

Eq 1: $Cl_i = \theta_{pop} * exp^{\eta i}$

Eq 2: $V_i = \theta_{pop} * exp^{\eta i}$

Where θ_{pop} is the population parameter for clearance and volume of distribution, respectively, and ηi the normally distributed between-subject variability with mean 0 and variance ω^2.

The error model characterizing the residual variability (unexplained by the model) was defined by a proportional and an additive term:

Eq 3: $C_{obs,ik} = C_{pred,ik} * (1 + \varepsilon_{prop,ik}) + \varepsilon_{add,ik}$

Where $C_{obs,ik}$ is the k^{th} observed plasma concentration for the individual i, $C_{pred,ik}$ the predicted plasma concentration and $\varepsilon_{prop,ik}$ and $\varepsilon_{add,ik}$ are the residual random proportional and residual errors with a mean of 0 and a variance σ^2.

To account for variability in pharmacokinetic parameters due to the varying sizes of individual children, the parameter values were standardized *a priori* to a bodyweight (WT) of 70 kg using an allometric power model using equation 4 and 5:

Eq 4: $Cl_i = Cl * (WT/70)^{0.75}$

Eq 5: $V_i = V * (WT/70)$

2.) Covariate analysis

We expected that PK parameters would be influenced by:

1. *Demographic and clinical condition* (gender, main diagnosis leading to ECMO).
2. *Maturation*: Age-related maturation is a major factor influencing PK (clearance) in children (13). This was expected to have a major impact because the study population had a broad age range. Postmenstrual, postnatal and gestational age were tested.
3. *ECMO*: Physico-chemical interactions between clonidine and the ECMO circuit, such as increased clearance due to adsorption to the circuit and increase in volume of distribution (VD) due to the added extracorporeal circuit (3).
4. *Disease progression*: indications for ECMO, organ dysfunction or systemic inflammation may affect PK (14). Laboratory values served as surrogate markers of organ function (liver function test, urea and creatinine, lactate, albumin).

The covariate analysis was performed using the formulas described in table 1.

Multivariate analysis was carried out stepwise, including first the parameter leading to the highest decrease in OFV. All significant parameters in the univariate analysis were tested. A decrease in OFV of 10.8 (corresponding to a *p*-value of 0.001) was considered significant.

3.) Model validation

Bootstrap analysis was performed on the final model by the use of Perl speaks NONMEM (15). 1000 bootstrap data sets were generated by random sampling and replacement. Median parameter values, 2.5^{th} and 97.5^{th} percentiles of parameter distribution and standard error of the estimates generated, were compared to the parameters of the final model.

Table 1 : Covariate analysis

Equations	Covariate tested
Eq 6: $Cl = Cl_{base} * \theta^{CATEG}$ *Where :* - Cl_{base} corresponded to the Cl in individuals with CATEG = 0 *Example*: When testing gender, females were assigned CATEG = 0 and males CATEG = 1. The clearance in females was equal to $Cl_{base,}$ and θ is the Cl ratio of males over females.	*1.) Demographics and patient's characteristics:* Gender, ECMO-indication *3.) ECMO* Type of ECMO: VV-ECMO vs VA-ECMO *4.) Disease progression* CVVH: yes/no, use of inotrops: yes/no and diuretics: yes/no
Eq 7: $Cl = \theta_{pop} * (GA_i / \text{median } GA_{pop})^{\theta GA}$ Where: - GA_i is Gestational age of the an individual patient - Median GA_{pop} is median Gestational age of all patients *Example:* An individual with a GA_i value equal to the median of the population had a clearance value θ_{pop}.	*2.) Maturation of clearance:* Gestational age (GA) *4.) Disease progression:* Continuous variables like temperature, laboratory values (e.g creatinine, ALT), CVVH and ECMO flow, urine output
Eq 8: $Cli = \theta pop \cdot \frac{PNA^{Hill_{PNA}}}{T50_{PNA}^{Hill_{PNA}} + PNA^{Hill_{PNA}}}$ Where: - Hill refers to the Hill coefficient (shape) - $T50_{PNA}$ is the post-natal age (in weeks) at 50% of adult (full) maturation	*2.) Maturation of clearance:* Post-natal age (PNA) and post-menstrual age (PMA)
Eq 9: $Cli = Clbase \cdot (1 + delta\ Cl * \frac{tec^{\theta tEC}}{T50CL^{\theta tEC} + tec^{\theta tEC}})$ *Where:* - Cli is the clearance of an individual at different time aftercannulation (t_{EC}) - delta Cl is the maximal fractional increase or decrease of the PK parameter during ECMO - T50CL is the time to half of the maximal effect - θ_{tEC} corresponds to the Hill exponent determining the steepness of the change in clearance.	*3.) ECMO ** The ECMO effect on clearance and volume was tested with 3 different temporal covariates: A.) Time since start of the ECMO support (tEC) B.) Time since start of the clonidine while on ECMO support (tECCLO) C.) Time since discontinuation of ECMO support (tEND)
Eq 10: $V = V_{ECMO} - (V_{ECMO} - V_{NON}) * e^{(-tEC*0.693/t1/2)}$** *Where:* - V is the volume of distribution at different time after cannulation (tEC) - *VECMO is the maximal volume on ECMO* - *VNON is the volume of distribution off ECMO* - *t1/2 is the half-life of the change in volume of distribution.*	*3.) ECMO ** Change in volume of distribution on ECMO

*= Several other functions (linear, exponential and half-life model) were applied to evaluate possible relationships between the temporal covariates and CL and V.

**= from half-life model described by Ahsman et al. Population pharmacokinetics of midazolam and its metabolites during venoarterial extracorporeal membrane oxygenation in neonates. Clinical pharmacokinetics. 2010;49(6):407–79

The model was also validated using normalized prediction distribution errors (NPDEs) that simulate prediction discrepancies between the distribution predicted and the observations from the same individual. NPDEs were calculated using a commonly-used an R-package (16).

Table 2 Patient's characteristics and treatment (n = 22)

Age (month)	**1.0 (6.4)**
GA (week)	38.9 (5.6)
PMA (weeks)	42.8 (17.6)
Weight (kg)	4 (3.1)
Sex, male/female; n (%)	11/11 (50/50)
Survival; n (%)	17 (77.3%)
Diagnostic; n (%)	
• *Cardiac*	4 (18.2%)
• *Congenital diaphragmatic hernia*	3 (13.6%)
• *Meconium aspiration syndrome*	5 (22.7%)
• *PPHN*	1 (4.5%)
• *Pulmonary*	7 (31.8%)
• *Sepsis*	2 (9.1%)
Clonidine use	
• *Mean infusion dose, mcg/kg/h*	0.24 (0.15)
• *Time of start, days since ECMO start*	2.9 (4.4)
• *Patients on clonidine at ECMO start*	3 (13.6%)
• *Patients on clonidine at ECMO stop*	17 (77.3%)
Continuous sedative started after clonidine	
• *Pentobarbital*	3 (13.6%)
• *Propofol*	1 (4.5%)
• *Ketamine*	5 (22.7%)
Level of sedation (total number of observations = 706)	
• *Oversedation (COMFORT-B< 11)*	297 (42.1%)
• *Optimal sedation (COMFORT-B 11–12)*	398 (56.4%)
• *Undersedation (COMFORT-B > 22)*	11 (1.5%)
Therapeutic Hypothermia, n (%)	1 (4.5%)
Use of Diuretics	
• *Patient exposed to any diuretic, n (%)*	16 (72.7%)
• *Start prior to ECMO*	10 (45.4%)
• *Furosemide intermittent, n (%)*	14 (63.6%)
Dose (mg/kg/day)	1.3 (2.0)
• *Furosemide infusion, n (%)*	4 (18%)
Dose (mg/kg/h)	0.10 (0.07)
• *Spironolactone, n (%)*	7 (31.8%)
Dose (mg/kg/day)	2.1 (0.7)
• *Bumetanide, n (%)*	2 (9.1%)
Dose (mg/kg/day)	0.4 (0.1)

Table 2 Patient's characteristics and treatment (n = 22) (continued)

Age (month)	**1.0 (6.4)**
CVVH	
• *Patient with CVVH, n (%)*	20 (90.9%)
• *CVVH flow (ml/min)*	300 (200)
ECMO	
Modality :	
• *VA, n(%)*	7 (31.8%)
• *VV, n(%)*	15 (68.2%)
Duration (day)	6.2 (7.1)
2nd run, n (%)	2 (9.1%)
Circuit change	1 (4.5%)
Laboratory values	
• *Creatinine (µmol/L)*	27 (10)
• *Albumin (g/L)*	32 (9)
• *AST (IU/L)*	49 (143)
• *ALT (IU/L)*	19 (70)
• *GGT (IU/L)*	31 (46)

Values are expressed as median and interquartile range unless specified otherwise

Dosing simulations

Average curves for representative patients were simulated. Interpatient variability was not simulated due to the limited number of patients. Parameters were fixed to 3 different age values: 3 days, 1 month and 6 years. A start of clonidine infusion 24 hours after ECMO cannulation was assumed.

RESULTS

Twenty-two patients were included, with median age 1 month (IQR 6.4) and median weight 4 kg (IQR 3.1) at initiation of ECMO support. Demographics and treatment details are presented in Table 2. The median number of blood samples per patient was 12.5 (IQR: 13).

Plasma clonidine concentrations were obtained from 375 samples. Concentrations below the level of quantification (LOQ) represented 4.2% of all observations (n = 16: 15 during ECMO, 1 after ECMO) and were ignored during model building. In 4 patients (18.2%), a clonidine level was determined prior to ECMO start (5 samples) and in 8 patients (36.4%) samples were available after decannulation (17 samples) until 54 hours after ECMO decannulation. Figure 1 shows the individual clonidine concentrations plotted against time profiles.

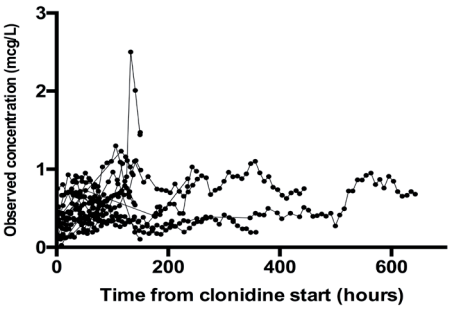

Figure 1: Individual clonidine concentration versus time profiles
For every patient the individual data are connected by a solid line.

Model development

Structural model

A one-compartment model was superior to a two-compartment model. The OFVs did not differ but in the latter model the precision of the estimated parameter was poor. The proportional error in the residual error model was very small and could be eliminated from the model without an increase of OFV. The a priori allometric scaling on clearance and volume resulted in a statistically significant improvement (decreases in OFV: -35.3; *p*-value< 0.001). Typical values and inter-patient variability for clearance and volume were 18.2 L/h/70kg and 33% (Clpop, IIV) and 470 L/70kg and 52% (Vpop, IIV) (Table 3).

Uni-covariate analysis

Table 3 gives an overview of the main models tested and their performance during univariate analysis.

1. Demographics

Gender and diagnosis were not significant covariates.

2. Maturation

Among all models accounting for the effect of age on clearance, the Hill equation using postnatal age gave the best fit to the data: OFV decreased by 158; the standard error of the estimate (SE) and goodness of fit plots were adequate. A relationship between gestational age and clearance was not detected.

3. ECMO

The increase in clearance and VD with time on ECMO were best described with sigmoidal Emax models. Time dependent changes in clearance or volume after ECMO decannula-

Table 3 Parameter estimates and bootstrap results

		Final model $Cl_i=Cl_{pop}*(WT/70)^{0.75}*(PNA^{\Theta 1}/(T50_{PNA}{}^{\Theta 1}+PNA^{\Theta 1}))*\Theta 2^{DIURETIC}$ $V_i=V_{pop}*(WT/70)*(1+Emax*t_{ec}{}^{\Theta 3}/T50_{EC}{}^{\Theta 3}+t_{ec}{}^{\Theta 3})$			
	Structural model	**Final model estimates**		**Bootstrap (1000 replicates)**	
Parameter	**Value (RSE)**	**Value (RSE)**	**Shrinkage**	**Median**	**2.5–57.5th percentile**
Fixed effects					
Cl_{pop} (L/h/70kg)	18.2 (8.3%)	29.9 (11.5%)		29.3	21.9–99.7
Θ1	-	3.02 (22.1%)		3.22	0.13–3.41
$T50_{PNA}$ (week)	-	1.13 (6.5%)		1.15	0.39–96*10^9
Θ2	-	0.659 (7.5%)		0.675	0.567–7.852
V_{pop} (L/70kg)	470 (16.9%)	454 (12.2%)		440	335–558
Emax on V	-	0.55 (32.9%)		0,55	0.30–0.53
$T50_{EC}$ on V	-	51.7 (4.6%)		52.1	45.9–96.6
Θ3	-	18.5 (53.5%)		18.0	5.0–01.1
Random effects					
Interindividual variability					
Cl (%)	33 (16%)	40 (27%)	3	37	16–61
V (%)	52 (53%)	44 (19%)	11	43	21–12
Error					
Proportional	0.281 (18.8%)	0.208 (6.5%)		0.204	0.179–9.231

Abbreviations: Cl_{pop}=clearance population; Cl_i=clearance individual; DIURETIC refers to the use of diuretic; Emax=maximal effect; OFV=objective function value; PNA=post-natal age ; T50=time to half of maximal effect; t_{ec} =time on ECMO; V=volume of distribution ; WT=weight

tion were not detected. Moreover, no relationship was found between the type of ECMO (VA vs VV) and volume or clearance.

4. Disease progression

Laboratory values were not significant covariates. Urinary output was proportional to clonidine clearance while the use of diuretics was negatively associated with clearance. The use of CVVH modelled as in Equation 6 increased the volume of distribution by 33% but did not statistically significantly improve the model (decrease in OFV 7.9). Therefore, it was not added to the final model.

Multi-covariate analysis

The Hill equation using PNA was the first implemented in the structural allometric model because it was the most significant (Table 4). Adding the effect of time on ECMO using the sigmoidal Emax model on clearance did not improve the OFV and time on ECMO was therefore not included in the model. Figure 2 shows the population and individual

Table 4: Covariate analysis

Model/Covariate	OFV	p-value	Remark
Structural model:			
1 compartment model	-943,4	NA	
+ allometric scaling with fixed exponents	-978,7	< 0.001	Used in further model building
Univariate analysis			
Maturation			
GA (Eq. 7)	-979,2	NS	
PNA (Eq. 8)	-1136,7	< 0.001	First covariate included in the model
ECMO-effect			
On Clearance			
Sigmoidal Emax model (Eq. 9)			
• t_{EC}	-999,4	< 0.001	
• t_{ECCLO}	-1033,1	< 0.001	
On Volume			
Sigmoidal Emax model (Eq. 9)			
• t_{EC}	-1007,1	< 0.001	
• t_{ECCLO}	-1024,6	< 0.001	
Covariate			
• Use of diuretics (Eq. 6)	-991,8	< 0.001	
• Urine output (Eq. 7)	-1023,9	< 0.001	Eq: $(UO/Median_{pop})^{\Theta UO}$
Multivariate analysis (stepwise inclusion)			
Base model with allometric scaling	-978,7	NA	
+ PNA (Hill equation) on Cl	-1136,7	< 0.001	Half of adult clearance at 1.2 weeks of age
+ Sigmoidal Emax model on V (t_{EC})	-1166,6	< 0.001	V á by 55% on ECMO
+ Diuretic use on Cl	-1185,9	< 0.001	Cl â by 34% with use of diuretics

Only the model giving the best fit to the data is reported for each parameter
Cl: clearance; Emax; Maximal effect, GA: gestational age, NS: not significant, PNA post-natal age, $t_{EC:}$ time since ECMO start, $t_{ECCLO:}$ time since clonidine start on ECMO

predictions versus observed clonidine levels (goodness of fit plots) on and off ECMO of the final model. Both urine output and use of diuretics further decreased the OFV but including both variables resulted in inflated residual standard error. Only the use of diuretics was included in the final model based on a lower standard error of the estimate. It was associated with decreased clearance (Θ DIUR = 0.66). The empirical Bayesian estimates of clearances during and off ECMO and CVVH, respectively, are depicted in Figure 3.

ECMO significantly increased VD by 55%. Maximal VD was reached 72 hours after initiation of ECMO.

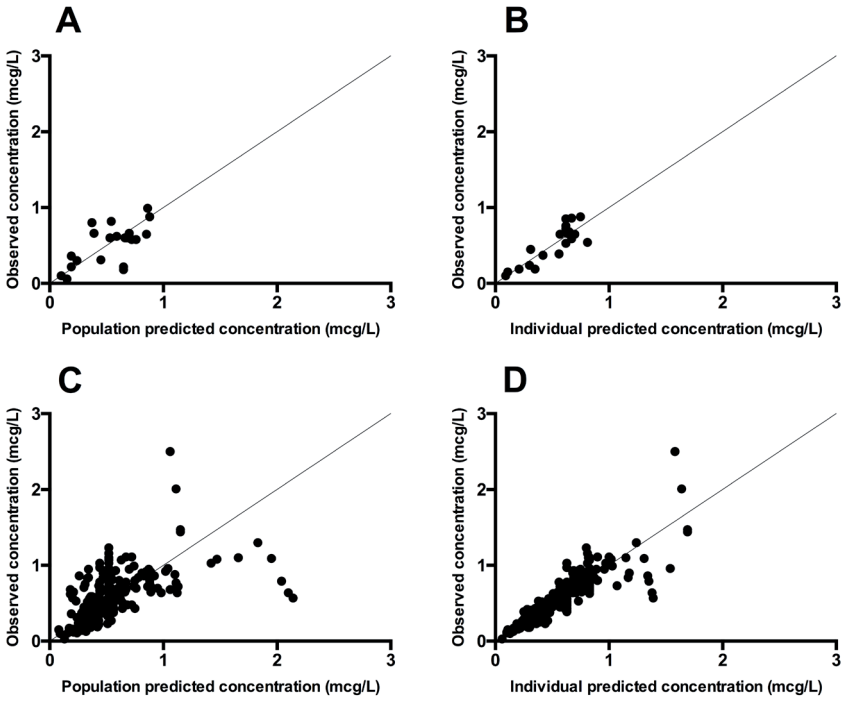

Figure 2: Population predicted (left) and individual predicted (right) plasma concentrations versus observed clonidine levels on (bottom) and off (top) ECMO.

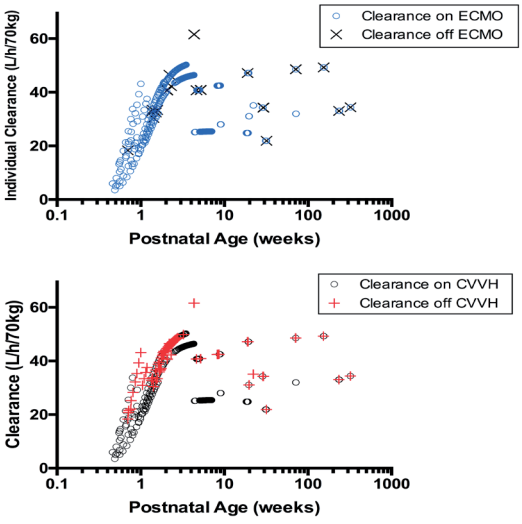

Figure 3: Empirical Bayesian estimates (EBE) of clearances during presence and absence of both ECMO (top) and CVVH (bottom). EBEs are plotted for every time point of blood sampling. Clearance values are allometrically scaled. For every patient the individual data are connected by a solid line.

Table 3 describes the parameter values and their corresponding interpatient variability. Goodness of fit plots of the final model are depicted in Figure 4. Typical values for clearance and VD were 29.9 L/70kg/h and 454 L/70kg. Introduction of the covariates to the structural model increased interpatient variability of clearance from 33 to 40% and reduced that of VD from 52 to 44%. The residual error decreased from 28% to 20%.

Model validation

The final model was tested with a bootstrap analysis; results are given in Table 4. 284 bootstrap runs were prematurely terminated. Validation with NPDEs resulted in a global adjusted *p*-value of 0.925, a normal distribution of errors and no trend in NPDE versus time and versus prediction.

Clearance simulations

Figure 5 shows the body-weight normalized clearance plotted against age, as predicted by the final model and two pediatric studies in non-ECMO patients (17, 18). The mature clearance in ECMO patients is double the clearance in patients not on ECMO.

Dosing simulations

When clonidine is started at 24 hours of ECMO support, a therapeutic clonidine plasma concentration (2ng/ml) can be reached within 1 hour as follows:

- *In a 3-day-old patient (3 kg):* with 3 boluses of 5 mcg/kg (20 minutes intervals) and an infusion of 0.12 mcg/kg/h.
- *In a 1-month-old child (4 kg):* with 3 boluses of 5 mcg/kg (20 minutes intervals) and an infusion of 2 mcg/kg/h.
- *In a 12-year–old child (35 kg):* with 3 boluses of 5 mcg/kg (20 minutes intervals) and an infusion of 1 mcg/kg/h.

DISCUSSION

This study is the first to describe the population PK of clonidine after intravenous administration to neonates and children on ECMO. The developed PK model shows that allometrically scaled clonidine clearance increases steeply with postnatal age, and reaches 70% of adult clearance at 10 days of postnatal age. Interestingly, the use of diuretics is associated with a lower clearance. The volume of distribution increases by 55% during ECMO.

A one-compartment model was superior to a two-compartment model. Clonidine PK in paediatrics has previously been described with one (18) and two-compartments models (17, 19). In the study by Potts et al (17) and Larsson et al (19), samples were avail-

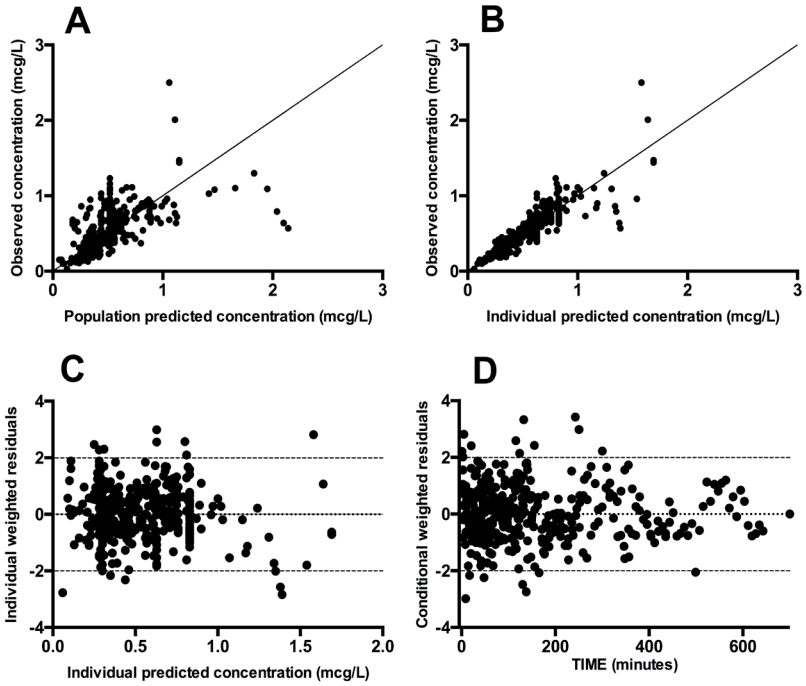

Figure 4: Goodness of fits plots for the final model of clonidine on ECMO
A: Population predicted clonidine concentration versus observed clonidine concentration
B: Individual predicted clonidine concentration versus observed clonidine concentration
C: Individual predicted concentration versus individual weighted residuals
D: Conditional weighted residuals versus time

able late after a single clonidine dose (until 24 hours), which might have made it easier to distinguish a second phase in the elimination (17). The clearance of clonidine in our study is double that reported in previous studies in non-ECMO patients. For other drugs studied this increase was maximally 50% (20). The use of CVVH in 90% of our patients may have influenced the clearance. The estimated clearance on ECMO was estimated at 30 L/h/70kg in our study while it was around 15 L/h/70kg in two previous pediatric studies (17, 18) (Figure 5). One of these two studies reported an apparent clearance value in 36 newborns (PNA: 8.8 ± 5.5 days) treated with oral clonidine for neonatal abstinence syndrome (18). To our knowledge, the bioavailability of clonidine in neonates has not yet been reported. Values of 50% and 90% have been reported for children and adults, respectively (19) (21). The other study (17) pooled data from 5 studies including 83 patients ranging from neonatal to adolescent age treated by intravenous, rectal and epidural clonidine for sedation prior or during general surgery and after heart surgery. In studies in adults not on ECMO, oral and sublingual clonidine clearance values were similar to those found in children (14 L/h/70 kg (22, 23)).

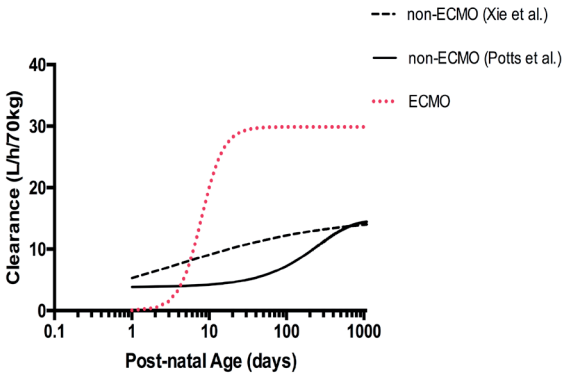

Figure 5: Predicted body-weight normalized clearance profile according to postnatal age in ECMO versus non-ECMO pediatric studies. Clearance is depicted only from day 3 (age of the youngest patients).
A: Predicted clearance during neonatal period
B: Predicted clearance from birth to 500 days of life

Several factors may explain the higher clearance values during ECMO. One factor is the extracorporeal technique. The blood in the ECMO circuit is in contact with a large surface of synthetic material that adsorbs drugs (24) and thereby increases clearance. Ex vivo studies of ECMO systems show that rapidity and extent of drug adsorption increases with lipophilicity (24, 25) and amount of protein bound (26). The adsorption of clonidine may be expected to be high: it is moderately lipophilic (log $P = 1.6$) (27) and slightly protein-bound (20–40%) (28). Ex-vivo studies on clonidine are lacking; still it would be useful to delineate the losses in the ECMO and CVVH circuits and compare adsorptive capacities of different type of ECMO system. Second, 90% of the patients were on continuous renal replacement therapy. Clonidine is considered poorly dialyzable and no dosing adjustment is recommended on dialysis (29, 30). However, its extraction ratio of 0.2–0.3 (30) and its physico-chemical properties (low molecular weight and slightly protein bound) suggest considerable clearance when renal replacement therapy is continuous, despite its large VD. The concentration of clonidine in the ultrafiltrate should be determined in future studies.

We found that postnatal age was the main determinant of bodyweight normalized clearance. This is in line with previous studies described in Figure 5 (17, 18). Interestingly, the sigmoidal model with PNA was described earlier by Xie et al. in a neonatal population treated with oral clonidine for neonatal abstinence syndrome. (18). These models using PNA should be interpreted with caution in the first days of life because they imply absent clearance at birth and therefore do not reflect the liver metabolism and renal clearance that start long before birth. ECMO is rarely initiated on the first day of life: the

youngest patients in our study were 3 days old (n = 4) and our results likely cannot be transposed to younger neonates.

Interestingly, maturation of clearance with postnatal age shows a different pattern in our study: it starts at a smaller baseline value and reaches adult value at an earlier age. In our ECMO-patients, 70% of adult clearance was reached at 1.5 weeks compared to 1 month (18) and 9 months (17) in previous pediatric studies. These various patterns of clearance maturation may at least be partially explained by different age distribution: the first study included only neonates (18) while the second included only a few neonates (17). The derived PK parameters should only be used within the age range studied. The oldest patient in our study was 6 years old and these parameters therefore cannot be applied to older children.

Like ECMO and clinical condition, age may affect two clearance pathways: GFR and CYP2D6 mediated drug metabolism. The expression and activity of CYP2D6 mature rapidly between birth and 1 week of age and reaches 85% of adult activity at a PNA of 2 weeks (31, 32). We found a similar pattern. However, renal function reaches adult values not until by 8 to 12 months of age (13), which corresponds to the pattern of clearance maturation in non-ECMO patients but is not supported by our study.

High collinearity between time-dependent variables is expected: the predominant effect of age on clearance may mask influential factors such as clinical condition, ECMO or CVVH. This confounding effect is inherent to ECMO studies. Postnatal age reliably estimates clearance but shouldn't be interpreted as the etiology of the increase in clearance with time. The low baseline clearance may reflect the patients' critical clinical condition at ECMO start, after which their renal and liver function recovered (14, 33). Moreover, the inflammatory response triggered by the disease or the start of ECMO (34) known to induce cytochrome 2D6 downregulation could contribute to the lower baseline clearance (14, 35). The influence of ECMO and CVVH on clearance probably drives the rapid increase of clearance with age.

Diuretics use was associated with a 34% lower clearance. Creatinine is cleared by CVVH and creatinine level could therefore not be used to estimate renal function. In our PICU, CVVH is used early or pre-emptively in patients on ECMO (2) and adequate urine output is aimed for while on CVVH. Our team has reported diuretic use as risk factor of acute kidney injury (AKI) post-ECMO in the same population (36). The doses of loop diuretics were the only factor associated with AKI. During ECMO, diuretics are used for oliguria that may be caused by excessive CVVH fluid removal or to AKI related to the patient's medical condition. Similarly, the decreased clonidine clearance associated with diuretic use in this study can reflect both conditions.

The VD was 454 L/70kg at ECMO start and increased by 55% during ECMO. In a study using a one-compartment pharmacokinetic model the VD of oral clonidine in non-ECMO neonates was 391 L/70kg (18)). High increases of VD have also been reported for

other drugs administered during ECMO (20, 37). To illustrate this: a doubling in case of a hydrophilic drug and a 400% increase for a lipophilic drug such as midazolam. ECMO can increase VD by several mechanisms. For hydrophilic drugs, the added volume of the circuit increases the central VD at ECMO initiation. But alternate hypotheses are more likely for a lipophilic drug like clonidine. Adsorption to the ECMO circuit may mimic an increase in VD. Moreover, a systemic inflammatory response, either associated with the patient's clinical condition or triggered by the ECMO system (34), induces a capillary leak and fluid retention that can change drug distribution and increase VD. While fluid retention is more likely to affect VD of hydrophilic drugs, the inflammatory response also involves the central nervous system and alters permeability of the blood-brain barrier (38) and may therefore impact VD of lipophilic drugs. Possible causes of the increase in VD of lipophilic drugs need to be further studied.

The composition of the ECMO system has an impact on plasma drug level (24) and may have influenced the pharmacokinetics of clonidine. At the time of the study a circuit with a high adsorptive capacity was used. Many PICUs have switched to circuits made from polymethylpentene hollow fibre, which are associated with less adsorption. Clearance may therefore be lower with the new generation of ECMO circuits. Moreover, the priming volume was higher than in the newer ECMO systems. Furthermore, the newer ECMO systems are likely to lead to less inflammation. Each of these properties may potentially influence clonidine PK.

In many PICUs the clonidine infusion rate has increased in recent years. At the time of our study it was 0.1–1 mcg/kg/h in our PICU versus 1–3 mcg/kg/h in a recent PICU trial (4, 39). The clonidine level obtained in this study can therefore not be compared with that obtained in more recent studies. The targeted clonidine plasma concentrations in the PICU have not yet been formally determined with PK/PD studies. Studies in healthy adult volunteers (40) and limited data in critically ill children (41) suggest a level of 2 ng/ml to ensure sedation and analgesia. The rapid increase in clearance during the first 2 weeks of life suggests that the infusion should regularly be incremented in early life. As we found that the clonidine clearance in children older than one month was twofold the adult clearance the infusion rate may need to be doubled from one month of PNA to reach the same steady state concentration. Currently, the maximal recommended bolus dose is 5 mcg/kg. We simulated the number of bolus doses of 5 mcg/kg needed to reach the target concentration of 2 ng/ml within one hour: three repeated bolus doses of 5 mcg/kg were needed. Our study proposes dosing recommendations based on available PK/PD data, and suggests that higher doses of clonidine infusion may be needed when ECMO is coupled to CVVH. This study draws a framework to delineate clonidine PK in other populations on different extracorporeal systems.

Limitations of the study

First, the single center nature of this study may limit its generalizability. Second, the newer generation of ECMO systems may have different influence on pharmacokinetics of clonidine. Moreover, this study involved a limited number of patients.

CONCLUSION

This study demonstrates that in children on the studied ECMO system combined with CVVH, the clonidine clearance is doubled and the volume of distribution is higher than reported in critically ill adults and children not on ECMO. Postnatal age is the main determinant of clearance maturation; the rapidity and extent of this maturation suggests an influence of ECMO, CVVH, CYP2D6 maturation and patient clinical condition.

This study delineates a framework for studies on pharmacokinetics of clonidine on other extracorporeal systems and illustrates how dosing guidelines should be developed to account for the diversity of situations encountered in the PICU.

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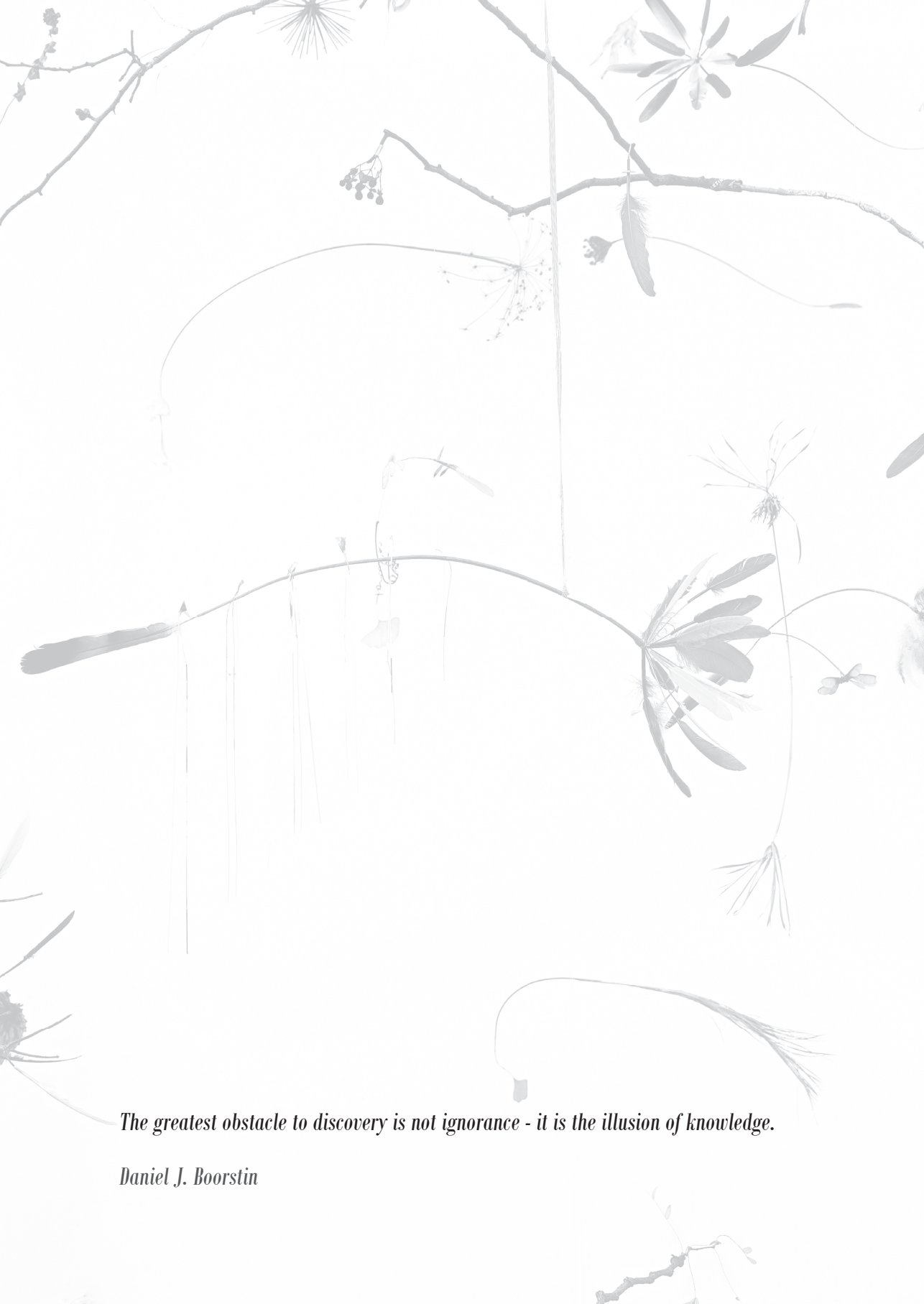

The greatest obstacle to discovery is not ignorance - it is the illusion of knowledge.

Daniel J. Boorstin

Chapter 7

Are young children in the pediatric intensive care at risk for suboptimal dosing with oral acetaminophen? Results of the first pediatric oral bioavailability microtracer study

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KEY POINTS:

Question: Are critically ill children at risk of suboptimal dosing with oral acetaminophen?
Finding: The bioavailability of oral acetaminophen in stable critically ill children is lower than generally assumed: 72% vs 90%, with individual values ranging from 11% to 91%. Hence, oral acetaminophen dosing leads to highly variable blood concentrations, which may put patients at risk of underdosing or toxicity.
Meaning: To ensure adequate pain treatment, intravenous dosing should be considered more often.

ABSTRACT:

Importance: The oral bioavailability of acetaminophen is thought to be almost complete, but it has never been determined in children. This may put children at risk of suboptimal acetaminophen dosing.
Objective: To determine oral acetaminophen bioavailability and its interindividual variability in stable children in the intensive care unit and to simulate exposure after oral and intravenous dosing.
Design: An innovative microtracer study design with concomitant administration of an oral ^{14}C radiolabeled acetaminophen microtracer in patients already receiving intravenous acetaminophen therapeutically. Patients were included from January 2014 until July 2015. Blood was drawn at 10 and 30 minutes, and 1, 2, 4, 6, 12 and 24 hours after acetaminophen administration. Population pharmacokinetic analysis of both therapeutic and oral microtracer doses of acetaminophen was conducted with NONMEM. Current dosing guidelines were used to simulate exposure and determine attainment of therapeutic concentrations.
Setting: Pediatric intensive care unit of a tertiary care hospital in the Netherlands.
Participants: Children up to 6 years who were prescribed intravenous acetaminophen were eligible. Exclusion criteria were: no arterial or central venous catheter in place, kidney or liver failure, gastrointestinal disorder or administration of more than one vasopressor. Of 232 potentially eligible patients, 118 were excluded and parents of 64 declined participation. Because two patients vomited the microtracer dose and one had missing dosing data, data of 47 patients were analyzed.
Exposure: A single oral ^{14}C-labelled acetaminophen microtracer (3 ng/kg) was administered concomitantly with therapeutically dosed intravenous acetaminophen administered per standard of care.
Main outcome and measure: Oral acetaminophen bioavailability

Results: The median age was 6.1 month (Q1-Q3: 1.8–20); the median body weight was 7.4 kg (Q1-Q3: 4.3–10.5). The median PRISM score was 16 (Q1-Q3: 5–29) and 20 patients (42.6%) were mechanically ventilated. Oral bioavailability was 72% (range 11% to 91%). With a standard dose of 15mg/kg 4 times daily, therapeutic steady-state concentrations (10 ng/ml) were 2.5 times more likely to be reached with intravenous than with oral acetaminophen.

Conclusions: Oral acetaminophen results in unpredictable and generally inadequate exposure in young children. To ensure adequate pain treatment, intravenous dosing may be preferable.

INTRODUCTION:

Acetaminophen is an effective analgesic [1] and antipyretic that is among the most commonly administered drugs to sick children. The intravenous (iv) route of administration is increasingly used, but it is unclear whether this should be preferred to the oral route[2]. One argument in favour of the iv route is a more predictable systemic exposure, as the oral absorption of drugs may be erratic [3]. This argument is a theoretical one, as its oral bioavailability has never been determined in children. Oral bioavailability is the fraction of the administered oral dose reaching the systemic circulation. It is generally assumed that acetaminophen oral bioavailability in children is almost complete [4] and therefore, most physicians prescribe the same oral and iv doses as recommended in labelled dosing guidelines (60 mg/kg/d; maximal dose: 1 gram) [5,6]. Interestingly, the assumption of almost complete oral bioavailability (91–97%) stems from a study in 30 healthy adults [7]. In other studies, bioavailability estimations were between 63 and 89% and 60–70% in 6 and 9 volunteers, respectively [8,9]. This suggests that oral bioavailability may be much lower and show more interindividual variability than currently assumed, which may affect the efficacy of oral acetaminophen in children. While previous efficacy studies have shown an analgesic or fever-reducing effect of oral acetaminophen in children with the use of current dosing guidelines, therapeutic failure in underdosed children may have been overlooked [4,10].

The study reported here was aimed to estimate the oral bioavailability of acetaminophen and its interindividual variability in children using the innovative microtracer bioavailability study design, with the ultimate goal to optimize current dosing guidelines. We have previously shown that microdosing is practically and ethically feasible to study acetaminophen pharmacokinetics in children [11].

METHODS:

Setting

This oral bioavailability study was part of a larger ^{14}C-microtracer study [11–13] carried out in the level III pediatric intensive care unit (PICU) of the Erasmus MC–Sophia Children's Hospital. The study was approved by the Dutch Central Committee on Research Involving Human Subjects (EudraCT 2011–005497–28). Parental written informed consent was obtained.

Population

The same patients as in the original study [11,12] were described, that is all patients up to 6 years of age admitted to the PICU who were prescribed iv acetaminophen and had an arterial or central venous catheter in place. To minimize interindividual variability due to severe critical illness, exclusion criteria were kidney and liver failure, gastrointestinal disorder, co-administration of drugs known to interact with acetaminophen pharmacokinetics (PK), the use of more than one vasopressor drug and extracorporeal membrane oxygenation (ECMO).

Study design

Traditionally, oral bioavailability is estimated by giving a drug dose via oral or iv route in the same person and then repeating this after an adequate wash-out period via the alternate route. After each dose, multiple blood samples are taken for estimation of pharmacokinetic parameters. The ratio of area under the curves after oral and iv dosing is considered to reflect the oral bioavailability

In children, a therapeutic drug dose only for research purposes, combined with repeated blood sampling is mostly neither ethically acceptable nor feasible [14]. Moreover, crossover studies do not provide an accurate estimation of bioavailability in individual children admitted to an intensive care unit because critical illness which influences pharmacokinetics, changes over time [15–17]. We chose to overcome these hurdles by the use of labelled non-therapeutic microtracer (< 1/1000 of therapeutic dose) given orally, while the patient receives the therapeutic drug via iv route at the same time.

Children were administered a single radiolabeled microtracer dose of acetaminophen (^{14}Cacetaminophen at 3.3 ng/kg, 60 Bq/kg, 0.25 ml/kg) orally at the same time therapeutic acetaminophen dose was given as per standard of care intravenously. The ^{14}Cacetaminophen formulation was prepared by adding ^{14}Cacetaminophen to a acetaminophen formulation for iv use; details on preparation have been previously described [11]. To ensure proper delivery to patients fed by a naso-gastic tube, adhesion studies were carried out by running the ^{14}Cacetaminophen formulation followed by 1 ml of saline through the gastric tube (all tubes in use at our PICU). Recovery was greater

than 95%. The therapeutic iv acetaminophen was dosed according to the Dutch Pediatric Handbook [18]: 20 mg/kg loading dose, followed by 10 mg/kg q6h (< 1 month of age) or 15 mg/kg q6h (≥ one month of age). Some children had already received multiple doses before the microtracer dose was given and information on these doses was included in the pharmacokinetic analyses.

Blood samples were drawn from the indwelling catheter just before administration of the acetaminophen microtracer dose and at 10 and 30 minutes, and 1, 2, 4, 6, 12, 24 hours after administration. After centrifugation, plasma was stored at -80°C until analysis.

Measurements

^{14}Cacetaminophen plasma concentrations were measured by liquid chromatography-accelerator mass spectrometry (LC+AMS) as previously described [11,19]. The LC+AMS qualification was performed in accordance with the recommendation of the European Bioanalytical Forum [20]. Therapeutic acetaminophen plasma concentrations were measured by liquid chromatography–mass spectrometry (LC-MS/MS)[21].

Data collection

Doses of therapeutic and radiolabeled acetaminophen and the respective timings of administration were collected. Patient characteristics and relevant clinical and laboratory measurements were prospectively collected.

DATA ANALYSIS

Pharmacokinetic analysis

Population pharmacokinetic (popPK) analysis was performed using the nonlinear mixed effect modeling NONMEM 7.3.0 software (Icon Development Solutions, Ellicott City, Maryland, USA). Log transformed therapeutic and ^{14}Cacetaminophen concentrations were modeled simultaneously. A structural pharmacokinetic model was developed to describe the typical pharmacokinetic parameters, together with a statistical model providing for the interindividual and unexplained variability. Then, potential covariates (Table 1) were tested for statistical significance. Covariates that were found to explain a part of the interindividual variability of pharmacokinetic parameters were included in the model. These covariates are clinical characteristics to be taken into account for an individual dosing regimen (e.g.: if weight is a significant covariate then doses are calculated per kg). The details of the analysis are available in the supplementary material (eMethods).

Table 1: Covariates tested for their influence on PK parameters

Type of data collected	Reason for collection	Potential covariates
Weight	Weight is often found a major predictor of PK variability in pediatric patients	• Weight at study day • Weight Standard deviation from 50th percentile for age and sex
Maturation	Age often found a major predictor of PK variability in pediatric patients [43,44]	• Post-natal age (PNA) • Post-menstrual age (PMA) • Gestational age (GA)
Diagnostic	Surgery and associated opioid use induced ileus that may influence oral absorption [15]	• Surgery
	Abdominal surgery induces gut edema and alters intestinal perfusion	• Abdominal surgery
Severity of disease	Severity of disease is associated to ileus, gut, edema and altered gut perfusion	• Severity scores: PELOD score, PRISM, PIM
Organ function	Organ failure may influence PK [45]	• Renal function: urea, creatinine z-score adjusted for gender and age • Liver function: ALT, AST, PA, Bilirubin, GGT • Number of organ dysfunction: defined as the number of organ with a positive PELOD score [46] • Other: albumin, lactate
Inflammation	Inflammation may have a major impact on PK [47]	• CRP • Leucocytes
Way of oral dose administration	Drug absorption is influenced by the place of administration	• Oral, naso-gastric tube, gastrostomy, duodenal tube
Oral feeding status	Critical illness is associated to gastro-intestinal dysmotility and food intolerance [17,48]	• Oral feeding status within the 24 hours prior to microtracer
Comedication	Slowing absorption [15]	• Opioids
	Increasing absorption [49,50]	• Prokinetics
	Influences absorption [15,51]	• Inotropes

Dosing simulations

To compare exposure after oral and iv administration, the concentration-time profiles until 24 hours after administration and mean steady-state concentrations were simulated using the model estimates from the current analysis. A mean steady-state concentration (Css) of 10mg/L (+/- 20% deviation) was targeted, as this is a threshold associated with adequate analgesia [22–24]. The dosing was as follows: similar oral and iv doses of 15mg/kg per dose every 6 hours (60 mg/kg/day) [5]. The highest recommended oral dosing regimen of 22.5 mg/kg/dose every 6 hours (90 mg/kg/day) was also simulated [25]. Simulations were performed for four age groups: 1 month, 6 month, one year and five years, assuming a typical weight of 4.5, 8, 10 and 18 kg, respectively, according to the CDC growth charts. For each dosing regimen and age group, 1000 simulations were per-

formed taking interindividual variability in the model parameters into account. Based on these simulations, the percentage of patients reaching the targeted mean Css of 10mg/L+/-20% in the iv acetaminophen group compared to the oral groups was computed.

RESULTS

Population

Of the 232 eligible patients in the original study, 118 were excluded. Sixty were excluded on the basis of exclusion criteria; for 21 patients the study drug was unavailable (outside office hours of pharmacy) and 37 patients participated in another clinical trial)[12]. Of the 114 parents/care-givers approached, 64 declined participation of their child and thus 50 patients were enrolled. Two patients were excluded as they threw up the microdose and for one dosing information was missing, leaving 47 patients with a median age of 6.1 month (Q1-Q3: 1.8–20) and a median body weight of 7.4 kg (Q1-Q3: 4.3–10.5). Thirty-seven patients (78.7%) had been admitted for postoperative care, and 12 of those (25.5%) had undergone abdominal surgery. The median PRISM score was 16 (Q1-Q3: 5–29) and 20 patients (42.6%) were mechanically ventilated. Patient characteristics and treatment are described in Table 2.

Dataset

The complete dataset included 250 and 314 radiolabeled and therapeutic acetaminophen concentrations, respectively. Twenty-three measurements below (BLOQ) and two above the limit of quantification (ULOQ) for radiolabelled and therapeutic acetaminophen, respectively, were excluded from the dataset as these measurements represented less than 10% of the total number of available measurements (8.4% and 0.6% for ^{14}Cacetaminophen and therapeutic acetaminophen, respectively). The median numbers of concentrations per patient included in the analysis were 6 (Q1-Q3: 5–6) and 7 (Q1-Q3: 6–8) for ^{14}Cacetaminophen and therapeutic acetaminophen, respectively.

PK model

A two-compartment model best described the time course of oral radiolabelled and iv therapeutic acetaminophen blood concentrations.

The mean oral bioavailability in the population was 72% (bootstrap confidence interval: 64–79%) with a high interindividual variability: individual bioavailability estimates ranged from 11% to 91%, implying that some patients absorbed only around 10% of the oral doses while in others the absorption was almost complete. The other PK parameters are provided in Table 3.

Table 2: Patients' characteristics and treatment (n = 47)

Patient characteristic	
Age (month)	6.1 (1.8–80)
Weight (kg)	7.4 (4.3–30.5)
Normalized weight for age (z-score), mean (SD)	-0.7 (1.2)
Sex, male, n (%)	38 (80.9%)
Gestational age (week)	39.9 (38–80)
Mortality rate; n (%)	0 (0%)
Mechanical ventilation on study day, n (%)	20 (42.6%)
Duration of PICU stay, days	3.8 (0.9–9.2)
Severity scores	
• PELOD (on study day)	10 (1–11)
• PIM II score	0.92 (0.2–2.88)
• PRISM	16 (5–59)
Diagnostic; n (%)	
• Surgical (total)	37 (78.7%)
o Of which Abdominal surgery	12 (25.5%)
• Medical	10 (21.3%)
Way of oral acetaminophen administration, n (%)	
• Oral	14 (29.8%)
• naso-gastric tube	22 (46.8%)
• duodenal	8 (17.0%)
• gastrostomy	3 (6.4%)
Orally fed patients*	23 (48.9%)
Comedications	
• Prokinetics	0 (0%)
• Opioids	43 (91.5%)
• Vasoactive-inotropic drugs	13 (27.7%)
Laboratory values at infusion start	
• Urea (mmol/L)	3.5 (2.3–3.9)
• Creatinine (µmol/L)	23 (18–84)
• ALT (U/L)	16 (10–04)
• GGT (U/L)	20 (10–01)
• Alkaline phosphatase (U/L)	151 (127–797)
• Leucocyte count (10^9 per L)	10.6 (8.1–13.8)
• CRP (mg/L)	5.9 (1.2–22)

Values are expressed as median and (Q1-Q3) unless specified otherwise

*= Feeding status was defined as oral feeding until 24 hours before microtracer dose

Abbreviations: ALT: alanine aminotransferase; CRP: C reactive protein; GGT: gamma-glutamyl transferase

Table 3: Parameter estimates from the structural and final model with bootstrap results

Parameter	Model parameters estimates (RSE%) [shrinkage %]	Bootstrap mean (Bootstrap RSE%)
Bioavailability		
F	0.718 (6%)	0.718 (6%)
Absorption rate constant		
ka (h^{-1})	2.15 (27%)	2.25 (32%)
Clearance		
CL	$CL = TVCL \times (BW/7.4)^{\theta CL}$	
TVCL ($L.h^{-1}.7.4kg^{-1}$)	1.95 (6%)	1.94 (7%)
Θ_{CL}	1.05 (12%)	1.06 (12%)
Inter-compartmental Clearance		
Q	$Q = TVQ \times (BW/7.4)$	
TVQ ($L.h^{-1}.8.6kg^{-1}$)	0.346 (12%)	0.372 (44%)
Volumes of distribution		
V1	$V1 = TVV1 \times (BW/7.4)^{\theta V1}$	
TVV1 ($L.8.6kg^{-1}$)	6.67 (5%)	6.62 (6%)
Θ_{V1}	0.702 (15%)	0.715 (16%)
V2	$V2 = V1 \times \Theta_{V2}$	
Θ_{V2} ($L.8.6kg^{-1}$)	0.502 (21%)	0.549 (30%)
Inter-individual variability		
ω CL	0.114 (23%) [7%]	0.109 (24%)
ω ka	2.45 (30%) [20%]	2.44 (32%)
ω F	1.31 (35%) [22%]	1.28 (37%)
Residual error		
Exponential error therapeutic acetaminophen	0.224 (16%) [5%]	0.218 (16%)
Exponential error radiolabeled acetaminophen	0.102 (19%) [16%]	0.101 (18%)

Abbreviations : RSE=residual standard error; BW= body weight; CL = population clearance; TVCL= typical population clearance for a 7.4kg child; ΘCL= estimated allometric exponent for clearance; Q = population inter-compartmental clearance; TVQ = typical population inter-compartmental clearance; V1 = population central volume of distribution; TVV1 = typical population central volume of distribution; ΘV1 = estimated allometric exponent for the central volume f distribution; V2 = population peripheral volume of distribution; Θ_{V2} = fraction of the population central volume of distribution representing the population peripheral volume of distribution. Typical population values (TV) correspond to the population parameter for a child of 7.4kg.

Bodyweight was the best predictor of clearance and volume of distribution and was therefore included in the structural model. After inclusion of bodyweight, age and other potential covariates tested were not found to be significant.

The interindividual variability in bioavailability could not be explained by any patient characteristic. Feeding status was also not a significant explanatory variable for bioavailability. Table 3 describes parameter estimates of the final model. All internal validation presented in the supplementary

eResults shows that the model described the data accurately and precisely.

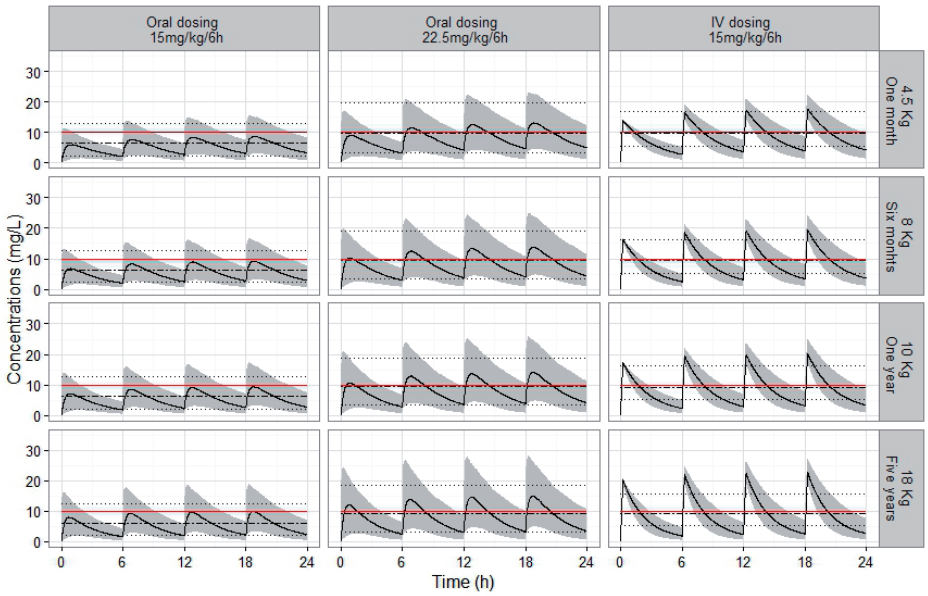

Figure 1: Simulated acetaminophen concentration time profiles over 24 hours after standard oral dose (60mg/kg/day - left), high oral doses (90mg/kg/day - middle) and iv dosing (right)
in four age groups, i.e. 1 month, 6 month, one year and five years of 4.5, 8, 10 and 18 kg**.** The dashed line shows the median of the mean steady-state concentration and the lower and upper dotted lines indicate the 5th and the 95th percentiles of the mean steady-state concentration respectively. The red line represents the targeted steady-state concentrations. Doses recommended by the Lexicomp Pediatric and Neonatal Handbook [5] were used for the oral and iv standard doses and the Dutch Pediatric Drug Handbook [18,34] for the high oral dose (90mg/kg/day).
Wide variability is seen with oral dosing while iv dosing leads to less variable steady-state concentrations. The mean targeted steady-state concentrations of 10mg/L are not reached with an oral dosing of 60 mg/kg/day while the same intravenous dosing allows reaching adequate systemic exposure. With the highest recommended oral dose, the mean targeted steady-state concentrations are reached but the important interindividual variability implies that some patients are underexposed and other overexposed.

Simulation

Figure 1 shows the median and the 90% prediction intervals of the simulated plasma concentrations over 24 hours after acetaminophen administration. Exposure after standard similar iv and oral doses (15mg/kg every 6 hours) led to adequate steady-state concentrations with the iv route (median mean Css corresponded to the targeted mean Css of 10mg/L) but most patients were underdosed with the same oral standard doses (median mean Css around 6.5mg/L). Patients were 2.5 times more likely to reach therapeutic blood concentrations with iv than with oral acetaminophen. Compared to the iv dosing, the highest oral dosing of 90mg/kg/day led to both higher and lower exposure in patients with bioavailability in the upper and lower range, respectively. Due to the high interindividual variability in oral bioavailability, patients were still 1.4 times more likely to be within the therapeutic range after iv dosing than after high oral doses.

DISCUSSION:

This innovative pediatric microtracer study enabled accurate estimation of acetaminophen oral bioavailability and its related interindividual variability. The mean oral bioavailability of acetaminophen in this stable PICU population was 72%. The very wide interindividual variability in bioavailability led to extremely variable acetaminophen exposure after oral dosing, which could not be explained by relevant patient characteristics.

The estimated oral and iv PK parameters are in line with previous estimates in children [24,26]. The wide interpatient variability in exposure after oral dosing has previously been shown in infants younger than 3 month admitted to the PICU [26]. Also in adults undergoing surgery, oral acetaminophen leads to more variable blood concentration than iv [27]. The present study disentangles for the first time the influence of bioavailability and clearance on drug exposure and shows that bioavailability is responsible for the widely variable acetaminophen exposure.

This first estimation of mean oral acetaminophen bioavailability in children is 72%. Reported estimations of oral bioavailability in adults as calculated by AUC range from 63% to 97% [7–9]. Lower exposure with oral versus iv acetaminophen has been shown in adults receiving acetaminophen for premedication before surgery [28].

One would expect that dosing guidelines reflect the oral bioavailability and resulting systemic exposure. If 72% of the oral dose reaches the systemic circulation, a one-third higher oral dose would be needed to reach the same blood level as an iv dose. The mean targeted steady-state concentrations are indeed reached with the highest recommended oral dose of 90 mg/kg/day (table 4) and an intravenous dose of 60 mg/kg/day. However, the variability in oral bioavailability is also important. Compared to intravenous, oral acetaminophen can lead to under and overdosing in patients with low and high oral

Table 4 Comparison between different dosing guidelines for acetaminophen in children (from birth until 6 years)

	Intravenous dosing	Maximal daily iv dose	Oral dosing	Maximal oral daily dose	Ratio maximal iv/oral dose
Perfalgan official label (EU)					
< 10kg	7.5 mg/kg every 6 h	30 mg/kg	Age based in all official product label		NA
> 10 kg to ≤ 33kg	15 mg/kg every 6 h	60mg/kg			NA
Ofirmev (USA)					
≥ 2 to 12 years old:	15 mg/kg every 6 h or 12.5 mg/kg every 4 h	75 mg/kg	Age based in all official product label		NA
British National Formulary [32]					
• Neonate	10 mg/kg every 4–6 h	30 mg/kg	Loading: 20 mg/kg Maintenance: 10–15 mg/kg every 6–8 h	60 mg/kg	50%
• Infant until 10kg	10 mg/kg every 4–6 h	30 mg/kg			40%
• Child weight 10–50 kg	15 mg/kg every 4–6 h	60 mg/kg	Loading: 20–00 mg/kg Maintenance: 15–20 mg/kg every 4–6 h	75 mg/kg	80%
Lexicomp [5]					
• Neonate	Loading: 20 mg/kg Maintenance: 10mg/kg every 6 h	40 mg/kg	10 to 15 mg/kg/dose every 4 to 6 hours	75 mg/kg	53%
• Infant until 2 years	7.5–55 mg/kg/dose every 6 h	60 mg/kg	10 to 15 mg/kg/dose every 4 to 6 hours	75 mg/kg	80%
• Children up to 50kg	15 mg/kg every 6 h or 12.5 mg/kg every 4 h	75 mg/kg			100%
Dutch Pediatric Drug Handbook [18,34]					
• Neonate	Loading: 20 mg/kg Maintenance: 10mg/kg every 6 h	40 mg/kg	Loading: 30 mg/kg Maintenance: 60 mg/kg/day in 3 doses (max 2–2 days)	60 mg/kg	67%
• 1 month to 18 years	Loading: 20 mg/kg Maintenance: 15mg/kg every 6 h	60 mg/kg	Loading: 40 mg/kg Maintenance: 90 mg/kg/day in 3 doses (max 2–2 days)	90 mg/kg	67%

bioavailability, respectively. The high oral dose (90 mg/kg/day) is recommended for short-term use only (max 2–3 days), which seems a rational decision in the light of our findings. Indeed, the wide interpatient variability found in this study implies a risk of overdosing in patients with oral bioavailability within the upper range. Acute liver failure in children receiving regular acetaminophen within the therapeutic dose range has been described [29,30]. Our data suggest over-exposure in some patients, although it cannot be ruled out that the reported cases were due to accidental overdosing. Known risk factors

for acetaminophen-induced liver failure are acute illness, fasting and co-medication with a CYP2E1 inducer [29,31]. Therefore, critically ill patients in particular may be at risk of acetaminophen-induced liver toxicity. Our findings suggest that oral acetaminophen doses higher than 60mg/kg/dose should be used only for short periods of time.

In the current study, oral bioavailability did not change in the age range studied from 0 to 6 years of age. This contrasts the practice in most dosing guidelines in which the ratio of oral to iv dosing increases with age (Table 4) [5,32].

Clinicians often assume that conditions for good oral drug absorption are met when patients are orally fed and have low disease severity. Our study suggests, however, that oral bioavailability of acetaminophen is independent of feeding status and disease severity, thus challenging the clinicians' reluctance to favour iv in stable patients or those tolerating oral food.

The risk of under-dosing and toxicity with oral dosing of acetaminophen suggests that the iv route should be preferred when safe and effective pain relief is warranted. Interestingly, and in contrast to Europe, iv acetaminophen is not licenced for children in Canada [33] and not for children below the age of 2 years in the United States [6].

This study has several strengths. First, it is novel in that it presents the first estimation of oral bioavailability of acetaminophen in children. While the results cannot be generalized to the very ill PICU population in view of the relatively low degree of disease severity, generalization to stable, hospitalized children may be acceptable. Second, the innovative study design may well serve as a blueprint to study dermal, rectal and nasal bioavailability of other drugs.

The following limitations should be addressed. First, we cannot exclude that the oral microtracer dose has contributed to the lower bioavailability and large interindividual variability observed. Such a low dose may contribute to more unexplained variability than does a therapeutic dose. However, uncompleted oral drug administration is highly unlikely as recovery from the feeding tube was almost complete [11]. Also saturation of intestinal drug metabolism with a therapeutic dose could result in higher systemic exposure than with a microtracer dose alone. Both scenarios are unlikely, however, as our results are in line with previous pediatric PK studies on oral and iv acetaminophen. These showed an oral to iv exposure ratio of 40% to 100%, which is within the range of the bioavailability data in the current study [5,18,32,34]. Moreover, similar PK results, i.e. dose-linearity, have been obtained with acetaminophen oral microdose and therapeutic dose in adults [35,36]. The current study was not designed to assess intra-individual variability in bioavailability that may influence acetaminophen exposure after multiple oral doses. Indeed, bioavailability was assessed on a single oral dose and then extrapolated to obtain steady-state concentrations. Third, we could not simultaneously study the impact of the different routes of administration on drug effectiveness. Considering that a clear concentration-effect relationship has been established for acetaminophen [37], we believe that our dosing simulations provide convinc-

ing evidence to support our claim that iv acetaminophen will lead to more effective and predictable systemic concentrations and consequently to better analgesia.

A limitation of our study design is the lack of comparative efficacy and safety data. A recent systematic review on the efficacy of oral versus intravenous acetaminophen in adults, concluded that evidence is lacking to favour intravenous over oral acetaminophen [2]. This conclusion was however based on only 3 randomized efficacy trials in adults: i.e. one open-label study, one underpowered study and one in day-case surgery. In contrast, data from our group showed a very significant morphine sparing effect with IV acetaminophen (approximately 70% less) in neonates and infants after major surgery, which we did not find with rectal acetaminophen, showing a similar variable absorption and bioavailability to our current oral data [38,39]. Another review showed opioid sparing effects of perioperative acetaminophen and NSAIDs in children but concluded that insufficient data are present to distinguish between drugs and/or formulations [10].

Significant decreases in blood pressure have been reported in an observational study [40] and two recent placebo controlled trials in adults [41,42]. While in the observational study, half of the critically ill patients showed a > 15% decrease in blood pressure and a third needed therapeutic intervention (increased inotropic support, filling requirements), the placebo-controlled trials are much more reassuring. In critically ill patients with fever, blood pressure was normal or high before dosing and resulted in normotensive blood pressure after acetaminophen IV [41]. In the other study in healthy adults, only a small and transient decrease in blood pressure was found [42]. In addition, no serious hemodynamic adverse events were reported in our randomized controlled trial comparing acetaminophen IV vs morphine IV for pre-emptive anesthesia after major surgery [1]. Hence, these data are rather reassuring as to the hemodynamic safety of IV acetaminophen, in both adults and children.

CONCLUSION

Our innovative microtracer study design made clear that acetaminophen bioavailability is lower than generally assumed and shows a large inter-individual variability in stable pediatric intensive care patients until 6 years. Oral dosing will result in an unpredictable, likely lower systemic exposure with increased risks of therapeutic failure and increased risk of toxicity when oral doses are increased to overcome the low bioavailability. These PK data suggest that iv acetaminophen should be preferred over oral acetaminophen for the treatment of acute pain in hospitalized children.

Acknowledgments: We thank Joke Dunk for her help in data collection. Ko Hagoort is thanked for editing the manuscript.

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SUPPLEMENTARY EMETHODS

Population pharmacokinetic analyses

Before log transformation, radiolabeled concentrations in mBq/mL were transformed in mg/L of paracetamol equivalent, with 1 mBq corresponding to 5,31–14 gram of paracetamol. R (version 3.0.2) (1) and Pirana (version 2.7.1) software (2) were used to build the database, visualize the results and evaluate the output. The final model consisted of 1) a structural submodel, 2) a statistical submodel, 3) covariate submodel.

For the covariate submodel, covariates as described in table 1 (original manuscript) were tested in order to explain the interindividual variability of the PK parameters. A *p*-value of < 0.001 assuming a $\chi 2$ distribution was chosen as statistically significant, corresponding to a decrease in objective function of 10.8 or more between nested models. Goodness of fit plots, shrinkage and confidence interval in parameter estimates were also evaluated during model building and covariate analysis. The model was validated internally.

1. Structural model

The structural model was parameterised using population pharmacokinetic parameters describing the absorption, distribution and elimination of the drug using ADVAN6 (with differential equations). Therapeutic (cold) paracetamol had been given rectally to 12 patients (10 prior and 2 during the study) and orally to 2 patients prior to study inclusion. To account for exposure from the rectal doses given prior to inclusion, the absorption rate and lag-time for this administration route were fixed to literature values (3) and bioavailability was estimated. One, two, and three compartment models, first and zero order oral absorption and an oral absorption lag time were tested.

2. Statistical model

For the statistical model, log-normally distributed inter-individual variability was tested on each parameter. The interindividual variability reflects the differences in pharmacokinetic parameters between patients due to their individual characteristics. The residual error corresponds to the remaining unexplained variability, including for instance measurement error. For the residual error, separate exponential errors were estimated for 14Cparacetamol and cold paracetamol.

3. Covariate analysis

Bodyweight and age (PMA and GA) were tested first. Then, other covariates were tested in a stepwise manner (forward inclusion and backward exclusion). Covariates leading to a significant decrease in objective function value (p value < 0.001 assuming a $\chi 2$ distribution) and a decrease in the interindividual variability or residual error were included in the model.

4. Internal model validation

Internal validation was performed using a framework for the evaluation of paediatric population models (4). The condition number was computed to assess ill-conditioning (a condition number of 1000 or greater indicates a serious ill-conditioning). Goodness of fit was assessed by visualization of population and individual predicted concentrations versus observed concentrations of cold and radiolabelled paracetamol for the total population as well as for subsets stratified on body weight. Conditional weighted residual errors (CWRES) versus time and versus population predicted concentrations were assessed to evaluate the residual error model adequacy and structural model bias. In order to asses model stability and obtain reliable standard error estimates, a bootstrap was performed. Bootstrap analysis was performed on the final model by the use of Perl speaks NONMEM (5) in order to obtain reliable estimates of the model parameter uncertainty. 1000 bootstrap data sets were generated by random sampling with replacement, with stratification on the covariates included in the final model. Histogram of NPDE (normalised prediction distribution errors) distribution, scatter plots of the NPDE versus time and of the NPDE versus log population predicted concentrations for cold and radiolabelled paracetamol were performed using an R-package (6). These allow to verify the model adequacy by comparison of the distribution of NPDE to the theoretical distribution. Finally, plots of the etas versus the model covariates were assessed to verify the covariate model adequacy.

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SUPPLEMENTARY ERESULTS

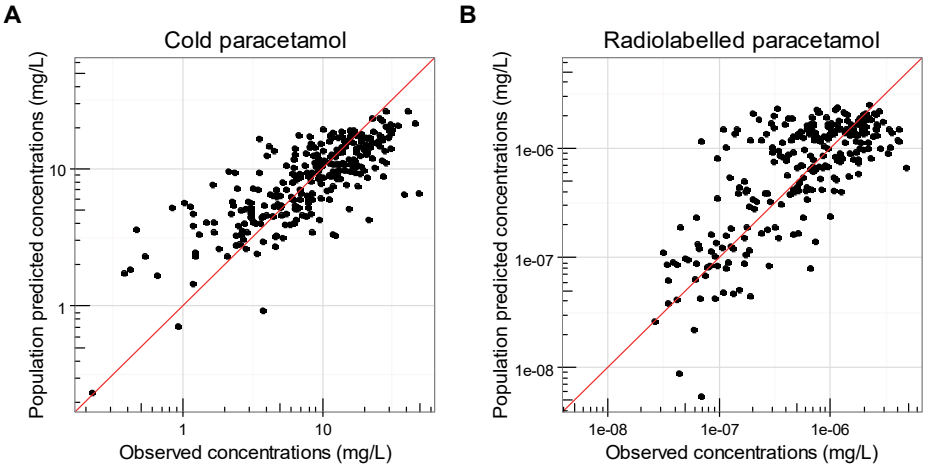
Model validation results

The condition number of the final model was 30.4, which is below the serious ill-conditioning threshold of 1000.

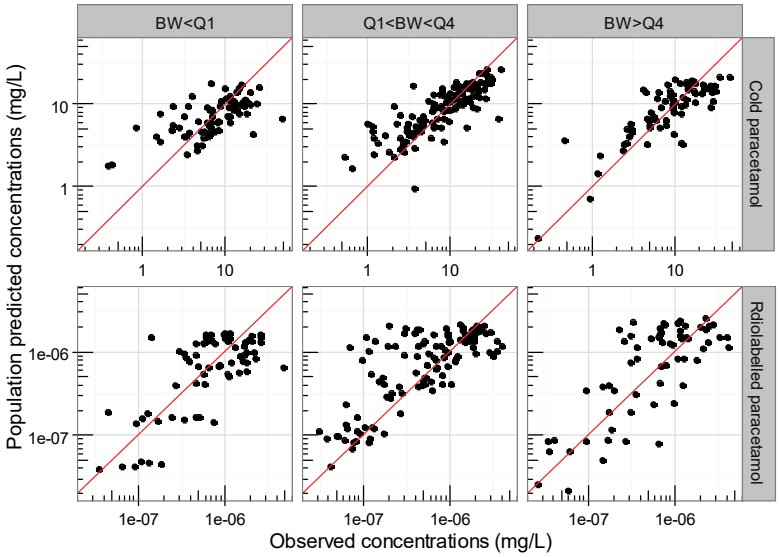
Population and individual predicted concentrations versus observed concentrations for the total population as well as for subsets based on body weight did not show any trends except for very low concentrations of cold paracetamol, indicating that the final model was able to predict oral and intravenous paracetamol level without bias (eFigure 1 to 4).

The plot of CWRES (conditional weighted residual error) versus time and versus population predictions with and without stratification of bodyweight did not show any trends, meaning that the error model chosen appropriately describes the error distribution and no model bias is compensated by the residual error (eFigure 5 to 8). For all parameters, bootstrap estimates were close to the NONMEM run values and the bootstrap percentile 95% confidence interval did not include 0. The variability estimates from the bootstrap were all lower than 40%. Shrinkage on CL was low (7%) and shrinkage on other parameters (ka and F) was around 20%. NPDE showed no trends with time or concentrations for both radiolabelled and cold paracetamol (eFigure 10). The mean and variance of the NPDE for cold and radiolabelled paracetamol were not statistically significantly different from 0 and 1 respectively. The comparison of the distribution of NPDE to the theoretical distribution therefore confirm the model adequacy.

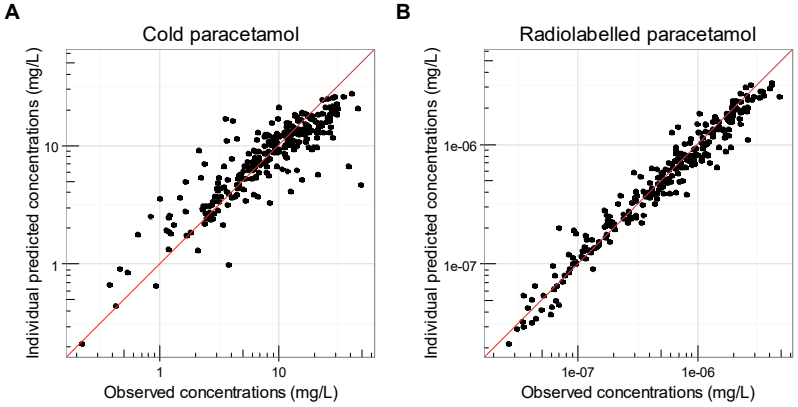
No trends of eta clearance, eta bioavailability and eta absorption rate versus bodyweight were observed after inclusion of body weight as covariate (eFigure 9), confirming that the covariate submodel well describes the observed trends with bodyweight.



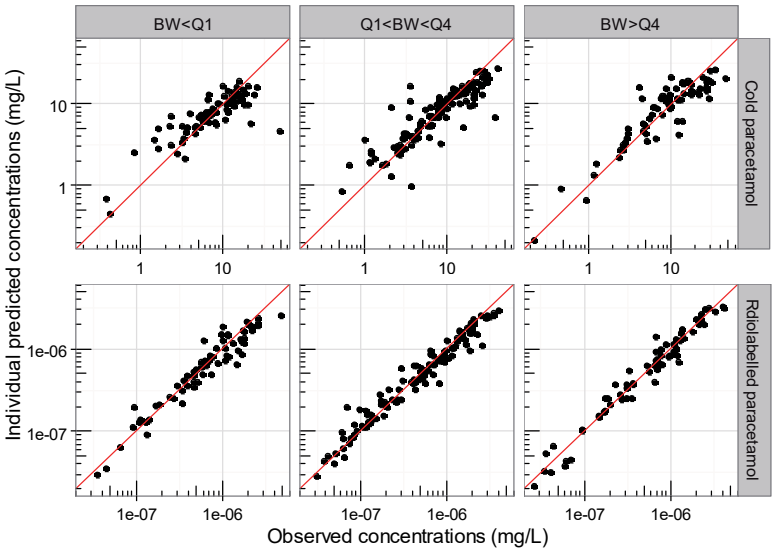
eFigure 1 Population predicted concentrations versus observed concentrations for cold (A) and radiolabelled (B) paracetamol.



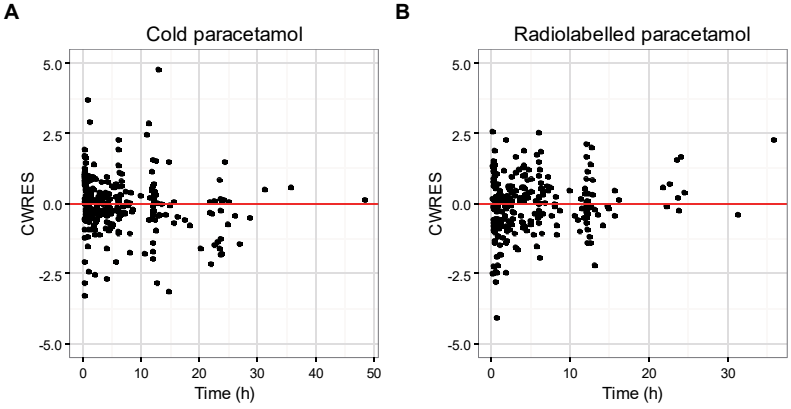
eFigure 2 Population predicted concentrations versus observed concentrations stratified on bodyweight. Stratification was performed with 3 body weight (BW) groups: patients from 2 to 5 kg corresponding to BW inferior to the 1st interquartile (BW<Q1), patients from 5 to 11kg corresponding to BW between the 1st and 4th interquartile (Q1 <BW<Q4) and patients from 11kg to 23 kg corresponding to BW greater than the 4th interquartile (BW>Q4).



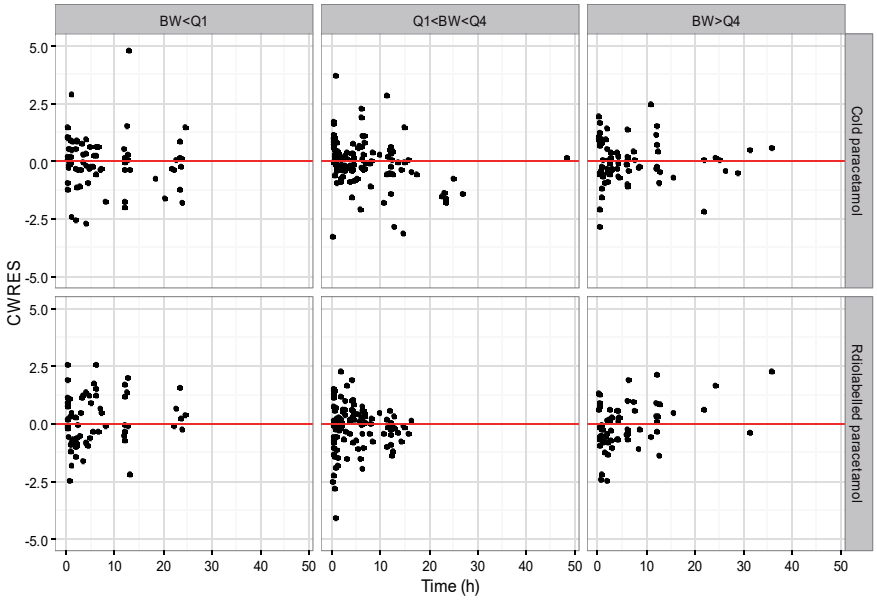
eFigure 3 Individual predicted concentrations versus observed concentrations for cold (A) and radiolabelled (B) paracetamol.



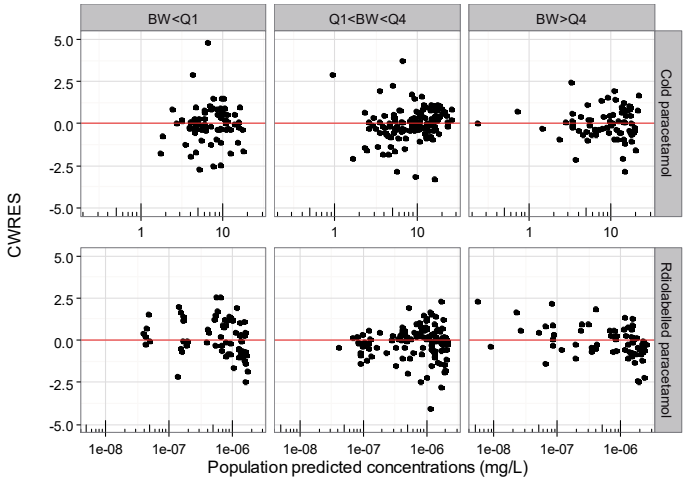
eFigure 4 Individual predicted concentrations versus observed concentrations stratified on bodyweight. Stratification was performed with 3 body weight (BW) groups: patients from 2 to 5 kg corresponding to BW inferior to the 1st interquartile (BW<Q1), patients from 5 to 11kg corresponding to BW between the 1st and 4th interquartile (Q1 <BW<Q4) and patients from 11kg to 23 kg corresponding to BW greater than the 4th interquartile (BW>Q4).



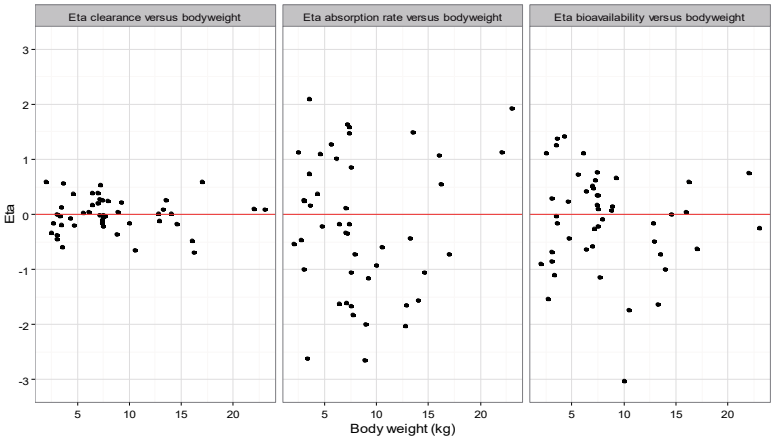
eFigure 5 CWRES versus time for cold (A) and radiolabelled (B) paracetamol.



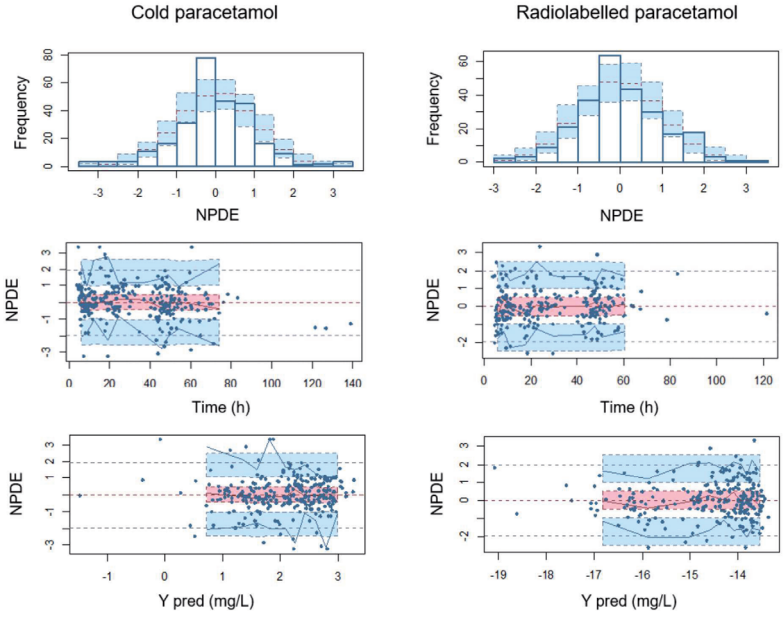
eFigure 6 CWRES versus time for cold and radiolabelled paracetamol stratified on body weight. Stratification was performed with 3 body weight (BW) groups: patients from 2 to 5 kg corresponding to BW inferior to the 1st interquartile (BW<Q1), patients from 5 to 11kg corresponding to BW between the 1st and 4th interquartile (Q1 <BW<Q4) and patients from 11kg to 23 kg corresponding to BW greater than the 4th interquartile (BW>Q4).



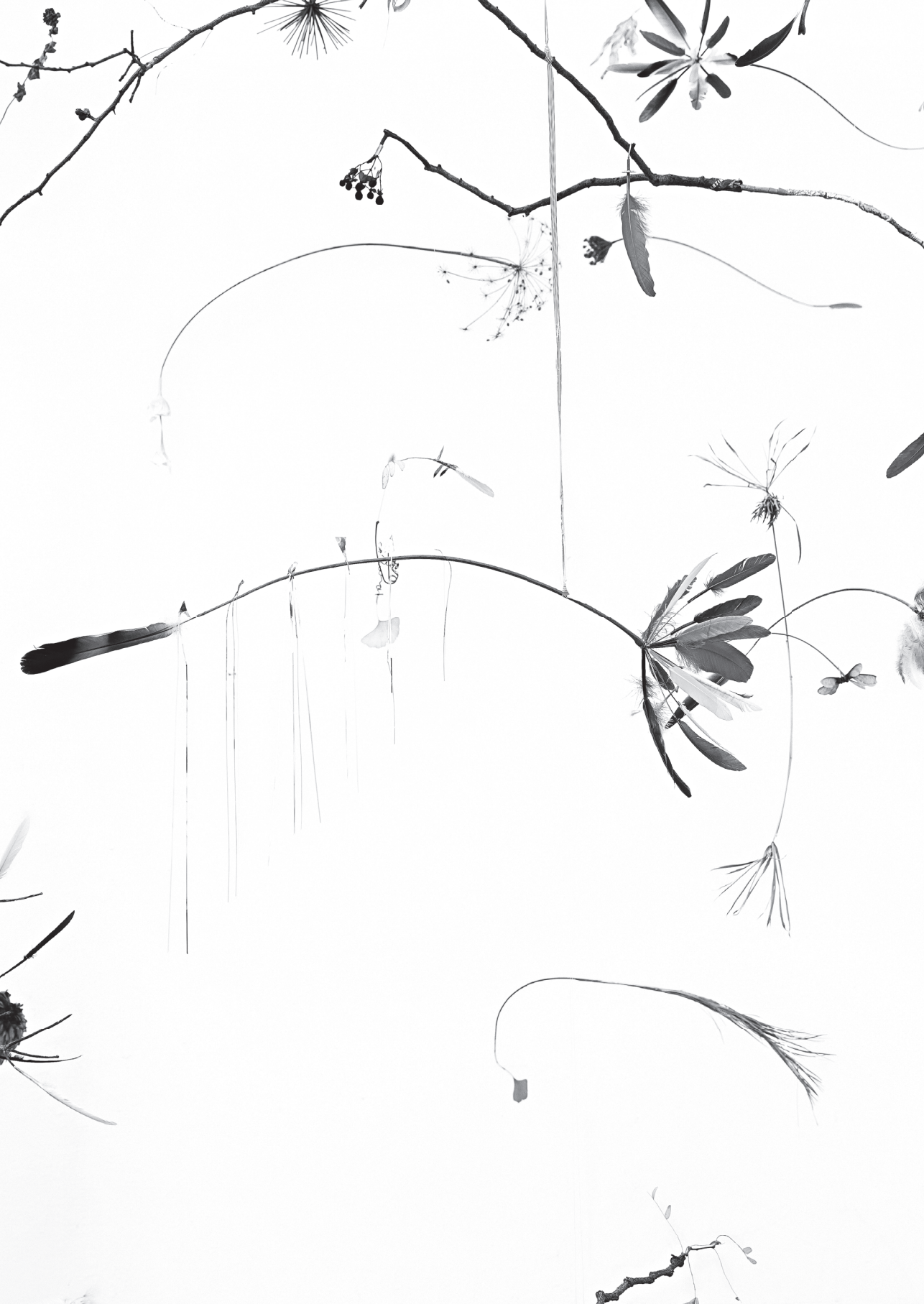
eFigure 8 CWRES versus population predicted concentrations for cold and radiolabelled paracetamol stratified on body weight. Stratification was performed with 3 body weight (BW) groups: patients from 2 to 5 kg corresponding to BW inferior to the 1st interquartile (BW<Q1), patients from 5 to 11kg corresponding to BW between the 1st and 4th interquartile (Q1 <BW<Q4) and patients from 11kg to 23 kg corresponding to BW greater than the 4th interquartile (BW>Q4).



eFigure 9 Eta on clearance, absorption rate and bioavailability versus body weight.

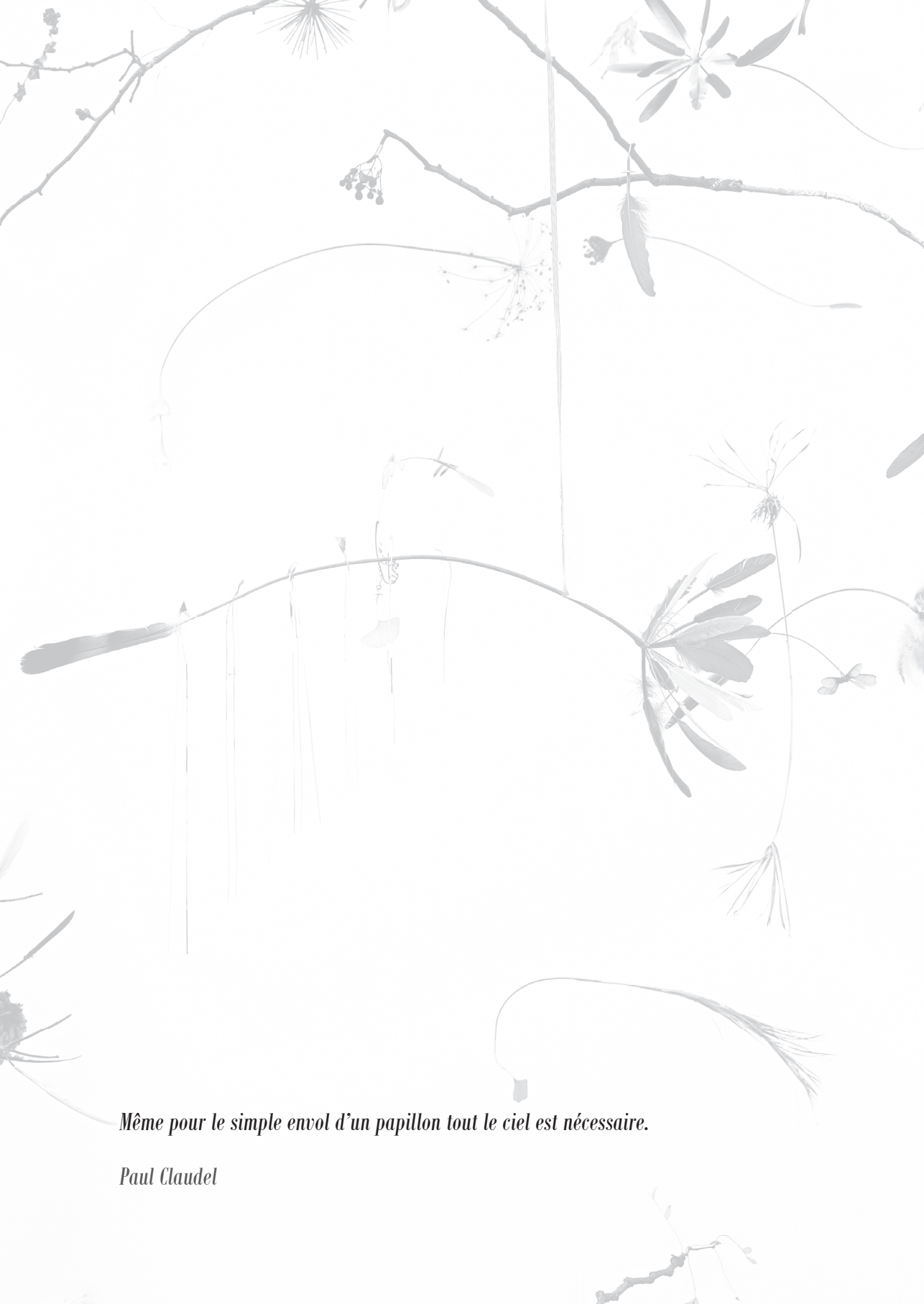


eFigure 10 Histogram of NPDE distribution, scatter plots of the NPDE versus time and of the NPDE versus log population predicted concentrations for cold (left part of the figure) and radiolabelled (right part of the figure) paracetamol. The blue area delimited by dotted lines represent the theoretical distribution and the plain lines represent the distribution of the npde. The blue and the pink shaded areas of the scatter plots represent the 95% prediction interval of the 2.5 and 97.5th percentile and of the median respectively. Y pred is the empirical mean of the simulated predicted distribution for each observation on the log domain.



PART IV

PHARMACODYNAMICS OF ANALGOSEDATION IN THE PICU



Même pour le simple envol d'un papillon tout le ciel est nécessaire.

Paul Claudel

Chapter 8

A comparative analysis of pre-emptive versus targeted sedation on cardiovascular stability after high-risk cardiac surgery in infants

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PEDIATR CRIT CARE MED. 2016 APR;17(4):321-31.

ABSTRACT

Objective:

To compare the effect of two sedation practices on cardiovascular stability during the early post-operative period in young infants following cardiac surgery: the routine early use of midazolam infusion (pre-emptive sedation) and the discretionary use of sedatives tailored to the patient's clinical condition (targeted sedation).

Design:

Retrospective cohort study with matched controls.

Setting:

A 15 bedded pediatric cardiac ICU.

Patients:

Sedation strategies were compared by matching patients before and after the introduction of a targeted sedation guideline, replacing the existing practice of pre-emptive sedation. Inclusion criteria were age < 6 months and cardiopulmonary bypass time > 150 minutes. Matching criteria were surgical procedure, age, duration of cardiopulmonary bypass and cross-clamp.

The main outcome was cardiovascular instability, defined by the presence of one of the following criteria in the first 12 hours after PICU admission: 1) simultaneous administration of ≥ 2 inotropic or vasopressor drugs; 2) administration of > 60ml/kg fluid boluses. Secondary outcomes were: 1) markers of cardiac output adequacy (heart rate, blood pressure, vasoactive inotropic score, urine output, volume of fluid boluses, central venous oxygen saturation, lactate); 2) occurrence of adverse events (cardiac arrest, extracorporeal membrane oxygenation, death); 3) sedatives administered and depth of sedation.

Interventions:

Introduction of a guideline of targeted sedation

Measurements and Main results:

Thirty-three patients with pre-emptive sedation were matched to 33 patients with targeted sedation. Targeted sedation resulted in less frequent oversedation, without compromising cardiovascular stability, as indicated by similar occurrence of cardiovascular instability (68.8% with pre-emptive sedation vs. 62.5% with targeted sedation; $p = 0.53$) and adverse events, and similar markers of cardiac output adequacy. While all pre-emptively sedated patients received an infusion of midazolam in the first 12 hours

after surgery, only 19.4% of patients in the targeted sedation group received a sedative infusion ($p < 0.001$).

Conclusion:

Our data suggest that after high-risk cardiac surgery in young infants, routine sedation with midazolam may not prevent low cardiac output syndrome. When accompanied by a careful assessment of level of sedation, routine sedation of infants after high risk cardiac surgery can be avoided without compromising hemodynamic stability or patient safety. The potential benefit of this approach is reduced exposure to sedative.

INTRODUCTION

Despite significant advances in surgical, perioperative and intensive care, infants undergoing major heart surgery remain at high risk for adverse events like cardiac arrest, need for extracorporeal membrane oxygenation (ECMO) or death (1). Young age (2, 3), long cardiopulmonary bypass time (4) and complex surgery (2) are risk factors for these negative outcomes.

After open-heart surgery with cardiopulmonary bypass (CPB), cardiac output decreases significantly, the nadir being usually between 9 and 12 hours after CPB (5). Cardiac surgery and CPB increase oxygen consumption (6). This combination of decreased cardiac output and increased oxygen requirements can lead to a state of insufficient oxygen delivery - low cardiac output syndrome - that results in increased morbidity (7).

After high-risk heart surgery, sedation is not only indicated to reduce anxiety and distress, but profound sedation is also routinely used to prevent low cardiac output syndrome (7) by blunting stress response (8) and decreasing energy expenditure and myocardial oxygen demand (9).

On the other hand, accumulating data suggest that profound sedation may be detrimental. It is associated with increased duration of mechanical ventilation and ICU stay (10) and increased risk of tolerance and withdrawal (11, 12). Moreover, benzodiazepines, commonly used for sedation after heart surgery, may have adverse hemodynamic and respiratory effects (13, 14) and concerns are rising about their neurotoxicity (15–17). Dosing is usually not based on solid pharmacokinetic data and does not take the changes in the volume of distribution and/or clearance into account.

Whether sedating every patient after high risk surgery improves hemodynamic stability compared to the use of sedation tailored to the patient's clinical condition is unknown. This absence of data may contribute to the wide use of routine sedation in this setting that contrasts with the general tendency to avoid oversedation in the PICU to prevent withdrawal (11). Therefore, we compared cardiovascular stability of young

infants at high risk of low cardiac output syndrome receiving two sedation practices: the routine early use of continuous midazolam infusions (pre-emptive sedation) and the discretionary use of sedative drugs tailored to the patient's clinical condition (targeted sedation).

METHODS

Setting

The cardiac ICU at the Royal Children's Hospital Melbourne is a 15 bedded tertiary and quaternary referral unit. The institutional ethics review committee at the Royal Children's Hospital Melbourne approved the study and waived the need for patient consent.

Study design:

Retrospective cohort study with matched controls, comparing patients receiving routine midazolam infusion with patients treated with discretionary use of sedatives.

Patients

We identified, between January 2011 (when medical records became available electronically) and October 2013, all patients with a postconceptional age > 37 weeks and postnatal age < 6 months who underwent cardiac surgery with a CPB time greater than 150 minutes. We selected high-risk surgeries based on this cut-off point of CPB duration as it is an independent predictor of major adverse events (4).

The study period included 10 months before and 24 months after the introduction of a targeted sedation guideline (TARG), replacing the pre-emptive routine use of continuous midazolam infusions (PES) following cardiac surgery. Each patient identified from the PES group was matched with a patient from the TARG group (1:1 matching) with the same congenital heart lesion and surgery. They were also matched on the basis of age, duration of CPB and aortic cross-clamp. Patients were first matched by surgery and then matches were selected by classifying patients in ascending order of duration of CPB and by selecting the patient with the most similar combination of age and duration of CPB and cross-clamp. Patients who came back from the operating room on extracorporeal life support were excluded.

During the study period, the only change to the postoperative management was the introduction of the new sedation guideline. There were no changes to anaesthetic or operative management or procedures. The cardiac surgical team was composed of three cardiac surgeons that did not change during the study period. Although perioperative anaesthetic management was not strictly protocolized, the following approach is standard at our institution for this patient group: Sevoflurane was administered to facilitate

venous and arterial cannulation and then discontinued. Fentanyl was used for induction and sternotomy (total dose 75–100 mcg/kg) and morphine (500 mcg/kg) was given as a loading dose while on bypass. Isoflurane 1–2% was administered by the perfusionist to control hypertension and provide myocardial pre-conditioning.

Differences in preemptive and targeted sedation practices are summarized in table 1. The main difference is avoidance of routine use of midazolam infusion with the targeted sedation practice (TARG).

Table 1 : Differences in sedation practices between group treated with routine midazolam infusion (PES) and discretionary use of sedatives (TARG)

	Preemptive sedation (PES)	**Discretionary sedation (TARG)**
Sedation practice:		
- Use of a guideline	No	Yes
- Scale used	Movements in response to stimulation (0 - absence, P – purposeful, N - normal)*	COMFORT-B score
- Definition of adequate sedation	Clinical assessment	10–00
- Titration by:		
• Nurses	According to doctor's prescription	Within boundary of protocol
• Doctors	When deemed necessary to insure patient's safety	
Analgesia and sedation:		
- Routine morphine infusion	Yes	Yes
- Routine sedative infusion	Yes	No
- Recommended sedative	Midazolam	Clonidine

* = 11 patient in the preemptive sedation group were assessed by COMFORT-B score (because the introduction of this score predated the introduction of the sedation guideline).

Targeted sedation guideline (TARG)

With the introduction of this guideline, sedative drugs were titrated by bedside nurses to target optimal sedation as defined by a COMFORT Behavior © (COMFORT-B) score (18) between 10 and 20. Education about the targeted sedation guideline and COMFORT-B assessment was provided with theoretical courses and bedside teaching to nursing and medical teams prior to implementation. COMFORT-B score was assessed every 4 hours.

In infants, differentiating pain from anxiety can be difficult. Aggressive pain control was prioritized in the post-operative period and then sedation was optimized. Morphine was the first agent used because it provides pain relief and sedation. When pain relief was ensured by adequate doses of morphine, clonidine was started. This drug was favoured over midazolam because no data point to neurotoxicity (16, 19).

The targeted sedation guideline is shown in Figure 1. Patients came back from the operating room on an infusion of morphine (10–40mcg/kg/h). If 3 boluses of morphine (0.1mg/kg) were needed for sedation or treatment of pain, the infusion was increased

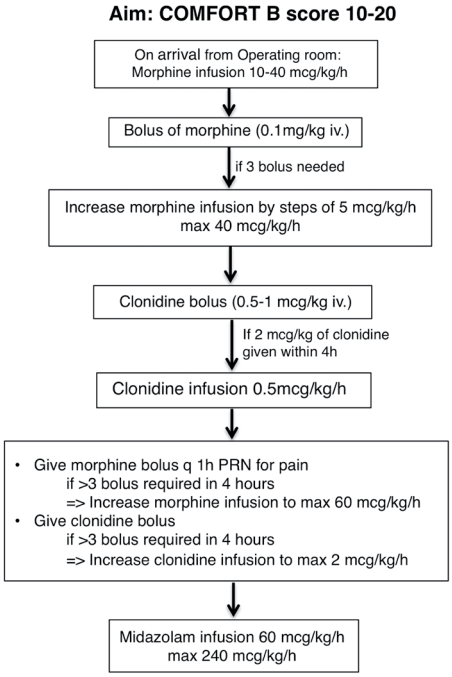

Figure 1: Sedation guideline for ventilated children less than one year
This figure describes the dose escalation used to get Comfort B scores between 10 and 20 or to target profound sedation in an unstable child.

incrementally to a maximum of 40 mcg/kg/h. Bolus doses of clonidine (0.5–1mcg/kg/dose) were administered each hour until adequate sedation was achieved. If the targeted COMFORT-B scores were not achieved despite a total bolus dose of clonidine of 2 mcg/kg in 4 hours, an infusion of clonidine was started at 0.5 mcg/kg/h and increased if necessary to a maximum of 2 mcg/kg/h. If sedation remained inadequate, a midazolam infusion was started (60 mcg/kg/h). Prior to start of the infusion, a bolus of midazolam (0.1 mg/kg) was considered in hemodynamically stable patients.

Pre-emptive sedation practice (PES)

This sedation practice was used prior to the introduction of the new guideline. (October 2011). The sedation and analgesia were managed according to physician's orders. Simple scoring of response to stimulation was used: 0 - absence, *P* - purposeful and N - normal movements. Patients with a score of 0 were considered to be oversedated. This scale only provides assessment of the level of consciousness and did not guide titration of sedation that relied on the clinical judgement of nurses and physicians. The introduction of the COMFORT-B score was part of the new unit sedation practice and predated the

TARG sedation guideline by a short time. Therefore, some patients in the PES group were assessed with COMFORT-B scores.

A combination of morphine (20–40mcg/kg/h) and midazolam infusions (60–180 mcg/kg/h) was given routinely to all infants after complex heart surgery. Boluses of morphine (0.1mg/kg) or fentanyl (1–2mcg/kg) were used for analgesia, while boluses of midazolam (0.1 mg/kg) were occasionally given for sedation in stable patients. The infusion of midazolam was usually titrated to achieve profound sedation during the night after the surgery. Usually, if the patient remained hemodynamically stable, weaning was commenced in the morning, otherwise the midazolam infusion was continued.

Management of the patient with low cardiac output syndrome

A guideline for management of low cardiac output following heart surgery was in place during the study period. First line measures were fluid expansion, increased inotropy and/or afterload reduction, target haemoglobin levels, optimization of heart rate and maintenance of normothermia. Deep sedation was advocated as a second-line therapy, with neuromuscular blockade in persistent cases.

Data collection:

Patient characteristics

The following patient characteristics were collected: age, sex, weight, diagnosis, surgical procedure, CPB and cross-clamp time, associated anomalies, delayed chest closure. RACHS-1 score was used to classify surgical risk (20).

Primary outcome: Cardiovascular instability

Cardiovascular instability was defined as the presence of at least one of the following criteria in the 12 hours following admission to PICU:

- Simultaneous administration of ≥ 2 inotropic or vasopressor infusions
- Administration of > 60ml/kg of volume boluses.

Secondary outcomes: Cardiovascular parameters and markers of CO adequacy

The following hourly hemodynamic variables and indirect cardiovascular markers from the first 12 hours following PICU admission were retrieved from the ICU paper chart: heart rate, blood pressure, fluid bolus administration, urine output and fluid balance. All fluids administered by bolus were recorded, including crystalloids, colloids and blood products. Vasoactive-inotropic score (VIS) was calculated using the formula: 1*(dopamine + dobutamine (mcg/kg/min)) + 10 * milrinone (mcg/kg/min) + 100 * (epinephrine + norepinephrine (mcg/kg/min)) + 10 000 * vasopressin (U/kg/min) (21).

Central venous saturation and arterial lactate values for the same period were collected from the electronic laboratory reporting system.

Secondary outcome: sedation and analgesia

Hourly doses of continuous sedative and opioid drugs were extracted from the ICU paper chart and bolus doses of sedatives, analgesics and muscle relaxants from the paper medical prescription charts. Fentanyl was converted to morphine equivalent by multiplying the dose by 100 as previously reported (22). The need for continuous sedatives was recorded during the entire PICU stay.

Sedation scores reported during the first 12 hours following PICU admission were extracted.

For comparison of depth of sedation, only patients with available COMFORT-B scores were included. A COMFORT-B score < 10 was considered oversedation, scores ranging from 10 to 20 were considered optimal sedation and scores > 20 were considered undersedation. Some patients did not have COMFORT-B scores due to regular use of neuro-muscular blocking agents. In the PES group, some patients were assessed on the previous sedation scale (and not with COMFORT-B scores).

To take the change in the sedation scale into account, oversedation was defined as either:

- COMFORT-B score < 10
- 'Absent movement to stimulation' on the previous sedation scale (as this reflects decreased level of consciousness).
- Regular use of neuro-muscular blockade (as this implies profound sedation)

Secondary outcomes: others

Sedation scores and administration of analgesic, sedative and neuromuscular blocking drugs were recorded for the first 12 hours after PICU admission. Other outcomes (time to chest closure, use of peritoneal dialysis and temporary cardiac pacing, duration of intubation and PICU stay) and adverse events (unplanned extubation, ECMO, cardiac arrest and death) were recorded for the entire PICU admission.

Statistical analysis

The average value of hourly hemodynamic parameters, indirect cardiovascular markers and COMFORT-B score in the first 12 hours of PICU admission was used for between group comparisons. The distribution of the data was compared between the patients in the PES and TARG groups using statistical tests for paired data, to take into account the effects of the matching procedure, for all variables except the sedation scores. Normally distributed data were described using mean and SD and analysed using the paired t-test. Continuous data that were not normally distributed were described using median and interquartile range (IQR) and analysed using the Wilcoxon signed-rank test. Sedation scores were analyzed using the Mann-Whitney test due to the non-normal distribution and the presence of many missing values.

The McNemar's test was used for categorical variables. All analyses were conducted using STATA 13.0 (College Station, TX). All statistical tests were two-sided and used a significance level of 5%.

RESULTS

Patients

We identified 41 patients who received pre-emptive sedation (PES). Three were excluded because they were on extracorporeal life support on admission to the PICU, three were premature and for two no match could be found in the TARG group. The remaining 33 patients were matched to 33 patients (among 100 potential matches) in the TARG group.

Surgeries performed are described in Table 2. The mean RACHS score was 4. Other patient characteristics are shown in Table 3. There was no significant difference in age between the two groups, however patients in the PES group weighed less than patients in the TARG group (mean weight 3.4 *vs* 3.8 kg, $p = 0.026$).

Table 2: Cardiac pathologies with the number of pairs from the two sedation protocols and corresponding RACHS-1 scores (n = 33 pairs)

Pathology	n of pairs	RACHS-1*
Arterial swith operation for TGA		
• with IVS	7	3
• with VSD repair	4	4
• VSD closure and hypoplastic aortic arch repair	1	4
Truncus arteriosus repair	1	4
• with aortic arch repair	1	5
Complete AVSD repair	3	3
• with pulmonary valve repair	1	3
RV-PA conduit and PA repair for Pulmonary Atresia	1	3
TOF: complete repair	2	2
HLHS:		
• Norwood stage 1 repair	7	6
• Glenn shunt	1	2
Hypoplastic Aortic Arch repair	3	4
• with tricuspid valve repair	1	4

*=RACHS-1 score evaluates risk of mortality for children after heart surgery and divides surgical procedures into 6 risk categories. 1 is the lowest and 6 the maximal risk category (20).

Abbreviations of congenital heart disease: AVSD : atrio-ventricular septal defect ; DORV : double outlet right ventricule ; HLHS: Hypoplastic left heart syndrome; IVS : intact ventricular septum ; PA: pulmonary artery; RV-PA conduit: right ventricular to pulmonary artery conduit; TGA: Transposition of the great arteries; TOF : tetralogy of Fallot ; VSD : ventricular septal defect

Table 3: Patients characteristics (n = 66)

	Elective sedation Group (PES) n = 33	Targeted sedation Group (TARG) n = 33	p-value
Matching variables:			
• Age in days, median (IQR)	8 (62)	9 (44)	0.12
• Duration of CBP in minutes, median (IQR)	193 (49)	191(62)	0.50
• Duration of cross-clamp in minutes, mean (SD)	114 (38)	116 (40)	0.52
Age categories, n (%)			
0–0 month	23 (69.7%)	24 (72.7%)	0.32
1–1 months	10 (30.3%)	9 (27.3%)	
Sex, male, n (%)	24 (72.7%)	15 (45.5%)	0.020
Weight in kg, median (IQR)	3.4 (0.8)	3.8 (1.3)	0.026
Associated anomalies, n (%)	8 (24.2%)	5 (15.2%)	0.18
Delayed sternal closure, n (%)	14 (42.4%)	12 (36.4%)	0.53

Abbreviations: CPB: cardio-pulmonary bypass; IQR: interquartile range; SD: standard deviation

Cardiovascular outcomes

The proportion of patients with cardiovascular instability was not significantly different between groups; 68.8% in the PES vs 62.5% in the TARG group ($p = 0.53$), as shown in Figure 2. Table 4 describes secondary outcome: cardiovascular parameters and indirect

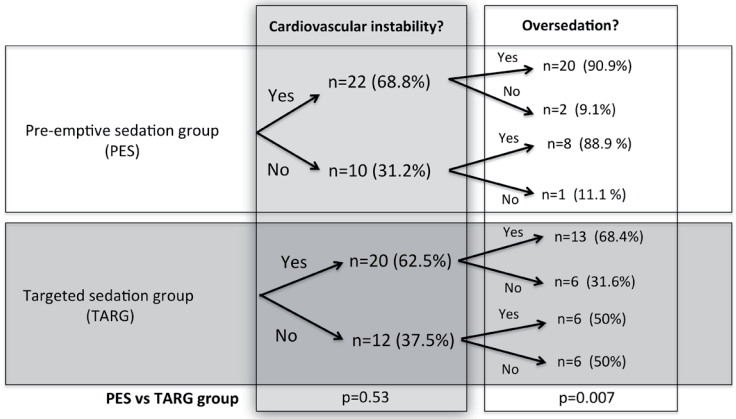

Figure 2: Occurrence of oversedation according to cardiovascular instability
Cardiovascular instability was defined as presence of at least one of the following criteria in the 12 hours following admission to PICU: 1.) need for ≥ 2 inotropic or vasopressor agent; 2.) > 60ml/kg of filling.
Oversedation was defined as either neuromuscular blockade or absence of movement on previous sedation scale or Comfort-B score < 10 on all observations in the first 12h of PICU admission.
Data of patients on ECMO were omitted (n = 1 per group) and 2 patients had no sedation scoring recorded (n = 1 per group).

Table 4: Cardiovascular parameters and markers of CO adequacy and other secondary outcomes

	Elective sedation group (PES) n = 33	Targeted sedation group (TARG) n = 33	p-value
Cardiovascular parameters and markers of CO adequacy[$]			
Heart Rate, mean (SD)	149 (14.8)	153 (13.5)	0.13
Blood pressure (mmHg), median (IQR)			
systolic	65.4 (5.6)	66.4 (10.4)	0.25
mean	50.1 (4.8)	49.2 (6.7)	0.64
diastolic	40.1 (5.4)	38.3 (8.8)	0.45
Central venous pressure (mmHg), median (IQR)	6.3 (2.8)	7.7 (4.3)	0.43
Left Atrial Pressure (mmHg)*, median (IQR)	6.3 (3.1)	5.4 (2.3)	0.38
Vasoactive Inotropic Score, median (IQR)	6.8 (4.3)	5.9 (4.3)	0.54
Urine output (ml/kg/h), median (IQR)	1.4 (1.0)	0.8 (1.0)	0.07
Fluid balance (ml/kg), mean (SD)	23.1 (29.7)	29.7 (25.7)	0.35
Amount of filling (ml/kg), mean (SD)	38.0 (25.5)	30.8 (25.3)	0.18
Lactate, median (IQR)	2.0 (1.5)	1.9 (1.3)	0.30
Central Mixed venous saturation ($ScvO_2$), mean (SD)	56.6 (9.7)	57.5 (10.5)	0.85
Patient management:			
• Duration until chest closure (Days), median (IQR)	0 (2)	0 (2)	0.50
• Number of patient with peritoneal Dialysis, n (%)	18 (54.5%)	13 (39.4%)	0.17
• Temporary cardiac pacing, n (%)	10 (30.3%)	7 (21.2%)	0.26
Adverse events, n (%)			
Unplanned extubation	1 (3.0%)	1 (3.0%)	1.00
ECMO	3 (9.1%)	2 (6.1%)	0.65
Cardiac arrest	3 (9.1%)	3 (9.1%)	1.00
Death	0 (0%)	0 (0%)	NA
Days of mechanical ventilation, median (IQR)	3.3 (4.0)	2.8 (4.0)	0.87
Days of PICU stay, median (IQR)	4.9 (4.7)	4.8 (4.9)	0.56

$ One patient per group has been excluded due to ECMO started early after admission
* Left atrial pressure was available in 19 patients in PES group and 17 patients in TARG group

markers of cardiovascular stability. Vital signs were not significantly different between groups. Amount of fluid bolus administration, fluid balance, urine output, vasoactive inotropic score, $ScvO_2$ and lactate were not statistically different between groups.

Secondary outcomes

Sedation and analgesia

Figure 3 describes infusion of analgesics and sedatives at PICU admission and divides patients according to the need for opioids and sedatives in addition to infusions started on admission. All patients in the PES group received a midazolam infusion on PICU

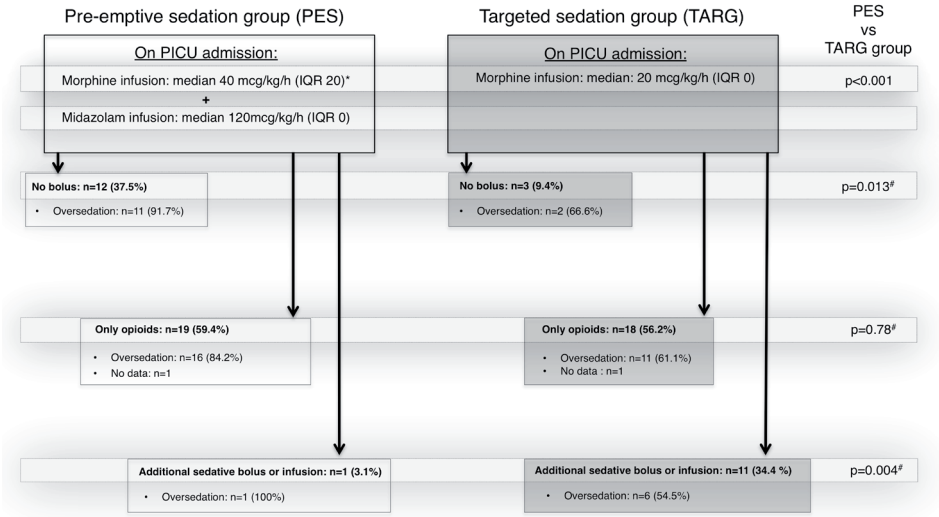

Figure 3: Need for additional analgesic and sedative medication and proportion of profoundly sedated patients during first 12 hours of PICU admission by group.
Oversedation was defined as either neuromuscular blockade or absence of movement on previous sedation scale or Comfort-B score < 10 on all observations in the first 12h of PICU admission.
*= one patient on Fentanyl 3mcg/kg/h was excluded from the comparison of morphine doses
= p value calculated using McNemar's test on 31 pairs (2 patients on ECMO excluded)

admission while none did in TARG group. The infusion rate at which morphine was commenced was higher in the PES compared to the TARG group. 37.5% of patients in the PES group did not receive any bolus of opioid or sedative during the first 12 hours compared to 9.4% in TARG group ($p = 0.013$). More patients in the TARG group received any additional sedative during the first 12 hours of admission. The number of patients exposed to a sedative decreased with the introduction of the targeted sedation guideline: all patients in PES group were exposed to a sedative (midazolam infusion) compared to 34.4% in the TARG group ($p < 0.001$).

Table 5 compares amount of opioids, sedatives and neuromuscular blockers received, along with COMFORT-B scores and incidence of oversedation during the first 12 hours of PICU admission. Fewer patients in the PES group received morphine boluses, and the amount received was lower than in the TARG group. However, there was no statistically significant difference in the total cumulative amount of morphine (infusion plus boluses). The cumulative doses of sedatives were lower in the TARG group: high dose midazolam were used before the introduction of targeted sedation guideline (median midazolam dose in 12 hours: 1440 mcg/kg in PES vs 0 in TARG group ($p < 0.001$) while small doses of clonidine were used after (mean clonidine dose: 0+/-0 mcg/kg in PES compared to 0.81+/-2.40 in TARG group; $p < 0.015$). While all patients in the PES group

Table 5: Use of analgesic, sedative, and neuromuscular blocking agents and sedation scores during the first 12 hours of PICU admission.

	Elective sedation Group (PES) n = 32[$]	Targeted sedation Group (TARG) n = 32[$]	p-value
Analgosedative and neuromuscular blocking drugs			
Number of patients exposed to a bolus			
Morphine; n (%)	2 (6.5%)	20 (64.5%)	< 0.001
Fentanyl; n (%)	17 (54.8%)	12 (38.7%)	0.25
Midazolam; n (%)	1 (3.2%)	2 (6.5%)	0.56
Clonidine; n (%)	0 (0%)	5 (16.1%)	0.025
Vecuronium; n (%)	18 (58.1%)	17 (54.8%)	0.78
Total amount of bolus			
Morphine (mcg/kg); median (IQR)	0 (0)	163 (631)	< 0.001
Fentanyl (mcg/kg); median (IQR)	3.4 (8.6)	0 (8.2)	0.21
Midazolam (mg/kg) mean (SD), median (IQR)*	0.01 (0.05); 0 (0)	0.027 (0.13); 0 (0)	0.56
Clonidine (mcg/kg) mean (SD), median (IQR)*	0 (0); 0 (0)	0.4 (1.1); 0 (0)	0.026
Vecuronium (mg/kg); mean (SD)	0.18 (0.21)	0.18 (0.21)	0.88
Total amount (continuous and bolus)			
Morphine (mcg/kg); median (IQR)	480 (90)	461 (603)	0.08
Morphine equivalent (mcg/kg); median (IQR)	705.8 (862.2)	881.4 (764.6)	0.69
Clonidine (mcg/kg) mean (SD); median (IQR)*	0 (0); 0 (0)	0.81 (2.40); 0 (0)	0.015
Midazolam (mcg/kg); median (IQR)	1440 (300)	0 (0)	< 0.001
Sedative infusion			
In the first 12 hours			
Patient exposed to a sedative infusion n (%)	33 (100%)	6 (19.4%)	< 0.001
Midazolam	33 (100%)	4 (12.9%)	< 0.001
Clonidine	0 (0%)	2 (6.5%)	0.16
Timing of start (h after PICU admission); median (IQR)	0 (0)	6.5 (7)	< 0.001
During entire PICU stay			
Patient exposed to a sedative infusion, n (%)	33 (100%)	15 (46.9%)	< 0.001
Timing of start (h after PICU admission), median (IQR)	0 (0)	23 (32)	< 0.001
Comfort B score per patient, median (IQR)			
Mean score	6 (2.5)	8 (5.3)	0.18
% of score per patient indicating oversedation	100 (17)	100 (67)	0.26
	n = 11[#]	**n = 24[##]**	
Incidence of Oversedation, n (%)			
Patients with only COMFORT-B scores < 10	8 (72.7%)	13 (54.2%)	_
Absent movement on previous sedation scale	11 (35.5%)	-	-
Regular use of neuro-muscular blockade	9 (29.0%)	6 (19.4%)	0.41
Total	**28 (90.3%)**	**19 (61.3%)**	**0.007**

$ One patient per group has been excluded due to ECMO started early after admission

* data were not normally distributed and comparison were done with Wilcoxon signed-rank test, Mean and SD are mentioned for improving clarity.

only patients with Comfort B scores were included in this analysis. Since this sedation scale was introduced around the time of the sedation protocol, many patients do not have any available Comfort-B score.

missing patients are patients without observation of Comfort B scores due to missing data or when Comfort-B score could not be assessed the regular use of neuro-muscular blocker. Data on ECMO were omitted.

received a continuous infusion of sedative in the first 12h of PICU, only six patients (19.4%) did in the TARG group; $p < 0.0001$. The TARG guideline was violated in four of these who received an infusion of midazolam instead of clonidine. Patients in the PES group were more deeply sedated, with oversedation occurring in 90.3% of patients in PES group compared to 61.3% in TARG group ($p = 0.007$).

Duration of intubation, length of stay and adverse events

Durations of mechanical ventilation and PICU stay were not significantly different between groups (Table 4). Finally, there was no difference in the incidence of adverse events throughout the PICU admission: three patients (9.1%) needed ECMO in the PES group compared to two in the TARG group (6.1%); $p = 0.65$. In both groups, three patients (9.1%) had a cardiac arrest; $p = 1.00$. No deaths occurred in either group.

DISCUSSION

Our data show that in young infants after high-risk cardiac surgery avoiding routine midazolam use by introducing a sedation guideline is feasible and does not compromise cardiovascular stability. Sedation practice tailored to the patient's clinical condition (targeted sedation) may also reduce sedative exposure and occurrence of oversedation.

The constraints of the retrospective design meant that we were not able to diagnose low cardiac output syndrome. Therefore, we used cardiovascular-targeted treatment, physiological and laboratory variables and occurrence of adverse events to infer cardiovascular instability. The study focused on the first 12 hours after admission from the operating room because this is the time of maximum potential instability and the period during which most infants are deeply sedated. The two treatment criteria used as primary outcome to define cardiovascular instability (administration of > 60 ml/kg fluid bolus, or the use of more than one inotropic or vasopressor infusion) indicate deviation from the usual routine postoperative care consisting of prophylactic use of a single vasoactive agent and restrictive fluid management (23). A second inotrope and volume expansion are standard approaches to the management of low cardiac output syndrome following cardiac surgery. The absence of difference in primary outcome suggests that the occurrence of this complication is comparable between groups. The similar cardiovascular parameters further indicate that avoiding routine midazolam is safe in this high-risk population. 70% of our patients were neonates, known for their limited ability to increase stroke volume in response to higher preload (24). The main mechanism to increase cardiac output in this population is heart rate acceleration and inotropic drug administration. The absence of any difference in heart rate and vasoactive inotropic score in the presence of similar blood pressure and $ScvO_2$ (known to vary

with cardiac index) suggests that discretionary use of sedation does not compromise cardiac output. Adverse events usually follow hemodynamic deterioration. Therefore it is not surprising that in the presence of comparable cardiovascular parameters the occurrence of major adverse events was similar in both groups.

There is growing interest in management of analgesia and sedation after heart surgery (25), but studies using a pharmacokinetic and pharmacodynamic approach are still missing (26). The cardiovascular effect of various sedative agents in the post-operative period has been reported (13, 25) but our study is the first to address the effect of routine pre-emptive use of sedation compared to individualized sedation on cardiovascular stability.

The introduction of the targeted sedation (TARG) guideline discouraged the use of routine midazolam infusion. Instead, the discretionary use of a targeted clonidine infusion and lower doses of continuous morphine were recommended. We observed very good adherence to this guideline with complete avoidance of routine sedative infusion on PICU admission and lower continuous morphine rates. With the new approach, sedation could be better individualized as suggested by fewer patients not needing any bolus (i.e less oversedation by routine infusions) and more patients treated with sedatives given in addition to baseline infusions (i.e targeted instead of routine sedation). The higher clonidine use reflected the TARG guideline. However, even in the TARG group, midazolam was favoured over clonidine when continuous sedation was started early after surgery. This deviation from guideline with otherwise good adherence may reflect concerns about clonidine-induced bradycardia and hypotension in unstable patients. Duffett et al. reported factors influencing treatment choice in the PICU (27) and showed that published guidelines have less influence on treatment choice than severity of illness, physiologic rationale and potential for adverse effects. The same reasons may have influenced the instances of out-of- guideline choice of sedative infusion in our study.

Despite the use of clonidine, which has documented bradycardic and hypotensive effects, in the TARG group, heart rate and blood pressure were similar between groups. The absence of difference may be due to the relatively small proportion (around 20%) of patients exposed to clonidine. Moreover, a clonidine-induced decrease in heart rate and blood pressure is likely to take many hours to develop and may not have been evident this early after surgery (28).

Interestingly, the reduction in continuous morphine resulted in higher use of boluses while the total amount was comparable. This was not the case with sedation: avoidance of routine midazolam reduced exposure to sedative: only one third of the patients were exposed to a sedative (mainly clonidine) and the cumulative dose decreased. In PICU patients, exposure to midazolam is associated with increased risk of withdrawal (11), whereas clonidine is frequently used for prevention (29) and treatment of withdrawal

states (30). Further studies will be needed to assess if this approach to sedation decreases sedative withdrawal.

Decreasing the use of analgesic and sedative drugs is of major importance in neonates and young infants. The neurotoxic effect of benzodiazepines have been demonstrated in animal studies (16, 17). Before more evidence becomes available from large prospective pediatric studies, the animal data should motivate a decrease in sedative exposure (31). Our study suggests that cardiovascular safety can be preserved while a) minimising sedative exposure and b) favouring a drug that has not thus far been linked to neurotoxicity (19), over a benzodiazepine. Both of these benefits are in accordance with the Food and Drug Administration (FDA) and the International Anesthesia Research Society (IARS) sponsored SmartTots (Strategies for Mitigating Anesthesia-Related Neurotoxicity in Tots) recommended approach to design of clinical studies (31). This is also important to the parents who are increasingly aware of the recommendation to avoid anesthesia at an early age.

We found a high prevalence of oversedation: 61.3% of the patients in the targeted group were oversedated, compared to 90.3% in PES group. Vet et al. showed that oversedation is still prevalent in the PICU: most studies report oversedation in the range of 40–65% of patients or measurements (32). The incidence of oversedation in the TARG group was at the upper limit of this range, while in the PES group it was even higher. However, this is in accordance with previously reported sedation levels after pediatric heart surgery (33) and is probably reflective of the high-risk infant population studied: deep sedation is a common approach to the infant with post-operative cardiovascular instability. The aim of sedation is to decrease energy expenditure and improve the balance between oxygen consumption and delivery. However, sedatives also have adverse hemodynamic effects (e.g vasodilation, myocardial depression) that may compromise cardiovascular stability (13). Therefore, the impact of level of sedation on hemodynamics may depend on the balance between desired (sedative) and unwanted (hemodynamic) effects of sedatives, and may vary with depth of sedation. Future studies will be needed to assess the effect of further lightening sedation in this group.

Implementing a sedation guideline is a way of targeting predefined sedation goals. In adult intensive care, implementation of a guideline has been shown to decrease days of mechanical ventilation and ICU stay (34). However, more recent adult studies have not confirmed these findings (35). The growing awareness of the deleterious effect of oversedation and general tendency to avoid it may explain these differences in results over time. The effect of protocolizing sedation is not clear in paediatric ICU, but all studies are recent and therefore avoidance of oversedation may already have entered PICU practice. A recent large, cluster randomized trial of protocolized sedation compared to usual practice in PICU did not show any difference in days of mechanical ventilation (36). Several non-randomized trials conducted in children have reported conflicting results

on outcomes like length of PICU stay, duration of mechanical ventilation or the need for analgesia and sedation (37). Our study was not primarily designed to study such outcomes, but does show the absence of deleterious cardiovascular effects of avoiding routine midazolam infusion and tailoring sedation to patient's clinical condition. This is of importance since this particular indication for routine sedation is common and has not yet been systematically studied.

Our study has several limitations. Its single-centre nature may limit generalizability of the results to other units. We did not have measurements of cardiac output and so relied on bed-side tools used by the clinician to infer adequacy of cardiac output. Moreover, the main sedative used changed with the onset of the guideline (from high dose midazolam to low dose clonidine), which conflates the effects of sedative agents and sedation strategies. The COMFORT-B score was essentially introduced contemporaneously with the new guideline, and we concede that comparison of sedation level between groups is compromised by the use of two different methods. Oversedation was defined using parameters from whichever sedation scale was used for each patient. Since these scales have not been equilibrated with each other, this comparison has an inherent imprecision and should be interpreted with some caution. On the other hand both sedation scales were used by experienced ICU staff members, and there is a high degree of correlation between COMFORT-B scale scores and the expert opinion of ICU staff (18, 38). The introduction of the COMFORT-B score with the new sedation guideline may have enhanced the awareness of oversedation and undersedation, as it demands a careful evaluation of the patient's behavioral response. Our study can not differentiate between the effects of the dosing of analgosedative drugs and the greater attention given to sedation practice. As with any retrospective study, conditions were not controlled during the study period. Nevertheless, the relatively short period of study and the absence of other changes to patient management confer a degree of reliability on the data. The very high-risk population and matched groups design further improve the quality of the data.

CONCLUSION

Our data suggest that after high-risk cardiac surgery in young infants, routine sedation with midazolam may not prevent low cardiac output syndrome. When accompanied by a careful assessment of level of sedation, routine sedation of infants after high risk cardiac surgery can be avoided without compromising hemodynamic stability or patient safety. The potential benefit of this approach is reduced exposure to sedative.

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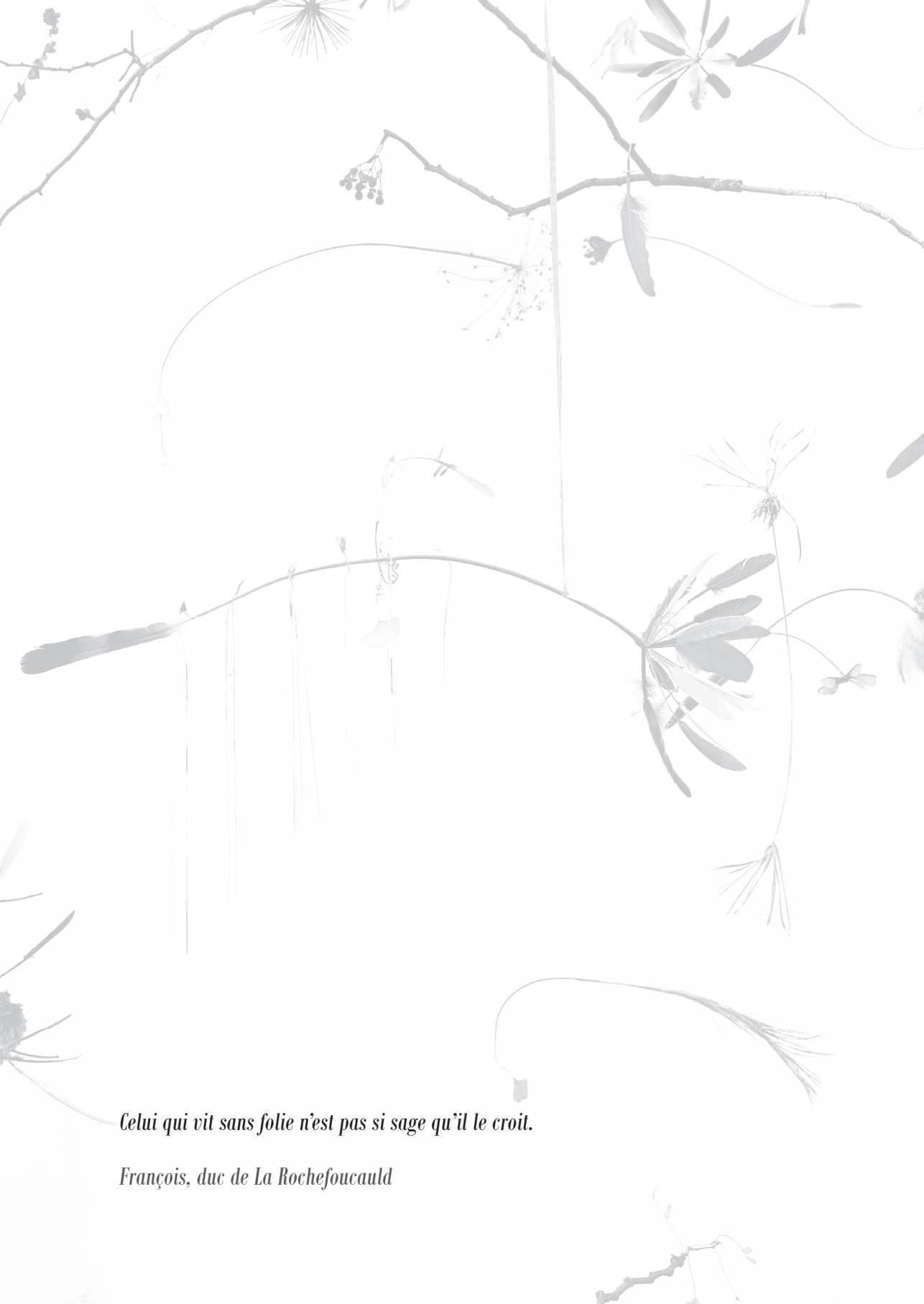

Celui qui vit sans folie n'est pas si sage qu'il le croit.

François, duc de La Rochefoucauld

Chapter 9

Clonidine as a first line sedative agent after neonatal cardiac surgery: retrospective cohort study

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ABSTRACT

Objective:

To determine the cardiovascular tolerance of clonidine used as a first line sedative after cardiac surgery in small infants.

Design:

Retrospective chart review.

Setting:

A tertiary and quaternary referral cardiac pediatric intensive care unit.

Patients:

All infants younger than 2 months who received a clonidine infusion for sedation after cardiac surgery from October 2011 to July 2013.

Interventions:

None

Measurement and Main results:

Heart rate, blood pressure, central venous and left atrial pressure, vasoactive inotropic score, volume of fluid bolus, lactate and central mixed venous saturation were assessed. Pre-infusion values were compared to post-infusion values. Of 224 potentially eligible patients, only 23 infants met inclusion criteria, as most patients only received high doses morphine, and some midazolam instead of clonidine. Clonidine was started at a median of 12 hours after surgery (Q1-Q3: 5–23), infusion rate was 0.5–2mcg/kg/h for a median duration of 30 hours (Q1-Q3: 12–54). Heart rate decreased (maximal mean decrease: 12% (149 bpm (SD17) to 131 bpm (SD17); $p < 0.0001$). Apart from a transient and limited drop in diastolic blood pressure of 13% (maximal mean decrease: from 42.8mmHg (SD5.9) to 37.1 mmHg (SD 4.0); $p = 0.018$), all other cardiovascular parameters were stable or improved. A contemporaneous cohort of patients who received midazolam, did so sooner after surgery, stayed longer in the PICU and showed less favorable hemodynamics.

Conclusion:

Intravenous clonidine as sedative added to morphine in selected patients appears hemodynamically safe. The observed decrease in heart rate and diastolic blood pressure seem of minimal clinical importance as all other hemodynamic parameters remained stable or improved. The safety of clonidine given early after cardiac surgery as alternative to midazolam merits further study.

INTRODUCTION

Following cardiac surgery in children, pain is controlled with an opioid. While opioids may also provide sedation, a benzodiazepine is often added if adequate sedation is not achieved with an opioid alone (1, 2). The use of alpha-2 agonists, which have both analgesic and sedative properties, is increasing in the PICU (3–6). Enthusiasm for these agents is driven by concerns about the neurotoxic effects of benzodiazepines (3) and by the absence of clinically significant respiratory depression with α-2-agonists (4). However, their use in the early post-operative period after cardiac surgery raises concerns. Myocardial function decreases in the early postoperative period after cardiac surgery and the consequent low cardiac output syndrome is associated with worse outcome (5). Maximal decrease in cardiac output occurs in most patients by 12 hours but may happen as late as 24 hours (5). Because these agents induce bradycardia and hypotension (6–8), they could further compromise CO (9). On the other hand, decreasing heart rate and blood pressure may be beneficial when cardiac output is limited by high afterload or when tachycardia leads to impaired force–frequency relation (10).

Dexmedetomidine is increasingly used for sedation after cardiac surgery. Available studies document good sedative effect and a well-tolerated decrease in heart rate (HR) and blood pressure (BP) (6, 11–13). However, the hemodynamic side effects occasionally necessitate discontinuation of dexmedetomidine or additional cardiovascular support (6, 11–13).

We can find only two studies documenting the sedative effects of clonidine following cardiac surgery. Both used smaller doses than currently recommended (maximal dose in previous studies: 1 mcg/kg/h for 6 hours (2); actual dosing: 2–3 mcg/kg/h for longer than 24 hours) (14)). On these relatively low doses, no changes in heart rate and blood pressure have been reported. Moreover, these studies targeted a specific population: they included only hemodynamically stable patients and neither included neonates (2, 15).

Neonates may be more susceptible to the adverse effects of clonidine. Approximately half of a clonidine dose undergoes renal elimination and the other half is metabolized in the liver (16) (mainly by CYP2D6 (17)). At 1 month of age, neonates have 30–70% of body weight corrected adult clearance (18, 19) due to immaturity of renal excretion and liver metabolism. Moreover, cardiac surgery with cardiopulmonary bypass has the potential to produce acute kidney injury that may further decrease clearance (20). Assuming a concentration-response relationship for the hemodynamic adverse events of clonidine and the precarious hemodynamics of neonates following cardiac surgery, this group is probably the most vulnerable to adverse effects.

In October 2011 we introduced a nurse-tailored sedation protocol advocating clonidine, rather than midazolam, as the primary sedative in children less than 12 months

old in PICU. Considering the potential detrimental hemodynamic effects of clonidine, we conducted a study in the most at risk population: neonates and young infants who received a clonidine infusion in the first 48 hours after cardiac surgery. We also compared the hemodynamic stability of patients treated with clonidine as per protocol with children who received another sedative as deviation from protocol.

MATERIALS AND METHODS

The institutional ethics review committee at the Royal Children's Hospital Melbourne approved the study. The cardiac ICU at the Royal Children's Hospital Melbourne is a 15 bedded tertiary and quaternary referral unit.

Patients

We identified all consecutively admitted infants with a post-natal age of > 37 weeks and under the age of 2 months who underwent a cardiac surgery from October 2011 to July 2013. Sedatives received within 48 hours of admission were recorded and patients were divided into 2 groups according to adherence to protocol:

1. Adherent to protocol:
- Only opioid: no infusion of sedative was used
- Clonidine: clonidine was added to the opioid infusion
2. Protocol deviation:
- Other sedative: an infusion of another sedative was added to the opioid infusion

Patients on extracorporeal membrane oxygenation (ECMO) or receiving cardiac pacing on arrival to the PICU were excluded.

Sedation protocol

With the introduction of the new protocol in October 2011, sedative drugs were titrated by bedside nurses to target optimal sedation as defined by the COMFORT Behavior © (COMFORT-B) scale (21). Nurses assessed COMFORT-B scores (21) every 4 hours or when clinically indicated. A COMFORT-B score between 10 and 20 was targeted in stable patients while highly unstable patients (e.g. low cardiac output syndrome or pulmonary hypertensive crisis) were routinely more deeply sedated (COMFORT-B < 10). Nurses were allowed to titrate medication within the boundaries of the protocol, while physicians were allowed to deviate from the protocol when they considered that this was safer for the patient.

Patients came back from the operating room on an infusion of morphine (10–40 mcg/kg/h). If the patient was in pain or undersedated, a bolus of morphine (0.1mg/kg) was administered; if 3 boluses were needed, the infusion was increased in increments of 5

mcg/kg/h to a maximum of 40 mcg/kg/h. The first line sedative was clonidine. Bolus doses (0.5–1mcg/kg/dose) were given initially up to a cumulative dose of 2 mcg/kg, after which an infusion was started (at 0.5 mcg/kg/h) and incrementally increased to a maximum of 2 mcg/kg/h. If COMFORT-B scores remained > 20, a midazolam infusion was started (at 1 mcg/kg/min) and the physician was notified.

Anaesthetic and general post-operative PICU management

Anesthesia with high-dose opioids technique is used in our institution for neonates and small infants in whom post-operative mechanical ventilation is planned. Although anaesthetic management is not strictly protocolized, the following approach is standard at our institution for this patient group: sevoflurane is administered to facilitate venous and arterial cannulation and then discontinued. Fentanyl is used for induction and sternotomy (total dose 75–100 mcg/kg) and morphine (500 mcg/kg) is given as a loading dose while on bypass. Isoflurane 1–2% is administered by the perfusionist to control hypertension and provide myocardial pre-conditioning.

All young infants returned from the operating theatre with a peritoneal dialysis catheter and temporary epicardial pacing wires. Right atrial pressure and central venous oxygen saturation ($ScvO_2$) were measured via an internal jugular catheter.

General post-operative management was not strictly protocolized. Dobutamine was the standard inotrope used for prevention and treatment of low cardiac output syndrome. Other inotropes, vasodilators and vasopressors were used at the discretion of the treating intensivist.

Primary outcome measure

Cardiovascular tolerance of clonidine infusion as assessed by:

- Hemodynamic parameters: heart rate (HR), blood pressure (BP), left atrial and central venous pressure, vasoactive inotropic score (VIS), volume of fluid bolus administered
- Laboratory markers of cardiac output: ScvO2, serum lactate
- Indirect markers of organ perfusion: urine output

The start of the infusion or first clonidine bolus (whichever the first) was considered time 0 (t0). Summary measures of hemodynamic parameters (the mean of 4 hourly values) were calculated for baseline (before t0) and for each 4 hour interval thereafter until 48 hours.

Secondary outcome measures

- Sedation scores and analgesic needs after starting clonidine infusion.
- Adverse events defined as: need for cardiac pacing; arrhythmias; cardiac arrest; accidental extubation; ECMO or death.

Other Secondary outcome measure

- Comparison of the post-operative course of the cardio-vascular parameters of the clonidine group (as per protocol) with a group that received another sedative agent (protocol deviation). The mean of 4 hourly values of hemodynamic parameters was calculated from PICU admission until 48 hours after.

Procedure

Data were retrieved from the paper ICU chart. Vasoactive-inotropic score (VIS) was calculated as previously reported using the formula: 1*(dopamine + dobutamine (mcg/kg/min)) + 10 * milrinone (mcg/kg/min) + 100 * (epinephrine + norepinephrine mcg/kg/min) + 10 000 * vasopressin U/kg/min (22).

Laboratory data ($ScvO_2$, lactate, creatinine) were transcribed from the electronic laboratory results system. Bolus doses of sedatives and analgesics were extracted from the medical prescription charts.

Data were collected from PICU admission until 48 hours after the start of clonidine.

Statistics

Normality was tested on continuous variables. Normally distributed continuous data are presented as mean and standard deviation (SD) and non-normally distributed are presented as median and 1st and 3rd quartile (Q1-Q3). Discrete data are presented as number (%). Non-normally distributed data were analysed with Wilcoxon signed-rank test, while normally distributed data were analyzed with t-test. Categorical variables were analysed with Fischer's exact test and Pearson chi square tests. A mixed effects model was performed for intragroup differences over time. Repeated times were contrasted to the pre-treatment value. Between-group differences were assessed using a mixed model. To account for multiplicity, a conservative Bonferroni correction was applied. A p-value < 0.05 was considered significant. Analysis was conducted using STATA 13.0 (College Station, TX).

RESULTS

Patients

224 infants less than 2 months underwent cardiac surgery during the study period. 9 were excluded due to missing data.

The 215 remaining patient were divided in 2 groups as follows:

1. Adherent to protocol:

- Only opioid: 157 patients (73%): morphine n = 154, fentanyl n = 3
- Clonidine: 32 patients (14.9%)

2. Protocol deviation:
- Other sedative: 26 patients (12.1%). The sedatives received were: midazolam (n = 16), dexmedetomidine (n = 7), propofol (n = 1) and a combination of clonidine and midazolam (n = 2).

Patient's characteristics of each group are described in table 1.

In the clonidine group, 9 were excluded: 2 had cardiac pacing, 4 were on ECMO on PICU admission and 5 were premature, leaving a total of 23 patients. Table 2 describes their cardiac pathologies and operative procedures. Median age was 22 days (Q1-Q3: 6–47) and mean weight was 3.6 kg (SD 0.6). Six patients (26.1%) had associated anomalies. Five

Table 1. Demographics of eligible and included patients

	Per-protocol group		**Out of protocol group**		
	Only opioids	Clonidine	Other sedatives	*p*-value clonidine vs other sedatives	*p*-value clonidine vs opioids
Eligible patients	**n = 157**	**n = 32**	**n = 26**		
Age (day)	8 (3–38)	22 (6.5–58.5)	11.5 (2–25)	0.21	0.028
PICU stay (h)	4.8 (2.9–9.9)	5.0 (3.0–0.4)	8.8 (4.2–23.7)	0.05	0.99
Hospital stay (h)	18.3 (11.7–77.8)	19.9 (10.9–91.6)	29.8 (14.3–33.6)	0.23	0.47
Duration intubation (h)	2.6 (1.6–6.9)	3.4 (1.9–9.9)	6.2 (2.0–03.0)	0.25	0.12
RACHS score	3 (3–3)	3 (2.5–5.5)	3 (3–3)	0.25	0.14
Included patients		**n = 23**	**n = 10**		
Age (Days), Median (IQR)	-	22 (6–67)	6 (0–06)	0.16	
Sex (male), n (%)	-	13 (56.5%)	4 (40%)	0.47	
Weight (kg), Mean (SD)	-	3.6 (0.6)	3.5 (0.6)	0.48	
Associated anomalies, n (%)	-	6 (26.1%)	2 (20)	1.00	
RACHS score	-	3 (2–2)	3 (3–3)	0.40	
Minutes of :	-				
• CPB, Mean (SD)	-	126 (82)	140 (79)	0.65	
• Cross-clamp, Mean (SD)	-	71 (57)	70 (48)	0.94	
Delayed sternal closure, n (%)	-	5 (21.7%)	4 (40%)	0.40	
Sedation start, h after PICU admission	-	12 (5–53)	4 (1–1)	0.010	
Peritoneal dialysis, n (%)	-	8 (34.8%)	6 (60%)	0.26	
Duration of intubation (Days) Median (IQR)	-	2.0 (1.6–6.7)	3.7 (2.0–0.7)	0.13	
Days of:					
• PICU stay, Median (IQR)	-	5 (3–3)	10 (4–43)	0.036	
• Hospital stay, Median (IQR)	-	18 (10–09)	22 (14–42)	0.22	

Table 2: Cardiac pathologies in clonidine group

Pathology	n
Arterial switch operation	
• with intact ventricular septum	5
• with VSD repair	2
Repair of truncus arteriosus	1
VSD, ASD closure	4
Complete AVSD repair	
• simple	1
• unbalanced with pulmonary atresia and TAPVD	1
Modified BT shunt	4
Tetralogy of Fallot and aortic arch repair	1
Aortic valve repair	1
Complete repair TAPVD	1
End to side repair of coarctation of the aorta	2

Abbreviations of cardiac anomalies: ASD : Atrial septal defect ; AVSD : Atrio-ventricular septal defect ; BT shunt: Blalock-Taussig shunt; TAPVD : Total anomalous pulmonary venous drainage ; VSD : Ventricular septal defect

(21.7%) had delayed sternum closure. Median duration of stay was 5 days (Q1-Q3: 3–7) and duration of mechanical ventilation was 2.0 days (Q1-Q3: 1.6–3.7).

In the protocol deviation group, midazolam was chosen for comparison based on its frequency of administration. Among 16 patients in the midazolam group, 6 were excluded (2 were paced, 2 were on ECMO and 2 were premature). Patients in the midazolam group had similar demographic (age, weight, associated anomalies) and operative characteristics (RACHS score, duration CPB and cross-clamp) as the clonidine group. Midazolam was started earlier after PICU admission than clonidine (median time of start in midazolam vs clonidine group: 4 hours (Q1-Q3: 1–6) vs 12 hours (Q1-Q3: 5–23); $p = 0.010$). PICU stay was shorter in clonidine group compared to midazolam group: 5 days (Q1-Q3: 3–7) compared to 10 days (Q1-Q3: 4–13); $p = 0.036$.

Sedation and analgesia

Table 3 describes level of sedation and sedatives and analgesics in the clonidine group. Clonidine infusion rate was 0.5–2mcg/kg/h, with a median total dose of 21.5 mcg/kg (Q1-Q3: 11–55.5) and duration 30 hours (Q1-Q3: 12–54). 52% of patients received a bolus dose prior to commencement of infusion (median dose: 1.5 mcg/kg (Q1-Q3: 1.0–2.2). The median delay between bolus and infusion was 3 hours (Q1-Q3: 0–4). No other sedative was used prior to clonidine but 3 patients received midazolam while on clonidine (3 received boluses and in one patient, the bolus was followed by an infusion). All bolus doses were within the range recommended in the protocol, but infusion rates were

Table 3: Sedation scores, analgesics, sedatives and neuromuscular blockers

LEVEL OF SEDATION	
Mean COMFORT-B score Mean (SD)	
Before clonidine (up to 4h before) (n = 10)	11.3 (9.5–52)
After clonidine (until end of infusion) (n = 10)	11.3 (10.5–53.2); $p = 0.51$
Level of sedation during 72h # (total number of observations = 283)	
Oversedation (COMFORT-B< 10)	79 (27.9%)
Optimal sedation (COMFORT-B 10–00)	180 (63.6%)
Undersedation (COMFORT-B > 20)	24 (8.5%)
During clonidine infusion: patients with at least one episode of:	
Oversedation (COMFORT-B< 10)	13 (56.5%)
Optimal sedation (COMFORT-B 10–00)	19 (82.6%)
Undersedation (COMFORT-B > 20)	6 (26.1%)
BOLUS OF ANALGESICS, SEDATIVES AND NEUROMUSCULAR BLOCKERS	
Total dose per patient for 72h, Median (Q1-Q3)	
Morphine (mg/kg)	0.9 (0.6–6.4)
Fentanyl (mcg/kg)	5.2 (0–02.8)
Clonidine (mcg/kg)	0.8 (0–0.4)
Vecuronium (mg/kg)	0.3 (0–0.7)
Bolus, number of patients exposed during 72h, n (%)	
Morphine	23 (100%)
Fentanyl	13 (56.5%)
Clonidine	13 (56.5%)
Vecuronium	17 (73.9%)
CLONIDINE BOLUS AND INFUSION	
Bolus clonidine at infusion start	
Number of patient exposed, n (%)	12 (52.2%)
Delay between bolus and infusion, hours	3 (0–0)
Dose of bolus, mcg/kg	1.5 (1.0–0.2)
Clonidine infusion	
Rate	0.5–5 mcg/kg/h
Start (h after surgery), Mean (SD)	18.2 (10.8)
Duration (hours), Median (Q1-Q3)	30 (12–24)
Maximal duration of infusion	290 hours
Number of patient with infusion > 72 hours, n (%)	3 (13.0%)
Total dose (mcg/kg), Median (Q1-Q3)	21.5 (11–15.5)

Data on level of sedation during 72 hours have been calculated on the total number of observations (n = 283).
Normally distributed data were analyzed by paired t-test and reported with mean (SD).
Non-normally distributed data are expressed by median (Q1-Q3).

higher in 3 patients: 2 had morphine infusions 50–60 mcg/kg/h and 1 patient received 3mcg/kg/h of clonidine. Mean COMFORT-B score did not change after clonidine infusion.

Hemodynamic tolerance

Figure 1 shows the trend of heart rate (HR), systolic and diastolic blood pressure (SBP and DBP) and the central venous pressure (CVP). HR was significantly lower than baseline from 12 to 48 hours after clonidine start. Maximal decrease in heart rate corresponded to a mean 12% decrease from baseline (from 149 bpm (SD17) to 131 bpm (SD17) at 48 hours ($p < 0.0001$)). There were no significant changes in systolic blood pressure and CVP after clonidine start. Diastolic BP was slightly lower than baseline at 36 and 48 hours after clonidine start (maximal decrease from baseline mean 42.8mmHg (SD5.9) to mean 37.1 mmHg (SD4.0) at 48 hours; $p = 0.018$). Figure 2 shows that urine output increased during clonidine infusion, while the amount of fluid bolus administration, left atrial pressure and VIS did not change.

$ScvO_2$ showed a favourable trend (from 53.7 (10.8) at baseline to 58.9 (6.1) in the 24 hours following clonidine start, n = 12, $p = 0.14$) and lactate decreased (from median 1.7 mmol/L (Q1-Q3: 1.2–2.1) at baseline (n = 23) to 1.2 mmol/L (Q1-Q3: 1–1.3) 12 hours following clonidine start (n = 17), $p = 0.002$).

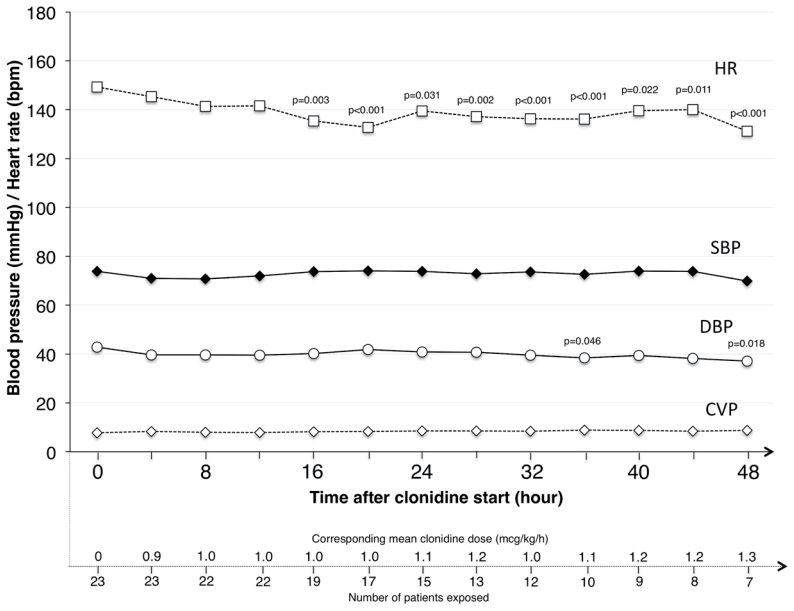

Figure 1: Effect of clonidine infusion on Heart rate (beat per minute) and systolic, diastolic blood pressure and central venous pressure (mmHg) compared to baseline value (start of clonidine).
Mean values and significant *p*-values are indicated.

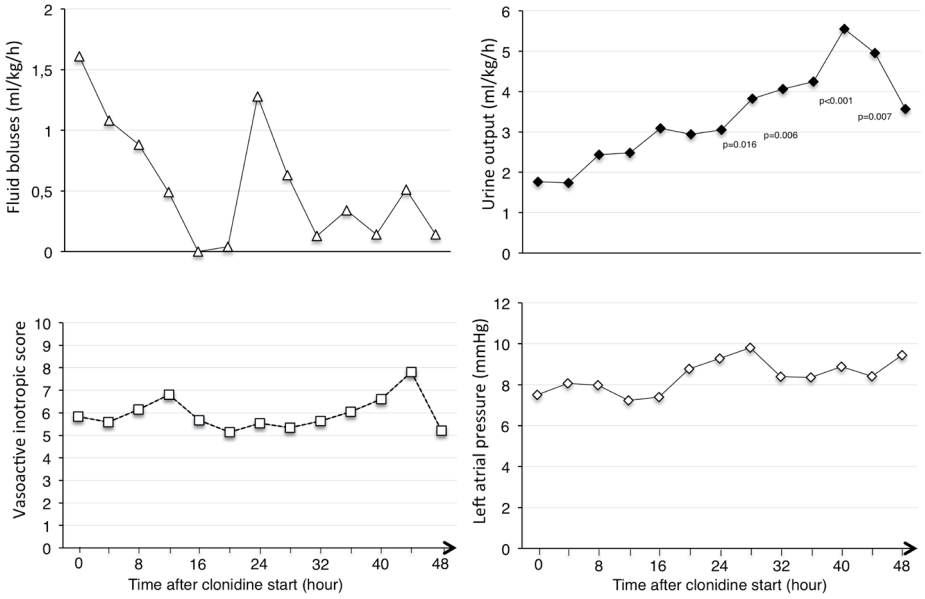

Figure 2: Effect of clonidine on fluid boluses, vasoactive inotropic score, urine output and Left Arterial Pressure (LAP) compared to baseline value (start of clonidine).
Mean values and significant *p*-values are indicated.
LAP was measured in 11 patients

Comparison of cardiovascular parameters in clonidine and midazolam groups

As shown in Figure 3, the clonidine and midazolam groups had similar heart rate on PICU admission but thereafter heart rate of the clonidine group decreased gradually. Systolic and diastolic blood pressures were higher in the clonidine group compared to the midazolam group. VIS score and the amount of fluid bolus received (Figure 4) were lower in the clonidine group. The serum lactate level was not statistically different between the 2 groups.

Adverse events

There were no instances of accidental extubation, cardiac arrest, ECMO or death. One patient (7 weeks old, recovering from ventricular septal defect and aortic valve repair) had clonidine ceased because of sinus bradycardia. Clonidine was stopped on post-operative day 3 after 35 hours of infusion (total clonidine dose: 39.5 mcg/kg, no bolus) when the heart rate fell to 100 beats per minute. 24 hours later he was temporarily at his backup atrial pacing rate of 80 bpm and was discharged from the PICU. This patient had ongoing well-tolerated sinus bradycardia for 5 days after cessation of clonidine infusion. The pacemaker was removed at day 7 after surgery when a Holter showed a sinus bradycardia with a minimal heart rate of 80 bpm. His renal and liver functions were similar to the other patient's values (maximal creatinine: 52 mmol/L (normal values: 15–33) and alanine aminotransferase (ALT): 49 U/L (Normal values: 12–45)).

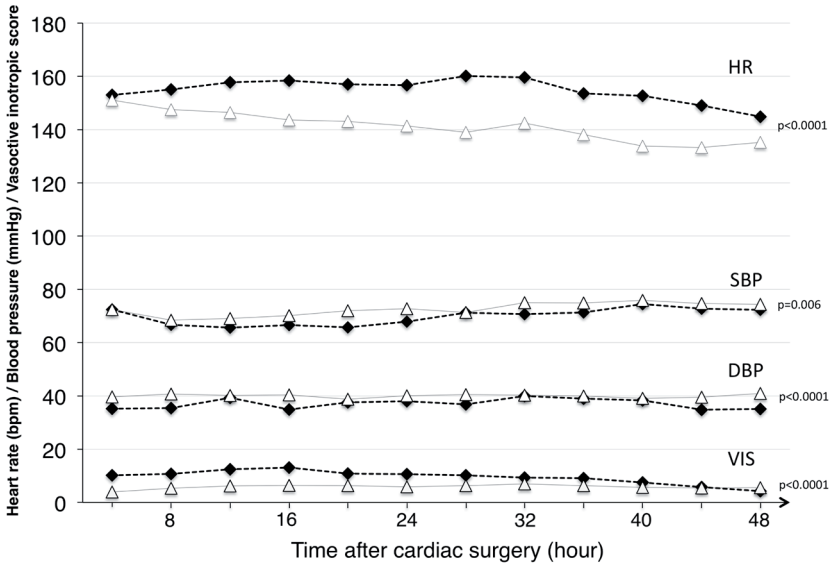

Figure 3: Comparison of clonidine and midazolam groups: Heart rate (beat per minute) and systolic, diastolic blood pressure (mmHg) and vasoactive inotropic score
Mean values and *p*-values are indicated.

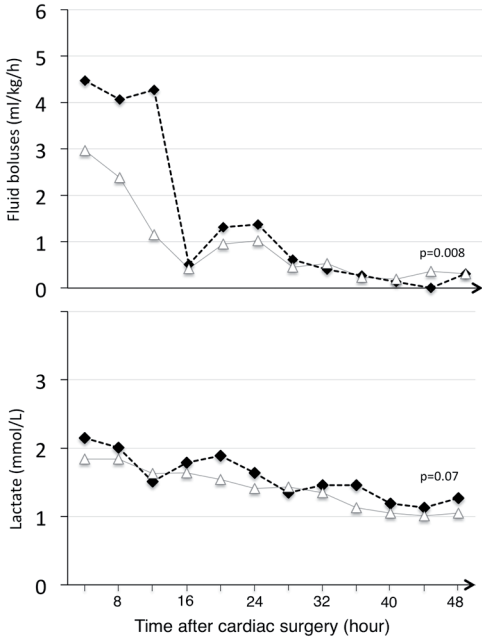

Figure 4: Comparison of clonidine and midazolam groups: lactate and fluid bolus
Mean values and *p*-values are indicated.

DISCUSSION

This is the first study reporting the use of intravenous clonidine for analgosedation after neonatal cardiac surgery and the first to include unstable patients. A maximal decrease in heart rate of 12% followed the start of clonidine. Cardiac output is directly proportional to heart rate. However, apart from the transient and limited decrease in diastolic blood pressure, no deterioration in markers of cardiac output was noted: systolic blood pressure, vasoactive inotropic score, central and left atrial pressure and filling requirements remained stable while urine output increased. Laboratory markers were favourable: $ScvO_2$ showed a trend toward improvement and serum lactate decreased. These data suggest that clonidine was well tolerated. However they do not distinguish between the hemodynamic effects of clonidine and the expected recovery following cardiac surgery.

The comparison with the midazolam group suggests that the gradual decrease in heart rate in the clonidine group was well tolerated: despite progressive bradycardia, blood pressure remained higher than in the midazolam group while inotrope score and the amount of administered fluid bolus remained lower. However, the different cardiovascular parameters of the midazolam group could also indicate more severe disease. Duffett et al. recently conducted a survey on factors influencing treatment choice in the PICU (23) and showed that published guidelines have less influence than severity of illness, physiologic rationale and potential for adverse effects. As the use of clonidine in this fragile population had not been previously reported, concerns about bradycardia and hypotension in unstable patients may have motivated protocol deviation. The same reason may explain why only half of the patients received a bolus of clonidine. Despite these limitations in interpretation of the data, our study suggests that clonidine is well tolerated after heart surgery in this high-risk population and should encourage study with a prospective design and a control group.

The mean COMFORT-B score did not change after starting the infusion. The mean COMFORT-B score of 11.3 pre and post-infusion suggest that rather deep sedation was targeted. Clonidine was probably needed to ensure adequate sedation after weaning from the remaining effect of high-dose opioid anesthesia.

Two previous studies report the use of clonidine for sedation after cardiac surgery (2, 15). The change in hemodynamic variables described in our study contradicts the data from both studies that reported stable cardiovascular parameters.

Ambrose et al. documented hemodynamic tolerance in 10 stable patients during 6 hours of clonidine infusion started 2 hours after cardiac surgery (2). Cardiac index, heart rate and blood pressure remained stable while in our cohort heart rate and diastolic blood pressure decreased. Our results may differ for several reasons. First, this earlier study used a fixed infusion rate of 1mcg/kg/h without bolus for 6 hours, whereas in our study clonidine was titrated up to 2mcg/kg/h for a median duration of 30 hours

and 52% of patients received a bolus. Less than half of steady state concentration is expected from the limited duration of infusion (6 hours) relative to clonidine's half-life (9 hours (19)). Second, age-related clonidine clearance may be different (18, 19, 24) but the age of the cardiac patients in the study by Ambrose et al. was not specified. Finally, only patients with stable or decreasing inotropic requirements were included while our study included all patients.

The second study by Arenas-Lopez et al. reported pharmacokinetics and cardiovascular stability in 16 infants aged one month to one year. No change in hemodynamics was noted after a single oral dose of clonidine (3mcg/kg) administered 2–6 hours after heart surgery. The difference in route of administration and dosing probably account for the absence of cardiovascular change. Taking the dosing and bioavailability into account (around 50% oral bioavailability (25)), our patients received more than 10 times greater total doses. Moreover, each patient reached maximal serum clonidine concentration at different times due to the wide variability in absorption, thus making any effect on hemodynamics more difficult to detect. Finally, patients in that study were older, more stable and had undergone less complex surgeries; a population that is less likely to experience adverse cardiovascular effects.

Recently, three randomized, controlled trials of clonidine in the PICU have been published (14, 24, 26), all reporting hemodynamic tolerance as a secondary outcome. The first compared the opioid and sedative sparing effect of placebo versus clonidine (fixed dose of 1 mcg/kg/h; median duration: 168 hours) in ventilated medical and surgical patients (24). While children up to 2 years old were included, this trial demonstrated decreased sedative and analgesic requirements only in neonates. A mild and well-tolerated decrease systolic and mean blood pressure was observed in the clonidine group compared to placebo but heart rate was similar between groups. The second trial (26) was a pilot study aiming to assess the feasibility of a multicentre trial comparing the opioid and benzodiazepine sparing effects of oral clonidine (5mcg/kg every 6 hours) to placebo. After inclusion of 50 ventilated patients (1 month to 18 years), the authors concluded that a large trial aiming to show major outcome differences (e.g duration of mechanical ventilation) was feasible. The incidence of significant hypotension and bradycardia was similar between groups. The third trial, the SLEEPS study, compared the efficacy of clonidine (0.75–3 µg/kg/hour) and midazolam (50–200 µg/kg/hour) for sedation in ventilated children (1 month-15 years)(14). Despite the recruitment of 129 children instead of 1000 planned, it showed non-inferiority of clonidine to midazolam. In the clonidine group, one patient developed profound self-resoluting bradycardia without hypotension. The incidence of hypotension was similar between groups. This trial included patients likely to require > 12 hours of mechanical ventilation among whom patients after cardiac surgery. But newborns, patients with delayed sternal closure and those needing of neuro-muscular blocking agents were excluded while they represent,

65%, 22% and 74% of our population respectively. Therefore, our study reports sedation with clonidine in the youngest and most unstable population studied to this point.

The occurrence of significant sinus bradycardia in a patient who required temporary cardiac pacing warrants caution, as this is a known adverse event of clonidine. A causality link cannot be formally discarded but appears very unlikely. Five days after having stopped the clonidine, theoretically allowing complete clearance of the drug, Holter monitoring showed maximal decrease in HR to 80 bpm. No significant rhythm anomaly has been documented in studies reporting clonidine use in the PICU (2, 8, 15, 24, 26, 27).

The occurrence of a well-tolerated decrease in heart rate with clonidine following cardiac surgery is similar to the effect reported with dexmedetomidine under similar circumstances. Clonidine has a similar pharmacodynamic profile to dexmedetomidine (4) but is much cheaper (28), which drives the continued use of clonidine in many institutions. However dexmedetomidine is favoured over clonidine after heart surgery due to the paucity of data on clonidine in this setting and a potential concern about clonidine's pharmacokinetic profile. The half-life of clonidine is much longer than that of dexmedetomidine (9 hours vs 2.4 hours, respectively in children (29)) and unlike dexmedetomidine, its clearance is decreased in renal failure (30). Hence, potential dose-related adverse cardiovascular effects may linger longer than with dexmedetomidine which is excreted more rapidly. Whether these theoretical concerns really translate into different safety profile of these drugs remains to be determined.

The drop in heart rate reported with dexmedetomidine is more pronounced than with clonidine (maximal drop in the current study 12% vs 13–18% with dexmedethomidine (6, 11, 31)). The reported effect of dexmedetomidine on blood pressure and doses of inotropic and vasoactive drugs has been variable (6, 7, 11, 12, 31). Expect from bradycardia, no rhythm anomalies were reported in the clonidine group. Absence of rhythm disturbance with dexmedetomidine has been systematically studied: Chrysostomou et al. analysed changes in ECG interval patterns in 51 children on dexmedetomidine infusions and did not find any change apart from the expected decrease in HR (32). Moreover, dexmedetomidine after cardiac surgery decreased the incidence of ventricular and supraventricular tachyarrythmias compared to fentanyl (31). As clonidine has similar pharmacodynamics to dexmedetomidine, it may also decrease the incidence of arrhythmia but, to date, no study has investigated this effect.

Our study has several limitations. First, it has the inherent limitations of a retrospective study and involves a limited number of patients. The observations were recorded hourly on paper charts and therefore transient cardiovascular changes may have been missed. Moreover, the hemodynamic effect of clonidine boluses could not be differentiated from the overall hemodynamic course. In addition, the data suggest that some of the more unstable patients were treated with midazolam instead of clonidine. This precludes any robust conclusion about safety. The good cardiovascular tolerance inferred from

markers of cardiac output does not rule out a decrease in cardiac output. Our study is based on "bed-side" tools used by the clinician to get an approximation of adequacy of cardiac output, but more direct measurements are lacking. Half of the patients received clonidine within 12 hours after surgery. However, a significant proportion would not have achieved maximal concentration within the first 12 hours after surgery, when the decrease in cardiac output is most pronounced. Despite these limitations, this study reports clonidine use at relatively high doses in the most unstable population studied to date and known to have decreased drug clearance. Reporting a favourable cardiovascular profile in this vulnerable population provides useful information about the off-label use of clonidine.

CONCLUSION

Intravenous clonidine as a sedative added to morphine in selected patients appears hemodynamically safe. The observed decrease in heart rate and diastolic blood pressure seem of minimal clinical importance as all other hemodynamic parameters remained stable or improved. The safety of clonidine sedation early after infant pediatric cardiac surgery as an alternative to midazolam merits further investigation.

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Quand on parle d'un enfant, on n'exprime jamais l'objet lui-même;
mais l'espoir que l'on fonde en lui.

Johann Wolfgang von Goethe

Chapter 10

Hemodynamic tolerance to intravenous clonidine infusion in the pediatric intensive care unit

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SUBMITTED

ABSTRACT

Objective:

Clonidine is an antihypertensive drug used for analgo-sedation in the pediatric intensive care unit. Lack of reliable data on its hemodynamic tolerance limits its use. This study explores the hemodynamic tolerance of intravenous clonidine infusion in a broad population of children with high severity of disease.

Design:

Retrospective analysis of prospectively collected data.

Setting:

A tertiary and quaternary referral PICU

Patients:

Critically ill children aged 0–18 years who received an IV clonidine infusion for analgo-sedation of at least one hour.

Interventions:

None

Measurement and Main results:

The primary endpoints were incidence of bradycardia and hypotension. Secondary endpoints were changes in heart rate, blood pressure, vasoactive inotropic score, COMFORT-b score and body temperature during the infusion. The association of bradycardia with other hemodynamic parameters was explored, as well as potential risk factors for severe bradycardia.

186 children (median age 12.9 month (IQR: 3.5–60.6)) years and receiving a maximum median clonidine infusion of 0.7 mcg/kg/h (IQR: 0.3–1.5) were included. Severe bradycardia and systolic hypotension occurred in 72 patients (40.2%) and 105 patients (58%) respectively. Clonidine-associated bradycardia was hemodynamically well-tolerated, as it was not related with hypotension and the need for vasoactive drugs decreased in parallel with a sedation score guided clonidine infusion rate increase. Younger age was the only identified risk factor for clonidine-associated bradycardia.

Conclusion:

Although administration of clonidine is often associated with bradycardia and hypotension, these complications do not seem clinically significant in a mixed PICU population with a high degree of disease severity. Clonidine may have a vasoactive-inotropic sparing effect.

INTRODUCTION

Clonidine is licensed as an antihypertensive drug but is increasingly used off-label as analgo-sedative in the pediatric intensive care unit (PICU) (1, 2). The benefits of clonidine are that it does neither induce respiratory depression nor neurotoxicity (3). Because critical illness influences oral absorption of drugs, intravenous administration is favoured when reliable sedation is crucial (4). Clonidine can induce hypotension and bradycardia mainly by inhibiting cardiac and vascular sympathetic activities (5). For this reason, many physicians are reluctant to use clonidine, especially in less stable patients (6). As around half of clonidine is renally excreted and the other half is metabolized by the liver, the frequently occurring renal and hepatic failure in critically ill patients may lead to higher blood levels and likely more adverse hemodynamic events (7, 8).

To our knowledge, three studies have reported hemodynamic tolerance to clonidine as a primary outcome in the PICU (1, 9, 10). All focused solely on neonates and infants after heart surgery and only one included hemodynamically unstable patients (1). Clonidine was hemodynamically well tolerated in spite of its possibly hypotensive effect. Three randomized controlled trials (RCTs) reported hemodynamic tolerance as a secondary outcome but included only hemodynamically stable patients (11) with low disease severity (6, 11) or on fixed and relatively low dose of clonidine (1mcg/kg/h without loading dose (2) or 5mcg/kg every 6 hours oral (11)). Good hemodynamic tolerance was generally reported but the only RCT reporting inotropic needs showed increased needs of inotropes with clonidine compared to midazolam in a population with low severity of disease (6). This observation suggests that clonidine may not be hemodynamically well tolerated in more unstable patients. Indeed, trial conditions differ greatly from the common clinical use of clonidine administered as a second or third line sedative in patients with high severity of disease and with titration to a maximal infusion rate of 2 mcg/kg/h.

Therefore, the aims of the present study were to determine the incidence and severity of bradycardia and hypotension during a clonidine infusion used as an adjunctive sedative agent in a mixed population of PICU patients, to assess the risk factors of bradycardia and to identify the relation of clonidine-associated bradycardia with blood pressure and need for inotropes.

MATERIALS AND METHODS

Study design and setting

This is a retrospective cohort study used prospectively collected clinical data of patients admitted to the PICU of the Erasmus-MC Sophia Children's Hospital in Rotterdam between January 2011 and July 2014. The institutional ethics review committee waived the

need for approval and informed consent, according to the Dutch law on Human Medical Research.

Patients

All patients who received an infusion of clonidine of at least one hour were eligible. Exclusion criteria were clonidine infusion received during ECMO, active cardiac pacing and palliative care.

Current clinical care

The analgesia and sedation protocol used in our unit is nurse-led. Nurses titrate analgesic and sedative infusions according to this protocol on the guidance of the COMFORT behavior scale (COMFORT-b) and the Nurse Interpretation of Sedation Score (NISS), which both have been validated for use in the PICU (12–15). COMFORT-b score ranges from 6 to 30 (adequate sedation: 11–22; oversedation: < 11; undersedation: > 22) (12). Inter-observer variability among nurses is satisfactory (Cohen's $\kappa > 0.65$) (12). Midazolam is titrated first (up to 300 µg/kg/h); morphine is added in case of undersedation (up to 30 µg/kg/h) and clonidine is added if adequate sedation is still not achieved. At the physician's discretion, clonidine boluses (1–2 mcg/kg) are given at infusion start or when the infusion rate is increased due to breakthrough distress. Clonidine continuous infusion is started at 0.5–1 mcg/kg/h and uptitrated to 2 mcg/kg/h when needed. Other second line sedatives include esketamine, propofol and phenobarbital.

Primary outcomes

The primary outcomes were the incidences of bradycardia and hypotension during a clonidine infusion.

Bradycardia was defined as a time-weighted average heart rate (twa_HR) below the normal values for age (16) during three consecutive hours accompanied by a decrease in HR of at least 10% compared to the pre-infusion value. The pre-infusion value was defined as twa_HR during 4 hours prior to the first clonidine administration (infusion or first bolus). Time-weighted average corresponds to an area under the curve and is therefore more precise than the unweighted average because it is adjusted for the variation in time interval between consecutively measured values. Bradycardia was categorized as severe when twa_HR was below the 1st percentile (P1) and as moderate when twa_HR was below the 10th percentile (P10) (16).

Similarly, hypotension was defined as a time weighted average value of systolic blood pressure (twa_SBP) (17) or mean blood pressure below P5 (twa_MBP) during one hour (18).

Occurrences of bradycardia and hypotension were studied during a maximum of 7 days from start of the clonidine infusion.

Secondary outcomes

Change in clinical parameters after clonidine start

The hemodynamic tolerance to a clonidine infusion was also determined by delineating the trend in the following parameters after infusion start:

- Blood pressure (BP)
- Vasoactive-inotropic score (VIS)

Moreover, the following parameters were determined:

- COMFORT-b score
- Temperature

Pre-infusion values of these parameters were compared to values at six time points: 1, 6, 12, 24, 72 and 168 hours after infusion start.

Risk factors for severe bradycardia

The following risk factors were tested:

- **Clonidine associated factors**: maximal infusion rate and the use of a bolus dose at infusion start
- **Patient-associated factors**: age, PELOD 2 score (19), diagnosis and creatinine z-score (adjusted for sex and age-related changes in absolute creatinine concentrations (20-22)).

Relation of clonidine-associated severe bradycardia with blood pressure and need for inotropes and other clinical parameters.

Each patient's first episode of severe bradycardia (HR<P1) was determined. This was considered to have started at the moment when the first hourly HR value was below P10 and to have ended when the hourly HR value was higher than P10.

Values of BP, VIS, COMFORT-b and temperature at the start of this first episode were compared to values at four time points during severe bradycardia: 1, 6, 12, 24 hours. As bradycardic episodes lasted shorter than the duration of infusion, this outcome was studied until 24 hours or until the end of the first bradycardic episode.

Data collection

Data were retrieved from the patient data management system that prospectively stores real-time data of all parameters: HR, BP, temperature and COMFORT-B scores. All administered drugs – including vasoactive and inotropic drugs, analgesics and sedatives – are recorded with dosing and exact administration time. VIS was calculated from real-time infusion data as previously described: 1*(dopamine+dobutamine (mcg/kg/min)) + 10*milrinone (mcg/kg/min) + 100*(epinephrine + norepinephrine (mcg/kg/min)) + 10000*vasopressin (U/kg/min) (23). Every clonidine dose received before infusion start until one hour after was considered a bolus. Clonidine plasma levels were not measured.

Statistics

Continuous variables are summarized as means ± SD for normally distributed variables and as medians and interquartile ranges (IQR) for non-normally distributed variables. Categorical variables are summarized as percentages.

To determine the hemodynamic consequences of the clonidine infusion, pre-infusion values of HR, BP, VIS, COMFORT-b score, temperature and clonidine infusion rate were compared to post-infusion values using linear mixed models. The dependent variables in these models were the combined pre-infusion and post-infusion values of these parameters; the independent variable was the time point (coded as a categorical variable). A separate linear mixed model was estimated for each dependent variable, and a random intercept was included to account for the within-subject correlations. The results of the linear mixed models are summarized using the estimated marginal means, which are the predicted values of the dependent variable adjusted for the effect of the independent variable and missing observations in the dependent variable, as well as the associated 95% confidence intervals (CIs).

Risk factors related to severe bradycardia were delineated in multivariable logistic regression analysis. The independent variables studied were maximal clonidine infusion rate, bolus of clonidine at infusion start, PELOD score, creatinine z-score, diagnosis (surgical or medical) and age. Z-score of creatinine was determined for each value according to the age (20–22). When no creatinine value was available, a z-score of 0 was assumed. The *p*-value of the Hosmer and Lemeshow test was 0.275.

A similar analysis using linear mixed models was performed to study the trends of HR, BP, VIS COMFORT-b score, temperature and clonidine infusion rate during bradycardia. The association between occurrence of bradycardia and the presence of an arterial line was explored using a chi-square test. This test was also used to assess the association between the occurrence of bradycardia and hypotension.

All data management procedures were programmed in R (24), and all statistical methods were performed in SPSS. All statistical tests used a two-sided significance level of 0.05.

RESULTS

Patients

As detailed in Figure 1, of 226 eligible patients, 40 were excluded, leaving a total of 186 patients whose data were analyzed. Demographics and clonidine infusion details are described in table 1.

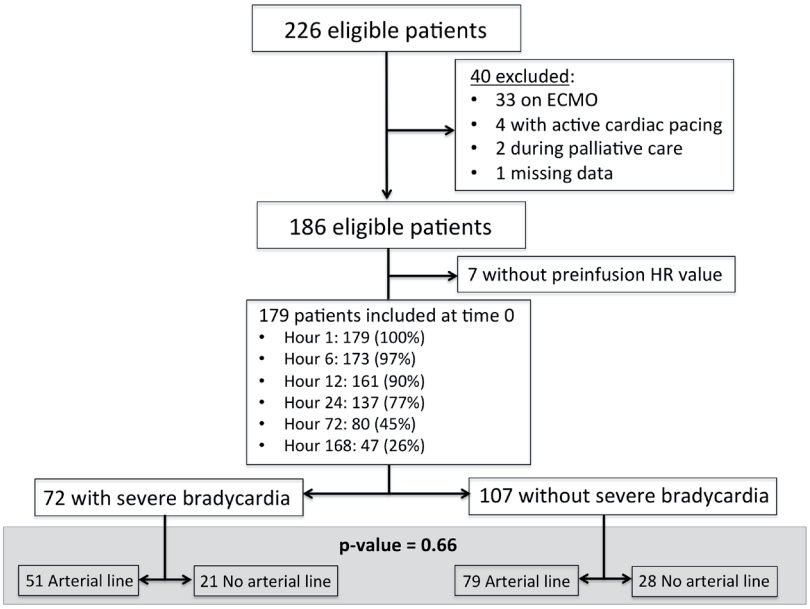

Figure 1: Patient inclusion flow chart
Number of eligible patients and reasons for exclusion are described. The numbers of remaining patients at different time-points during clonidine infusion are detailed. Patients are then divided into two groups according to the presence/absence of severe bradycardia. Each group is then further divided according to the presence of an arterial line for continuous blood pressure monitoring.

Primary outcomes

Incidences of bradycardia and hypotension

For 8 patients no pre-infusion HR values were available. Of the remaining 179 patients, 115 (64.3%) experienced bradycardia (twa_HR P10), which was severe (twa_HR P1) in 72 (40.2%). Severe bradycardia started at a mean infusion rate of 0.6 mcg/kg/hour (95% CI: 0.4–0.7). Of the 181 patients for whom hypotension information was available, 105 (58%) and 90 (49.7%) had hypotension (twa_BP P10) based on SBP and MBP, respectively. The proportion of patients with an invasive BP measurement did not differ between bradycardic and non-bradycardic patients (Figure 1).

Secondary outcomes

Change in clinical parameters after clonidine start

HR, BP, VIS and COMFORT-b all significantly decreased while body temperature increased after clonidine infusion start (Figure 2). Table 2 details the maximum changes in each parameter presented in Figure 2 with their respective timings after infusion start. As soon as one hour after infusion start, COMFORT-b score had decreased from 17.1 (95% CI: 15.8–18.5) to 13.7 (95% CI: 12.2–15.1), $p = 0.001$.

Table 1 Patient's characteristics and treatment (n = 186)

Patient's characteristics and treatment	Value
Age (month)	12.9 (3.5–50.6)
Weight (kg)	9.6 (4.7–78)
Sex, male; n (%)	99 (53.2%)
Mortality rate; n (%)	15 (8%)
Duration of PICU stay, days	10.5 (5–58).
PELOD II	5 (3–3)
PIM II predicted death rate	3.1 (1.3–3.2)
PRISM II	19 (11–16)
Diagnostic; n (%)	
• Surgical	92 (51.7%)
• Medical	86 (48.3%)
Clonidine use	
• Duration of PICU stay at infusion start, days	2 (1–1)
• Duration of infusion, hours	61.8 (24.7–754.8)
• Bolus at infusion start, n (%)	124 (69.3%)
• Maximal infusion rate	0.7 (0.3–3.5)
Laboratory values at infusion start	
• Urea*	5.1 (3.2–2.6)
• Creatinine (µmol/L)*	30 (20–01)
• ALT (IU/L)**	23 (14–42)
• CRP (n = 135)#	41 (11–17)

Values are expressed as median and (Q1-Q3) unless specified otherwise
* n = 161; **=n = 114; # n = 135

Risk factors associated with severe bradycardia

Age was the only risk factor significantly associated with severe bradycardia (OR 0.74 [95% CI: 0.64–0.85]; $p < 0.0001$) (Table 3 Supplemental Material).

Relation of clonidine-associated severe bradycardia with blood pressure, need for inotropes and other clinical parameters

In patients who at some point had severe bradycardia, SBP remained stable during the episode, despite a maximal decrease in HR of 17%, while MBP and DBP had decreased only slightly and the VIS had decreased by 19.3% at 6 hours (Figure 3). COMFORT-B score and temperature had decreased at one hour after bradycardia start but then increased again to stabilize at pre-bradycardia values. Table 2 details the maximal changes in each parameter with their respective timings.

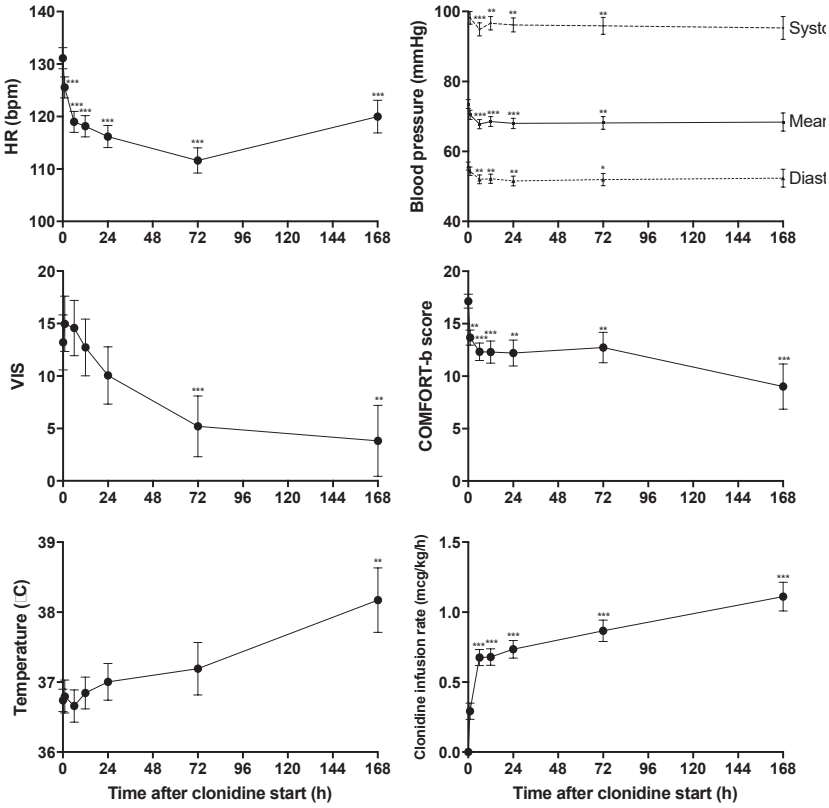

Figure 2: HR, BP, VIS, level of sedation, temperature and clonidine infusion rate after start of clonidine infusion
Estimated marginal means with their corresponding standard error based on the linear mixed model are reported. Time 0 corresponds to the beginning of the clonidine infusion (or loading dose whatever is first). Values were compared at six time-points after clonidine start: 1, 6, 12, 24, 72 and 168 hours.
*= *p*-value: 0.05–5.01; **= *p*-value: 0.01–1.001; ***= *p*-value: < 0.001

Table 2 : Incidence of bradycardia and hypotension during an infusion of clonidine

Incidence of hemodynamic events :	**n**	**%**
- BRADYCARDIA (n = 179)**		
Moderate bradycardia*	115	64.3
Severe bradycardia*	72	40.2
- HYPOTENSION (n = 181#)		
Systolic Blood Pressure	105	58
Mean Blood Pressure	90	49.7

* A patient was considered bradycardic it his average hourly heart rate (HR) value for age was < P1 (severe bradycardia) or P10 (moderate bradycardia) during 3 consecutive hours (16) and that it had decreased by at least 10% compared to preinfusion value.
** = 7 patients had missing pre-infusion HR value ; # = 5 patients had missing BP pre-infusion value

Table 3 : Risk factors associated to severe bradycardia : Logistic regression analysis

Variables*	OR [95%CI]	p-value
Clonidine-related		
Maximal infusion rate (mcg/kg/hour)	1,20 [0,72–2,01]	0,49
Bolus at infusion start (presence of absence)	0,78 [0,36–6,67]	0,52
Patient-related		
Age (years)	0,74 [0,64–4,85]	< 0.0001
Diagnosis (surgical or medical)	0,67 [0,34–4,35]	0,27
Creatinine (z-score)	0,94 [0,86–6,03]	0,16
PELOD 2 score	1,04 [0,91–1,19]	0,54

*= The Hosmer and Lemeshow test was used to assess the goodness of fit of the logistic regression (*p*-value = 0.28)

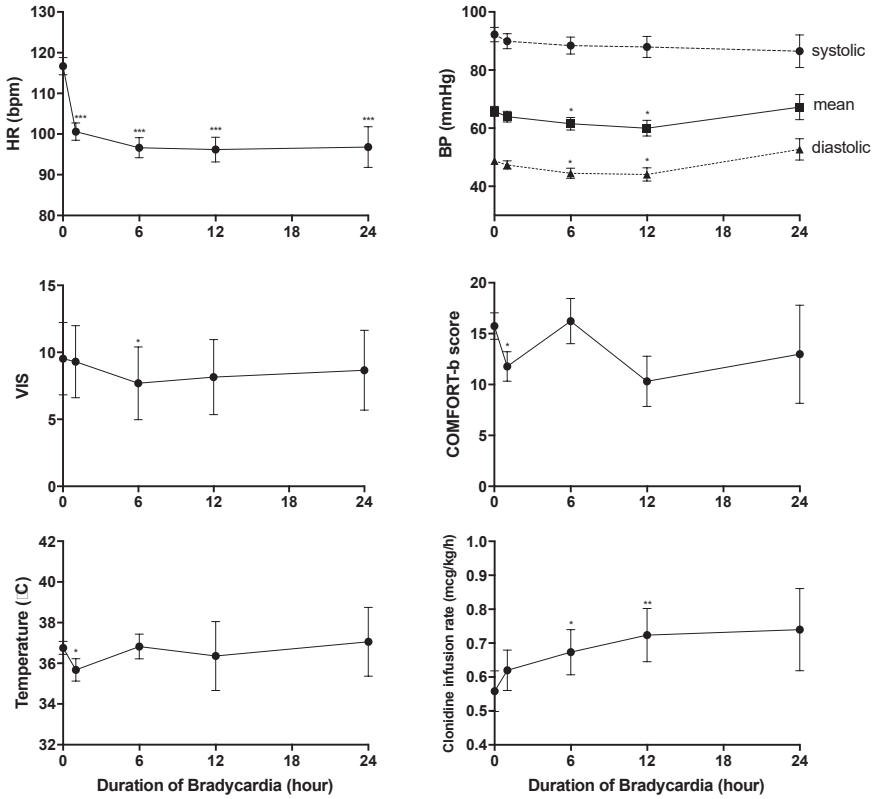

Figure 3: Relation of clonidine-associated severe bradycardia with BP, VIS, level of sedation, temperature and clonidine infusion rate

Estimated marginal means with their corresponding standard error based on the linear mixed model are reported. The first episode of severe bradycardia (HR<P1) was determined for each patient. Start of this episode (time 0) was defined as the first hourly HR value below P10; the end when the hourly HR value was higher than P10. Values were compared at four time-points during severe bradycardia: 1, 6, 12 and 24 hours.

*= *p*-value: 0.05–5.01; **= *p*-value: 0.01–1.001; ***= *p*-value: < 0.001

In addition, MBP and SBP hypotension were unrelated to the occurrence of severe bradycardia. MBP hypotension was found in 53.5% of patients with severe bradycardia ($p = 0.56$); SBP hypotension in 63.4% ($p = 0.30$).

DISCUSSION

This study is the first to document the incidences, clinical consequences and risk factors of bradycardia and hypotension in PICU patients with high disease severity (8% mortality rate) receiving a prolonged intravenous clonidine infusion for analgo-sedation. Severe bradycardia and systolic hypotension occurred in 40% and more than 50% of the patients, respectively. Younger age proved a risk factor for clonidine-associated bradycardia. Surprisingly, these complications do not appear to compromise hemodynamics as severe bradycardia was unrelated with hypotension, and the need for vasoactive drugs decreased with time in parallel with an increase in the clonidine infusion rate.

Good hemodynamic tolerance to clonidine has previously been shown in children under the age of 1 year after heart surgery in studies with sample sizes ranging from 10 to 50 (9) (1) (10) , of which only one included unstable patients (1). The current study broadens this finding to a wide mixed PICU population with high severity of illness and adds useful information to the off-label use of clonidine.

Three RCTs (2, 11, 25, 26) have reported on the hemodynamic tolerance to clonidine as a secondary outcome in a mixed PICU population. One (2) compared the opioid and sedative-sparing properties of clonidine versus placebo in 201 ventilated infants and demonstrated decreased sedative and analgesic requirements. HR was similar between groups while SBP and MBP decreased slightly in the clonidine group. Yet, hemodynamic tolerance could not be inferred from this study as the infants received a fixed low dose of clonidine (1 µg/kg/h) without loading dose (> 24h to reach steady-state concentrations (27)) while common clinical dosing implies the use of a loading dose and titration to higher infusion rates.

A second RCT concerned a pilot study on opioid and benzodiazepine sparing effects of oral clonidine in 50 ventilated patients (1 month-18 years) (28). The frequencies of hypotension and bradycardia did not differ between the clonidine group and a placebo group. Again, this finding cannot be generalised to the general PICU population as patients on inotropes were excluded and relatively low doses were administered (5 µg/kg every 6 hr orally, 50% oral bioavailability, equals approximately 0.4 mcg/kg/h IV infusion).

A third RCT, the SLEEPS study, compared the sedative properties of clonidine (0.75–3 µg/kg/hr) to midazolam (50–200 µg/kg/hr) in ventilated children (1 month-15 years). As recruitment proved difficult the study was severely underpowered (129 subjects instead

of the 1000 planned). The incidences of hypotension and bradycardia were similar between groups. Of note, and in contrast to what we found, the patients on clonidine consumed more inotropes during the first 12 hours than did patients on midazolam. This discrepancy cannot be attributed to the severity of disease as our population had a 10 times higher mortality rate. It may be explained perhaps by the higher loading (3 versus 2µg/kg in the current study) and starting infusion doses in the SLEEPS study (1.5 versus 0.3 mcg/kg/h in the current study). These results suggest that starting at low dose and titrating according to hemodynamic tolerance may be safer in unstable patients.

Bradycardia is often a concern because cardiac output is directly proportional to HR. Still, the good hemodynamic tolerance reported in this study and others suggests that compensating mechanisms may play a role. Decreasing HR may increase stroke volume and improve force-frequency relation (29). Moreover, a clonidine-associated blood pressure decrease may favour cardiac output by reducing afterload. Clonidine has been shown to suppress sympathetic hyperactivity (30) and to decrease oxygen consumption (31, 32). These mechanisms may compensate for the potential detrimental effect of HR decrease on cardiac output.

Interestingly, in our study the VIS decreased after clonidine start, suggesting that lower doses of inotropic and vasopressors drugs were administered. Similarly, adults undergoing general anesthesia and premedicated with clonidine had a higher BP response to vasopressors compared to a placebo group (33, 34). Recent animal studies (30) and case-reports have reported successful restoration of pressor responsiveness with clonidine in refractory septic shock (35). It was postulated that sepsis-associated sympathetic overactivation and consequent catecholamine increase downregulates α_1-receptors leading to vascular hyporesponsiveness restored by the clonidine sympatholytic effect that favours α1-receptor upregulation (35). These observations are in line with the decreased VIS following clonidine initiation in our mixed PICU population.

The rapid decrease in COMFORT-B score after clonidine start strongly suggests that clonidine is an effective sedative agent. Despite being underpowered, the SLEEPS study showed non-inferiority of clonidine vs midazolam from the proportion of patients adequately sedated clonidine at least 80% of the time (6). Similar studies are needed to confirm these interesting results.

During clonidine infusion, body temperature increased and reached significance at day 7 (mean 38.2 °C). The known pharmacological properties of clonidine include, however, a temperature decrease through central activation of postsynaptic alpha 2-adrenoceptors (36). Moreover, an RCT in an adult ICU showed a lower temperature and a lower relative risk of fever in patients receiving clonidine vs placebo (37). Our contradictory finding may be explained perhaps by a greater likelihood of secondary infection and concomitant fever in the 47/179 patients still receiving clonidine infusion at day 7.

This study is the first to specifically explore the hemodynamic effect of severe clonidine-associated bradycardia. This frequent complication was hemodynamically well-tolerated, which suggests that the fear of severe bradycardia may not be entirely justified. During severe bradycardia, SBP remained stable; MBP and DBP decreased minimally probably secondary to a prolonged diastole (giving more time for the physiologic decrease in diastolic pressure) while VIS tended to decrease and the clonidine infusion rate was further increased. Nevertheless, some patients may still be prone to develop clinically significant bradycardia or hypotension. In the SLEEPS study, one patient developed profound bradycardia upon which, despite stable BP, the study drug was discontinued and intervention was not needed. This patient tolerated bradycardia well, however, and discontinuation may not have been warranted. Outside a research setting, down-titration of clonidine and follow-up might have been an acceptable treatment option in this case.

In the present study younger children appeared to be more at risk for clonidine-associated bradycardia. Body-weight corrected clonidine clearance is indeed lower the first year of life (27, 38, 39), with expected subsequent higher blood levels suggesting a concentration-related lowering effect on HR. The association of HR decrease and age was also found at a later age, suggesting other factors.

The major strength of this study is its large population, which also is the broadest PICU population exposed to clonidine to date. Moreover, the use of clonidine as a second line sedative agent led to a sample of sicker patients than in previous studies, as reflected by a mortality rate more than twice the usual PICU mortality rate in PICUs in the Netherlands (8% vs 3.5% (40)) and higher than in previous studies (0.8% in the SLEEPS study (6) and 5.5% in the study by Hünseler et al (2)). Moreover, the included patients were prone to hemodynamic compromise due to the effect of disease and the concomitant use of other sedatives. Our results can therefore likely be generalized to most PICU patients. A second strength is unparalleled accuracy of the vital sign analysis, which was performed using values recorded per minute and weighting them according to the time between measurements.

The main limitation of the study lies in its observational nature. Clonidine may have been avoided in the most unstable patients, implying a possible 'bias by indication' that may have influenced the results. However, this type of bias is unlikely to be resolved with a RCT. One of the reasons for the low recruitment rate in the SLEEPS study was the physicians' reluctance to randomize the unstable patients for fear of hemodynamic adverse effects of clonidine (6). Nonetheless, taking into account that the choice of a sedative agent at the bedside is based on knowledge derived from population based studies, physiological knowledge and clinical judgement (41), these encouraging data should motivate the use of clonidine in the PICU. Furthermore, they should stimulate studies exploring the vasoactive-inotropic drug sparing effect of clonidine.

CONCLUSION

Clonidine is an effective sedative when given as an adjunct to morphine and midazolam. The often-associated bradycardia and hypotension do not seem clinically significant in a mixed PICU population with a high degree of disease severity. Clonidine may have a vasoactive-inotropic sparing effect.

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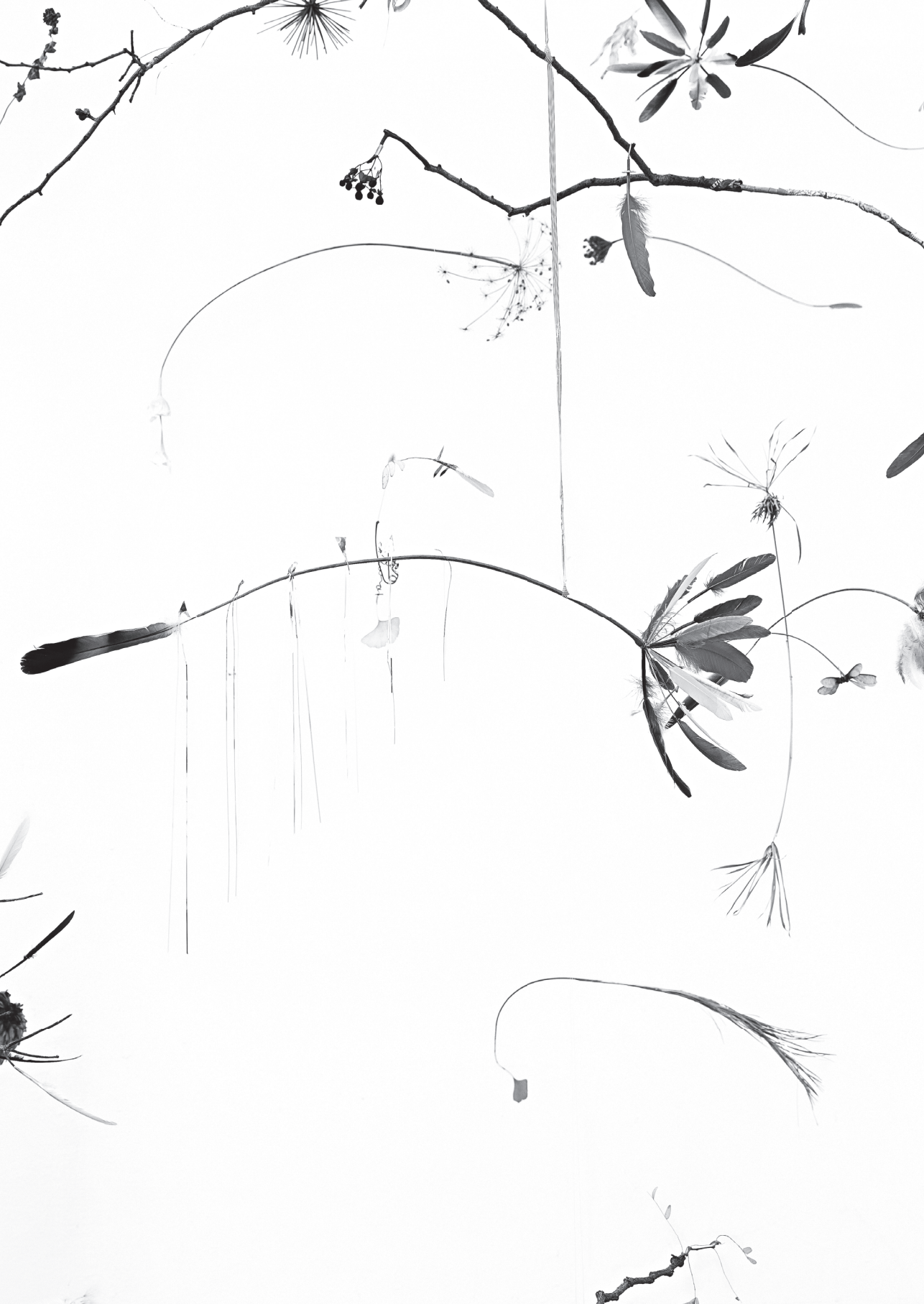

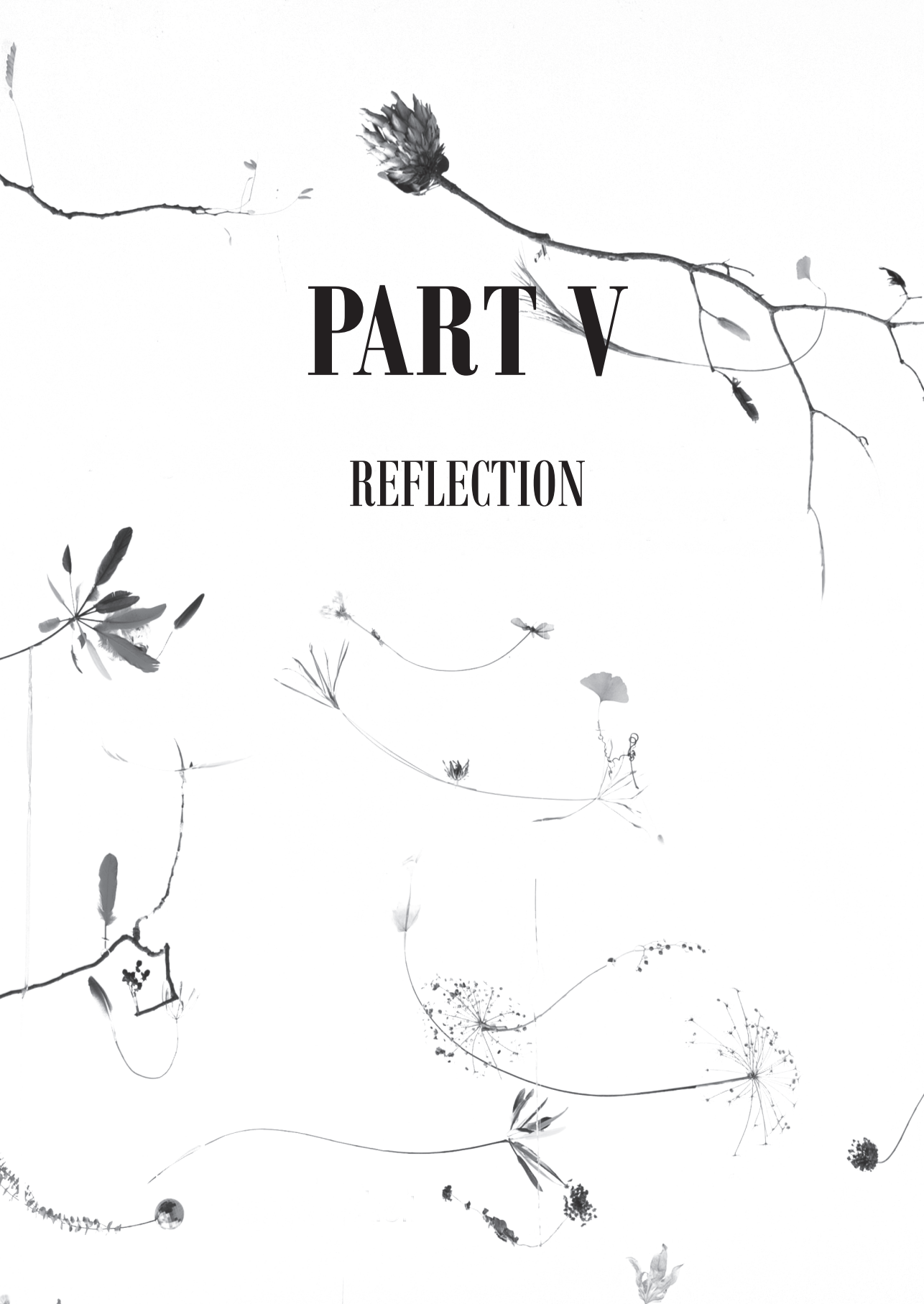

PART V

REFLECTION

“If it is known exactly what is going to be done, why do it?
“Si on sait exactement ce que l’on va faire à quoi bon le faire?”

Pablo Picasso

Chapter 11

General discussion

PEDIATRIC PHARMACOLOGY

In medicine and in particular in pharmacology, children have long been considered "small adults", but around 40 years ago it became clear that down scaling of adult doses could be detrimental to children because it did not respect the maturation processes unique to children (1). Likewise, the concept of dose-weight proportionality is not applicable during early life as renal and liver functions then are still maturing (2, 3). Unawareness of the immaturity of metabolic pathways has led to catastrophes like death from gray baby syndrome of neonates with immature glucuronidation pathway who had been given chloramphenicol (4, 5).

There is still a long way to go to a shift from empirical to evidence based and potentially individualized drug dosing in children (6). The ideal drug choice and dosing should take into account patient specific properties such as age, weight, disease severity, disease related treatment and genetics as well as drug specific properties such as ADME pathways and mechanism of action. Individualized drug dosing is highly challenging, however, especially in critically ill children whose properties keep changing during admission.

PICU PHARMACOLOGY

Critical illness impacts on each pharmacokinetic step (ADME) and pharmacodynamics. *Absorption* may be affected by the impact of disease on all factors involved, such as gastric pH, gastric emptying, intestinal drug transport and metabolism. Therefore, the oral route of administration is usually avoided (7, 8). *Volume of distribution* can be affected by a change in plasma albumin and total protein, total body water (e.g. generalized oedema) or the application of extracorporeal techniques like extracorporeal membrane oxygenation (ECMO) and continuous venous-venous hemofiltration (CVVH) that add an extra volume to the body. The liver is the main organ involved in drug *metabolism*. In phase I reactions, a reactive group is attached to the drug (e.g. oxidation, reduction, hydrolysis) while in phase II reactions drugs are conjugated with charged groups (e.g. glucuronidation, sulfation, methylation). After conjuguation, lipophilic drugs become more hydrophilic and can be excreted by the kidneys. Thus, drug *clearance* may be compromised by liver or kidney failure, which conditions are often seen among PICU patients (9, 10). Inflammation also affects drug metabolism and drug transport by up- or downregulating the expressions of cytochrome P450 enzymes and membrane transporters (11). For example, clearance of midazolam is only 30% in case of severe inflammation. This may lead to overdosing of metabolized drugs if doses are not decreased accordingly (12).

In addition, acute illness often involves specific treatments that also affect PK and PD. For example hypothermia slows drug metabolism (13), which can increase drug exposure and lead to overdosing (14). During ECMO treatment the plastic tubing and ECMO oxygenator adsorb drugs so that even in a closed ex vivo circuit the concentration decreases with time (15, 16). Studying drug PK during ECMO is needed to rationalize drug treatment of children on ECMO.

The effect of critical illness on organ function implies also changes in pharmacodynamics. Good knowledge of the interaction between a patient's clinical condition and adverse drug effect profile is important to determine the most ideal drug and dosing for the patient. For example, children with severely decreased heart function are at risk of fatal collapse caused by the cardiodepressant effect of analgesics and sedatives when rapidly injected. Slow injection and titrated dosing of sedatives and analgesics with limited cardiodepressant effect are required in this situation.

The current level of evidence on "PICU pharmacology" does not allow a rational drug choice and dosing guidelines taking into account the diversity of situations in the intensive care unit. In this regard, Duffett et al concluded that published guidelines have less influence on treatment choice than have severity of illness, physiologic rationale, and potential risk for adverse effects (17). Until results of dedicated studies become available, knowledge of pharmacology can help rationalizing drug choice and dosing in the critically ill and maximize the desired effect while minimizing adverse effects.

RESEARCH IN THE PICU

Children are considered vulnerable and therefore have long been excluded from clinical drug trials. Thus they are a kind of 'therapeutic orphans' in whom administering drugs in the absence of safety and efficacy data should be considered an experiment. Research on drugs in children is still trying to fill the gap where unfortunately the aim of protecting children led paradoxically to empirical and dangerous practices. But since new research methods have become available, research with a lesser burden can be undertaken.

Traditional drug study design implies administration of a non-therapeutic drug followed by extensive blood sampling but this is not an ethical option in children. The PK data presented in this thesis were generated using alternative study designs. One of these is what is known as opportunistic design: the study of a drug given as per standard of care. Both PK studies presented in this thesis were based on this study design. Sparse sampling implies collecting blood samples as part of routine blood sampling without the need of extra vascular access. Population PK analysis makes use of randomly collected and a lower number of blood samples, thus lowering the number of samples per patient (18). A microtracer design, a new and very innovative technique, was used in Chapter 7

to determine paracetamol bioavailability with an accuracy that is unique to this study design. For the first time in paediatrics, an oral radiolabeled microtracer was given simultaneously to an intravenous dose and coupled to a population PK analysis. Despite being the same molecule, the therapeutic iv dose can be quantified independently from the oral microtracer. These innovative approaches allow generating evidence-based drug regimens in critically ill children while minimizing burden and risks (19, 20).

Another barrier to PICU research is informed consent. Children in the PICU are especially vulnerable as the consent-seeking process may be threatened by altered consciousness, for instance due to sedation and disease, or communication problems when intubated, in addition to age-related limits to informed consent in neonates and young children. The acuity and life-threatening nature of illness puts great pressure on the informed consent processes as parents may be too overwhelmed to also think about their child's participation in a research study and attending medical staff may discourage the child's participation in a trial for fear of any burdens and risks of the trial (21, 22). Alternative forms of consent have newly been developed taking into account parental stress and the unpredictable reality of the acute critical care environment: deferred consent and continuous consent (or two-step consent). Deferred consent implies enrolling patients before consent is obtained and obtain informed consent after enrolment for the use of already collected information and ongoing participation (23). In continuous consent, in the first step only the most relevant information is given to parents to seek consent, followed in the second step by a deeper informed consent conversation (23). Data suggests that parents generally support both forms of consent, if adequately explained (24).

We suggest considering more systematically the use of alternative consent forms as these potentially can increase recruitment rates while preserving freedom of choice. Eventually this will help build solid knowledge on individual drugs in the PICU.

ANALGESICS AND SEDATIVES IN THE PICU

Neonates and children admitted to a PICU almost inevitably experience stress and pain (25). It is therefore not surprising that sedative and analgesic drugs are among the most common prescribed drugs in the PICU. Adequate sedation is defined as the level of sedation at which a patient is asleep but easily arousable (26). Sedation should be assessed using an instrument validated for PICU patients, such as the COMFORT scale (27), the COMFORT behavior scale (28–30), and the State Behavioral Scale (SBS) (31, 32). Both under- and oversedation are undesirable. Undersedation may cause distress and lead to unintentional extubation or catheter displacement while oversedation may delay recovery (33, 34) and induce tolerance and withdrawal syndrome (35, 36). Despite this knowledge, a tendency toward oversedation in the PICU setting has been described

(37). In addition to conscious sedation, deeper sedation may sometimes be targeted to guarantee hemodynamic stability, e.g. post cardiac surgery or in pulmonary hypertension. Interestingly, the benefits of deep sedation for these outcomes have not received much attention in clinical trials.

Reaching this ideal level of sedation and optimal safety requires good knowledge of PD and PD of analgo-sedative agents in a variety of different situations. Analgosedatives are the most studied drugs in the PICU (38) but most studies were conducted without prior pharmacokinetic data and therefore patients may not have reached comparable plasma levels, obscuring the pharmacodynamic effect (39). It is therefore of paramount importance to obtain pharmacokinetic data before conducting clinical research and include dosing in any prospective drug study.

Sedatives and analgesics can be titrated clinically but PK data are required to titrate rationally (40, 41), decide the most optimal route of administration (8, 42), choose the best agent for an individual patient in a specific situation (43), individualize dosing to the patient's individual characteristics (12, 44), optimize the effect of every sedative and analgesic used concomitantly and avoid accumulation and toxicities (45, 46). Rational use of analgosedatives in the PICU implies that every agent has to be studied in a variety of clinical conditions. First of all *disease-related PK changes* including inflammation and organ failure need to be determined. Second, *PK data in common care situations* need to be obtained to guide dosing, such as after cardio-pulmonary bypass (implying induced PK changes, hemodynamic instability and inflammation) or sepsis. Lastly, the *effect of treatment related PK changes* during interventions such as ECMO, CVVH or hypothermia has to be delineated.

We chose to study two specific situations related to PK of drugs in critically ill children, ECMO and oral absorption. In addition, we focused on the hemodynamic impact of different sedation regimens and more specifically that of clonidine for continuous sedation.

PK OF ANALGESICS AND SEDATIVES IN THE PICU

ECMO

This thesis presents the first estimations of PK parameters of intravenous clonidine in children on ECMO and CVVH (Chapter 5) using population PK. We found that on the particular ECMO system studied, clonidine PK is influenced by age, ECMO and administration of diuretics. The maturation of clearance was quicker in patients on ECMO: they reached 70% of adult clearance at 1.5 weeks on ECMO compared to 1 month (47) and 9 months (48) in patients not on ECMO. Clonidine clearance was two-fold that measured in patients not on ECMO and decreased by 30% with the use of diuretics. Volume of distribution increased by 55% during ECMO support. It proposes new individualized

dosing guidelines on this particular ECMO system with higher infusion rates and higher bolus dose to reach therapeutic levels. Besides the reported results, this study illustrates the difficulty to isolate the aetiology of PK changes. The quicker maturation of clearance than reported in patients not on ECMO illustrates that this parameter is driven by other mechanisms that could not be isolated because of co-linearity (as age parallels time on ECMO and clinical improvement during extracorporeal support). Moreover, the evolution in technology implies regular changes in ECMO systems. Newer systems are made from material with less adsorptive capacities (polymethylpentene hollow fibre), with lower priming volume and driving less inflammatory response at ECMO initiation (49). This implies that ECMO-PK studies will need to be regularly re-conducted. As this may be not feasible for financial and practical reasons, mechanistic models that take into account specific technical changes in the ECMO systems may be an interesting alternative. Physiologically based PK models taking into account in vitro ECMO data (coupled to CVVH or not) according to drug physicochemical properties models may simplify the difficult task of isolating the effect of ECMO from the patient's characteristics.

Oral bioavailability

The oral bioavailability of commonly used sedatives and analgesics (e.g. lorazepam, paracetamol) has not been determined in children in general and in the critically ill child in particular. Nevertheless, a high proportion of drugs are administered orally to critically ill children: 15% in ventilated children and 27% in non-ventilated (50), possibly without good efficacy or safety. Clinicians often base their decision about the route of administration according to the patient's clinical condition, availability of intravenous access, enteral food tolerance and availability or price of the oral versus the iv formulation. For life-saving drugs, the iv formulation is invariably preferred. Intravenous administration is usually preferred when a defined level of sedation must be maintained for conditions such as sepsis and traumatic brain injury) or their related management (ventilation, ECMO) because this is more reliable with quicker onset of effect. Chapter 7 of this thesis describes the first determination of oral bioavailability of paracetamol in children and in critically ill children in particular. For the first time in pediatrics we used an innovative microtracer study design coupled to population pharmacokinetics to obtain the oral bioavailability measure of paracetamol in children. The average oral bioavailability was 70%, which we found somewhat surprising as critical illness is often thought to severely reduce oral absorption. While this percentage was lower than in a study in healthy adults showing almost complete absorption (51), it was similar to that reported in other adult studies (52, 53). Hence, oral administration of drugs may result in adequate systemic exposures even in critically ill children. Caution is needed, however, as we have observed a wide interindividual variability in bioavailability (10–90%) in our patients. The systemic exposure may be unpredictable therefore, with risk of underdos-

ing in patients with low bioavailability and overdosing in patients with nearly complete bioavailability (when higher oral than intravenous dose are used). Importantly, none of the patient characteristics in our study has proved a predictor of bioavailability and feeding status as a surrogate marker of preserved gut function was not a significant covariate. The results of this study indicate that oral paracetamol likely not results in a consistent response and that intravenous administration is preferred if vascular access is in place. These data should motivate health regulatory agencies worldwide to license iv paracetamol for the broad pediatric age range. This study furthermore made clear that determining interindividual variability in bioavailability is of paramount importance. Based on mean population bioavailability the advocated oral dosing is often higher than the iv dosing, which may lead to overdosing in a patient with high bioavailability. Bioavailability studies are the only way to accurately disentangle bioavailability and clearance and their related interindividual variabilities that are otherwise confounded. In summary, obtaining more insight in children's individual bioavailability of much used drugs in the PICU may help improving drug dosing and its related safety.

CONCLUSIONS AND RECOMMENDATIONS:

- The interplay of ECMO coupled to CVVH and postnatal age significantly influences clonidine PK in critically ill neonates and young infants. As ECMO systems technically change rapidly, mechanistic models need to be developed to estimate exposure in these children.
- Oral bioavailability of paracetamol is 70% with a wide interindividual variability, which implies that plasma concentrations after oral dosing may widely vary with risk of under- and overdosing.
- Oral dosing guidelines based on mean population bioavailability may lead to inadequate drug efficacy and when a drug's bioavailability variability is high.

HEMODYNAMIC EFFECTS OF ANALGOSEDATION IN THE PICU

Hemodynamic stability after heart surgery, should we worry?

After cardiac surgery, oversedation is usually aimed for as it decreases oxygen consumption and promotes aerobic metabolism. Unfortunately, all sedatives have potential adverse hemodynamic effects, such as myocardial depression or vasodilation, which may counteract the expected decrease in oxygen consumption (54–56). This widely used clinical practice of oversedation during profound hemodynamic instability is empirical and not supported by objective data. Traditionally, infants undergoing heart

surgery were pre-emptively sedated during the first 12 to 24 hours postoperatively (57) to decrease oxygen consumption and prevent low cardiac output. But after the adverse effects of oversedation had been recognized, practice shifted from pre-emptive to targeted sedation based on hemodynamic stability). Nevertheless, numerous PICUs still favour pre-emptive sedation after heart surgery.

Chapter 8 retrospectively compares hemodynamic stability with two sedation practices after major heart surgery in young infants: pre-emptive (routine sedation with midazolam) and targeted sedation (aimed to reach a predefined level of sedation according to cardiovascular stability). We found that hemodynamic parameters and surrogate markers of cardiac output adequacy in the pre-emptively sedated group were comparable to those of the targeted sedation group. This questions the use of deep sedation to prevent low cardiac output as it might unnecessarily expose the children to sedatives that may cause neurotoxicity (58) and withdrawal (36).

The effect of sedatives on neurodevelopment is increasingly being debated (58–60). Neurotoxic effects of analgosedatives have been demonstrated in animal studies (16, 17) and in human studies, but these were confounded with the effect of disease. A recent large RCT showed similar neurodevelopment outcome at 2 years after awake-regional and general anaesthesia for inguinal hernioraphy in infancy (59). Other reassuring data have come from wide retrospective studies (58, 61, 62) but no study to date has addressed the long-term neurodevelopment outcome after prolonged use of analgosedatives in the PICU. Given the very active neurodevelopment in neonates and young infants, it would seem advisable to decrease the use of analgosedatives in this age group, at least until more evidence on the effects of their prolonged use becomes available. The FDA has incorporated this advice in the official label of most analgosedatives (63).

Hemodynamic stability with clonidine in the PICU

Clonidine is among the few analgosedatives that do not cause neurotoxicity in animals (64) and is therefore not included in the list of general analgosedatives affected by the FDA label change. These reassuring data on neurodevelopment along with the absence of respiratory depression (65) motivated its recent use in the PICU. But as clonidine was first licensed as an antihypertensive drug, physicians are often reluctant to use it for fear of its known bradycardic and hypotensive effect. A population that may be particularly prone to these adverse effects are neonates after heart surgery because their myocardial function decreases in the early postoperative period (57). Furthermore, small infants have limited ability to preserve cardiac output by increasing preload and may therefore be particularly prone to hemodynamic compromise in case of clonidine-associated bradycardia. These theoretical concerns may not be entirely justified as the study presented in Chapter 8 shows that clonidine infusion was hemodynamically well tolerated in 23 neonates after heart surgery. Heart rate decreased maximally 12% fol-

lowed the start of clonidine administration. Apart from a transient and limited decrease in diastolic blood pressure, no deterioration in markers of cardiac output was noted. These data suggest that clonidine was well tolerated. However, a subset of children with the highest degree of disease severity had been treated "off-protocol" with midazolam instead of clonidine, suggesting that clinicians may have been reluctant to administer clonidine in case of acute instability. Nonetheless, this is the first study on hemodynamic tolerance including unstable, post-cardiac surgery patients. These encouraging results motivated the next study, presented in Chapter 9, which describes the broadest mixed clonidine-exposed PICU population studied to date. This population was expected to be particularly vulnerable to the adverse hemodynamic effects of clonidine due to a high severity of illness score and the concomitant use of additional sedatives. However, clonidine was well tolerated. Our data are line with secondary outcomes reported in pediatric clonidine trials (66, 67). This study is also the first to specifically explore the hemodynamic effect of severe clonidine-associated bradycardia and shows that this complication is hemodynamically well tolerated. As clonidine is among the few sedatives not associated with neurotoxicity (58, 64, 68), the results of our study should favour its use in the PICU and motivate further studies in unstable patients.

CONCLUSIONS AND RECOMMENDATIONS:

- Tailored sedation early after heart surgery is hemodynamically well tolerated and pre-emptive sedation to prevent low cardiac output syndrome may not be necessary.
- Sedation as a way to decrease oxygen consumption (and balance oxygen consumption and delivery) should be questioned and systematically assessed.
- Despite its bradycardic and hypotensive effects, clonidine infusion used for sedation is well tolerated in patients at risk of hemodynamic adverse effects, including neonates after heart surgery and a broad mixed PICU population with high disease severity.
- Data on the pharmacodynamics (efficacy and safety) of commonly used sedatives is still missing. To ensure their applicability, these data should ideally be obtained in a population with clinical characteristics and severity of illness representative of the general PICU population.
- PD studies are needed to challenge the choice of a particular sedative or analgesic agent solely based on theoretical concerns taking into account physiological knowledge and potential interaction with the patient's disease.

In conclusion, the studies described in this thesis present interesting new data that support tailoring of drug therapy in critically ill children, taking into account critical illness, maturation, and intensive care therapies. The data also challenge general beliefs on the efficacy and safety of pharmacotherapy in the critically ill, concerning drug absorption, the need for deep sedation after cardiac surgery, and the risk of hemodynamic instability with clonidine.

So we may ask ourselves, are we really doing the right thing? Could our practices be detrimental to our patients' health? Until bedside therapeutic drug monitoring becomes widely available and non-invasive markers of cardiac output become reliable enough to avoid hemodynamic deterioration due to drug-disease interaction, we need to question the current practices. Every day, drugs are administered to critically ill children in the absence of reliable bioavailability data. Do we realize that a dosing regimen adapted to population oral bioavailability could be harmful on account of wide interindividual variability in bioavailability? That this could lead to under- but also overdosing? Sedation to decrease oxygen consumption is an attractive theoretical idea – but is it really justified? Is a lower level of sedation justifiable or should sedatives that potentially do not cause neurotoxicity be preferred? If we do follow the strategy suggested above, will we find out in 30 years that we have prevented neurotoxicity and have improved cognitive outcomes? Sedation and analgesia provision is certainly ***"more than sleep alone"***.

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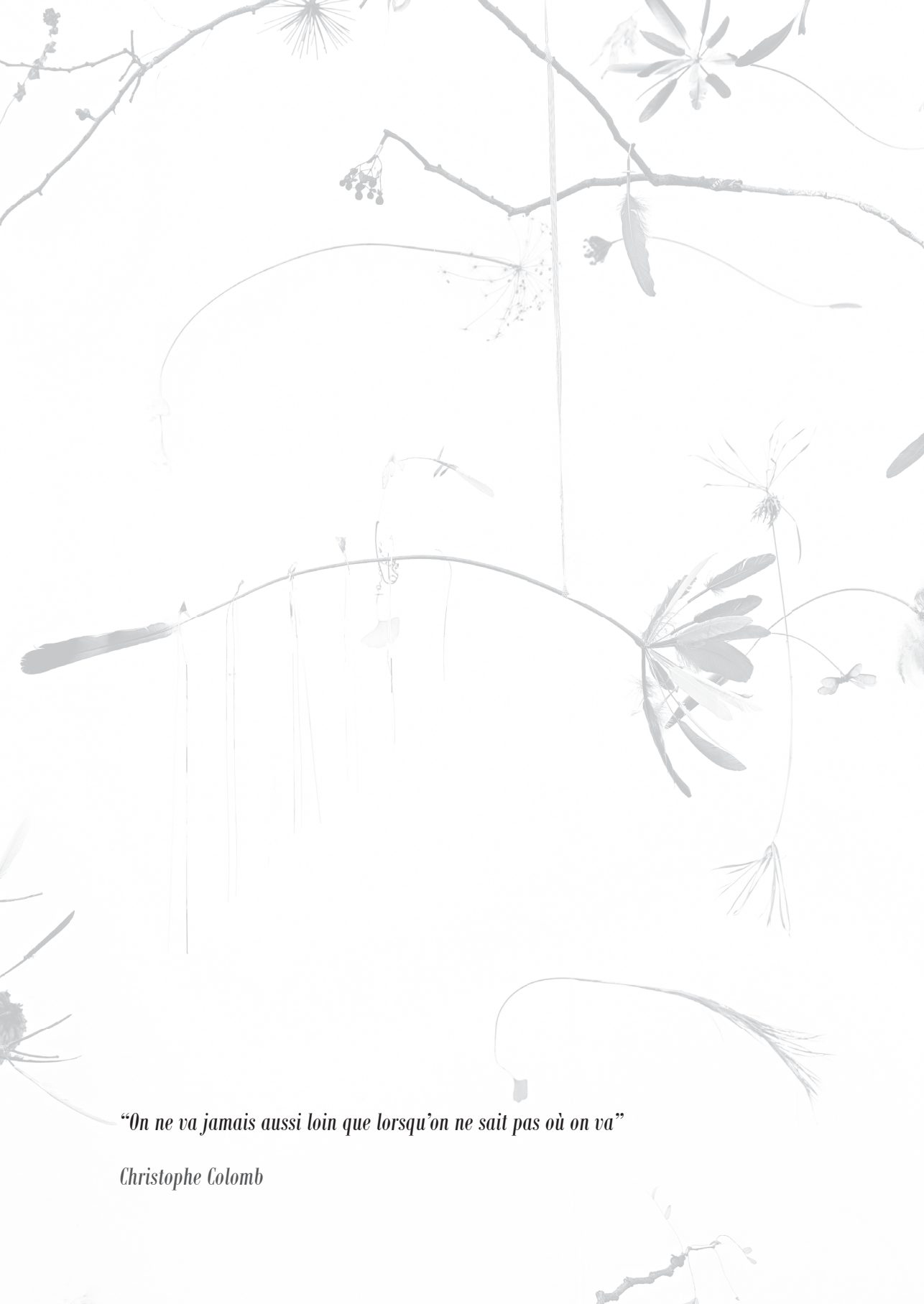

“On ne va jamais aussi loin que lorsqu’on ne sait pas où on va”

Christophe Colomb

Chapter 12

English and Dutch Summary

Pediatric dosing regimens have long been derived from adult dosing regimens. Although important progress has been made in pediatric clinical pharmacology, there is still a long way to go to shift from empirical to rational and individualized drug dosing. To get the desired effect while avoiding toxicities, pediatric dosing has to take into account the ontogeny of metabolizing and elimination processes that are unique to children.

The ideal drug choice and dosing should take into account patient-specific properties such as age, weight, disease severity, disease-related treatment and genetics as well as drug-specific properties such as ADME pathways and mechanism of action. Moreover, for critical ill children admitted to a PICU, matters are complicated by the effect of critical illness, the use of multiple drugs in the acutely ill child, and increased vulnerability to adverse effects.

Results of studies determining the pharmacokinetics (PK) and pharmacodynamics (PD) and their interactions with patient's characteristics and clinical condition are needed to design evidence-based drug regimens.

The aim of this thesis is:

1.) Review existing knowledge on PK, PD and ethical challenges in critically ill children, with a focus on analgosedatives.

2.) To study complex PICU pharmacokinetics using as examples:
   a.) the pharmacokinetics of clonidine in ECMO-treated patients
   b.) the oral bioavailability of paracetamol in critically ill patients

3.) To study hemodynamic efficacy and safety outcomes of analgosedatives, addressing the following questions:
   a.) Is hemodynamic stability similar in tailored sedation versus pre-emptive sedation after heart surgery in young infants?
   b.) What is the impact of clonidine on hemodynamic stability in neonates after heart surgery and in a general mixed PICU population?

Part I The impact of critical illness on pharmacokinetics (PK) and pharmacodynamics (PD) and challenges to improve knowledge on drugs in the pediatric intensive care unit

Chapter 2 delineates general principles governing PK-PD in the critically ill child to reduce the risk of improper dosing. Drug dosing in the critically ill child is a real challenge because in addition to the age-related variation in PK, the effect of acute illness and its treatment modalities impacts on every step of PK-PD. Our current knowledge does not allow for setting dosing guidelines accounting for the diversity of situations found in the PICU. PK-PD models taking into account patient characteristics, consequences of

critical illness and its treatment modalities are needed to facilitate individualized dosing. Conducting drug research in the vulnerable PICU population is hampered by practical, ethical, and scientific challenges, as reviewed in Chapters 3 and 4. Chapter 3 address the main ethical and practical issues specific to drug research in critically ill children and proposes to tailor the informed consent process to the reality of the acute care setting with the use of approaches known as 'deferred consent' and 'combined consent'. New methods to gain knowledge on drugs while limiting burden and risk are encouraged, such as *opportunistic studies* that derive PK of the drugs given per standard of care or *sparse blood sampling* methods that take advantage of sample leftovers or routine blood analysis. These randomly collected and limited blood samples per patient can be analyzed with population PK. Highly innovative microdosing studies are introduced as new techniques to gain insight into PK without exposing patients to therapeutic or adverse effects. Chapter 4 proposes the use of alternative forms of consent in a study on inotropic drugs in the acute care setting. Chapter 5 describes the current knowledge on PK and PD of analgosedatives in the critically ill, on sedation management, and on the specific PK-PD aspects of sedative drugs in the critically ill child and the consequences for dosing. Knowledge gaps still remain.

PART II Pharmacokinetics of analgosedation in the PICU

Chapters 6 and 7 provide new evidence on PK of analgesics and sedatives in critically ill children using the study design with minimized burden and risks described in Chapter 3. Chapter 6 illustrates how clonidine PK during extracorporeal membrane oxygenation (ECMO) and continuous veno-venous hemofiltration (CVVH) is influenced by age, disease and concomitant drugs and proposes new individualized dosing guidelines on this particular ECMO system. In children on ECMO, 70% of adult clearance was reached at 1.5 weeks, while previous studies have reported that this was reached after 1 month and 9 months, respectively, in patients not on ECMO. Clonidine clearance was two-fold that measured in patients not on ECMO and CVVH and decreased by 30% with the use of diuretics. Volume of distribution increased by 55% during ECMO support. In patients on ECMO, higher infusion rates and higher bolus doses are needed to reach therapeutic levels compared to patients not on ECMO. The study described in Chapter 7 was the first in paediatrics that used the innovative microtracer study design coupled to population pharmacokinetics to estimate paracetamol oral bioavailability in stable patients in the PICU up to the age of 6 years. The bioavailability was on average 70%, which is lower than generally assumed, with large interindividual variability (10–90%). Thus, oral administration of paracetamol may result in a low and unpredictable systemic exposure with higher probability of therapeutic failure. These PK data suggest that with regard to paracetamol for the treatment of acute pain in children the intravenous route is to be preferred over the oral route.

PART III Pharmacodynamics of sedatives and analgesics in the PICU

Chapter 8 retrospectively compares hemodynamic stability with two sedation practices after major heart surgery in young infants: pre-emptive (routine sedation with midazolam) and targeted sedation (discretionary use to predefined level of sedation). It appeared that pre-emptive sedation after high risk cardiac surgery cannot always prevent low cardiac output. To avoid exposing children unnecessarily to sedatives this strategy must be re-evaluated. Chapters 9 and 10 describe hemodynamic tolerance to sedation with a clonidine infusion in the PICU. The study presented in Chapter 9 included 23 neonates after high-risk heart surgery and good hemodynamic tolerance of IV clonidine as sedative added to morphine in selected patients. The study presented in Chapter 10 included a mixed PICU population with high disease severity, and who showed hemodynamic tolerance of a clonidine infusion used as a second line sedative. Young patients are at increased risk of clonidine associated bradycardia. This study is the first to specifically explore the hemodynamic effect of severe clonidine-associated bradycardia and shows that this complication is hemodynamically well tolerated. These findings should motivate the use of clonidine, which is among the few analgosedatives not associated with neurotoxicity in animals.

In Chapter 10, the results of our studies are discussed and recommendations for future research are given. We conclude that PK data are needed to tailor treatment to widely encountered interventions in the PICU, such as ECMO and CVVH. Also we suggest that clinicians' common beliefs need to be challenged by research. By showing that after high-risk cardiac surgery, targeted sedation (discretionary use to predefined level of sedation) compared to pre-emptive sedation (routine sedation with midazolam) does not result in any hemodynamic change, we encourage questioning the use of profound sedation to decrease oxygen consumption. Moreover, our findings about paracetamol bioavailability should encourage further bioavailability studies in the PICU where drugs are commonly given orally without data to justify this practice. We believe that long-term neurodevelopmental outcome should be taken into account when choosing sedation strategies. Animal data on neurotoxicity of commonly used sedatives led recently to an FDA warning and therefore, the hemodynamic tolerance shown with clonidine use is encouraging with regard to this drug, which is not associated with neurotoxicity.

De dosering van geneesmiddelen voor kinderen is lang gebaseerd geweest op doseringen voor volwassenen. Inmiddels is er grote vooruitgang geboekt op het gebied van de pediatrische klinische farmacologie, maar er is nog een lange weg te gaan om tot een verschuiving te komen van een empirische tot een rationale en geïndividualiseerde dosering. Om bij kinderen het gewenste effect te krijgen zonder toxiciteit moet rekening worden gehouden met de ontwikkelingsfysiologie van de specifieke metabolisatie- en eliminatieprocessen.

Idealiter wordt bij de keuze van een medicijn en de dosering rekening gehouden met de leeftijd van de patiënt, het gewicht, de ernst van de ziekte, de behandeling van de ziekte maar ook met genetische en medicijn-specifieke eigenschappen zoals ADME-pathways en het werkingsmechanisme. Voor ernstig zieke kinderen in de intensive care setting moet bovendien rekening worden gehouden met het effect van de ziekte, het gebruik van meerdere medicijnen tegelijk, en een grotere kans op nadelige bijwerkingen.

Een evidence-based medicamenteuze behandeling kan worden gerealiseerd aan de hand van de resultaten van studies naar de farmacokinetiek (PK) en farmacodynamiek (PD) van een medicijn en de interacties met de kenmerken en klinische conditie van de patiënt.

Mijn promotieonderzoek had als doel:

1.) De huidige kennis te inventariseren op het gebied van PK/PD en ethische aspecten bij ernstig zieke kinderen, met een focus op analgetica en sedativa.
2.) Inzicht te krijgen in de complexe farmacokinetiek in de kinder-intensive care setting, met als voorbeelden:
    a.) de farmacokinetiek van clonidine bij kinderen tijdens extracorporale membraanoxygenatie (ECMO)
    b.) de biologische beschikbaarheid van orale paracetamol bij ernstig zieke kinderen
3.) Het bestuderen van de hemodynamische werkzaamheid en veiligheid van analgosedativa, waarvoor de volgende onderzoeksvragen werden geformuleerd:
    a.) Is na een hartoperatie bij jonge kinderen de hemodynamische stabiliteit vergelijkbaar tussen sedatie-op-maat en preventieve sedatie?
    b.) Wat is de impact van clonidine op de hemodynamische stabiliteit bij neonaten na een hartoperatie en bij een algemene gemengde populatie in de kinder-intensive care setting?

Deel I De impact van een kritieke ziekte op de farmacokinetiek en farmocodynamiek en de uitdagingen voor kennisverwerving over medicijnen in de kinder-intensive care setting

hoofdstuk 2 schetst de algemene PK/PD principes die bij het kritiek zieke kind in het geding zijn; kennis hiervan kan het risico op onjuiste dosering verminderen. Het doseren van medicijnen bij deze kinderen vormt een echte uitdaging omdat naast de

leeftijdsgerelateerde variatie in PK, ook het effect van acute ziekte en de behandeling daarvan invloed heeft op iedere PK-PD stap. De huidige kennis is niet toereikend om doseringsrichtlijnen op te stellen voor de vele diverse situaties die zich kunnen voordoen in de kinder-intensive care setting. Om te komen tot geïndividualiseerde dosering zijn PK/PD modellen nodig die rekening houden met kenmerken van de patiënt, de gevolgen van kritieke ziekte en de behandeling daarvan. Medicijnonderzoek bij de kwetsbare populatie in de kinder-intensive care setting wordt bemoeilijkt door praktische, ethische, en wetenschappelijke belemmeringen volgens de literatuur beschreven in de hoofdstukken 3 en 4. Hoofdstuk 3 gaat in op de belangrijkste ethische en praktische zaken, met een pleidooi om het proces van *informed consent* aan te passen aan de realiteit in de acute care setting met benaderingen zoals 'uitgesteld consent' en 'gecombineerd consent'. Minder belastende en minder risicovolle methoden zijn bijvoorbeeld *opportunistic studies* naar de PK van medicijnen als standaardzorg of *sparse blood sampling*, met gebruikmaking van overgebleven bloed of het bloed dat routinematig wordt geanalyseerd. Deze bloedmonsters, willekeurig verzameld en een beperkt aantal per patiënt, kunnen worden geanalyseerd met populatie-PK. Ten slotte wordt aandacht geschonken aan zeer innovatieve microdosing studies die informatie kunnen opleveren over PK zonder patiënt bloot te stellen aan therapeutische of nadelige effecten. Hoofdstuk 4 geeft een voorstel voor het gebruik van alternatieve vormen van consent in een studie betreffende inotrope medicijnen in de acute zorg. Hoofdstuk 5 beschrijft de huidige kennis op het gebied van PK en PD van analgetica en sedativa bij kritieke ziekte, sedatiemanagement, en de specifieke PK-PD aspecten van sedativa bij het kritiek zieke kind en de consequenties daarvan voor de dosering. Er zijn nog steeds hiaten in de kennis.

DEEL II Farmacokinetiek of analgosedatie in de kinder-intensive care setting

Hoofdstukken 6 en 7 brengen nieuwe informatie over de PK van analgetica en sedativa bij kritiek zieke kinderen door toepassing van het onderzoeksdesign met een lage belasting en risico dat beschreven is in hoofdstuk 3. Hoofdstuk 6 geeft aan hoe de farmacokinetiek van clonidine tijdens ECMO-behandeling en continue veno-veneuze hemofiltratie (CVVH) wordt beïnvloed door leeftijd, ziekte en gebruik van andere medicijnen en geeft nieuwe geïndividualiseerde doseringsrichtlijnen tijdens behandeling met dit ECMO-systeem. Bij de onderzochte kinderen werd 70% van de klaring bij volwassenen bereikt na 1,5 week, terwijl in voorgaande studies bij patiënten zonder ECMO-ondersteuning kregen dit percentage pas werd bereikt na respectievelijk 1 maand en 9 maanden. De clonidineklaring was het dubbele van dat in patiënten zonder ECMO-ondersteuning en CVVH en werd 30% lager bij gebruik van plaspillen. Het distributievolume steeg met 55% tijdens ECMO-ondersteuning. Tijdens ECMO-behandeling zijn hogere infusiesnelheden en hogere bolusdoses nodig om de therapeutische concentraties te bereiken van

patiënten zonder ECMO-ondersteuning. Het onderzoek dat is beschreven in hoofdstuk 7 is het eerste bij kinderen dat gebruik maakte van het innovatieve microtracer design gekoppeld met populatiefarmacokinetiek. Het ging hierbij om het bepalen van de biologische beschikbaarheid van orale paracetamol bij stabiele kinderen tot de leeftijd van 6 jaar. De biologische beschikbaarheid was gemiddeld 70%, een lager percentage dan algemeen aangenomen, met een hoge interindividuele variabiliteit (10-90%). Dit impliceert dat orale toediening van paracetamol kan resulteren in een lage en niet te voorspellen systemische blootstelling met een grotere kans op therapiefalen. Deze farmacokinetische data geven aan dat wat betreft paracetamol voor de behandeling van acute pijn bij kinderen de intraveneuze route de voorkeur verdient boven de orale route.

DEEL III Pharmacodynamiek van sedativa en analgesica in de kinder-intensive care setting

Hoofdstuk 8 betreft een retrospectief onderzoek waarin de hemodynamische stabiliteit bij jonge kinderen na een grote hartoperatie wordt vergeleken voor twee verschillende sedatiemethoden: preventief (routinematig met midazolam) en doelgericht (naar believen tot een van tevoren bepaald niveau). Het bleek dat preventieve sedatie na een risicovolle hartoperatie niet altijd een lage cardiale output kan voorkomen. Met het oog op onnodige blootstelling aan sedativa dient deze strategie nader te worden bestudeerd. De hoofdstukken 9 en 10 gaan over hemodynamische tolerantie bij sedatie met een clonidine infusie. Het onderzoek in hoofdstuk 9 betrof 23 neonaten die een risicovolle hartoperatie hadden ondergaan; bij bepaalde geselecteerde patiënten was er een goede hemodynamische tolerantie van IV clonidine als een sedativum gegeven in aanvulling op morfine. Het onderzoek in hoofdstuk 10 betrof een gemengde populatie met zeer ernstige ziekte, en deze lieten hemodynamische tolerantie zien van een clonidine-infusie als tweedelijns-sedativum. Jonge kinderen hebben een groter risico op clonidine-geassocieerde bradycardia. Dit onderzoek is het eerste dat specifiek was gericht op het hemodynamische effect van ernstige clonidine-geassocieerde bradycardia en het laat zien dat deze complicatie hemodynamisch goed wordt getolereerd. Deze bevindingen breken een lans voor het gebruik van clonidine, een van de weinige analgosedativa die niet zijn geassocieerd met neurotoxiciteit bij dieren.

De bevindingen van alle studies worden besproken in hoofdstuk 10, met aanbevelingen voor nader onderzoek. We concluderen dat meer PK data nodig zijn om de behandeling toe te spitsen op veelvoorkomende interventies in de kinder-intensive care, zoals ECMO en CVVH. Ook wordt gesteld dat stellige overtuigingen van clinici moeten worden onderbouwd door onderzoeksresultaten. Omdat we hebben aangetoond dat doelgerichte sedatie na een grote hartoperatie vergeleken met preventieve sedatie geen hemodynamische veranderingen met zich meebrengt, zetten we vraagtekens bij de praktijk van diepe sedatie om de zuurstofconsumptie te verlagen. Verder wijzen onze

bevindingen over de biologische beschikbaarheid van paracetamol op de noodzaak van meer studies op dit gebied in de kinder-intensive care setting, waar medicineren meestal oraal worden toegediend zonder dat hier bewijs voor is. We vinden dat bij de keuze van de sedatiestrategie moet worden gedacht aan de neurologische ontwikkeling op de lange termijn. De Amerikaanse Food and Drug Administration (FDA) heeft recentelijk een waarschuwing doen uitgaan naar aanleiding van data uit dierstudies over de neurotoxiciteit van veel gebruikte sedativa; wat dat betreft is het bemoedigend dat clonidine – een medicijn dat niet is geassocieerd met neurotoxiciteit – een goede hemodynamische tolerantie liet zien.

LIST OF ABBREVIATIONS

AKI	Acute kidney injury
AS	Adequate sedation
AV	Atrio-ventricular
BP	Blood pressure
CAP-D	Cornwell Assessment Pediatric Delirium tool
Cl	Clearance
CO	cardiac output
COMFORT-b	COMFORT behavior scale
CPB	Cardio-pulmonary bypass
CrCl	Creatinine clearance
CRRT	Continuous renal replacement therapy
Css	Steady-state concentration
CVP	Central venous pressure
CVVH	Continuous veno-venous hemofiltration
ECMO	Extracorporeal membrane oxygenation
FDA	Food and Drug Administration
FOCE	First-order conditional estimation
GA	Gestational age
GABA	Gamma-amino butyric acid
GFR	Glomerular filtration rate
HR	Heart rate
ICC	Intraclass correlation coefficient
IQR	Interquartile range
IRB	Institutional Review Board
IV	Intravenous
LCOS	Low cardiac output syndrome
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
NISS	Nurse interpretation sedation score
NONMEM	Non-linear mixed effect modeling
NPDEs	Normalized prediction distribution errors
NRS	Numeric rating scale
OFV	Objective function value
OS	Oversedation
pCAM-ICU	pediatric Confusion Assessment Method for ICU
PD	Pharmacodynamic
PICU	Pediatric intensive care unit

PES	Preemptive sedation
PK	Pharmacokinetic
PMA	Post-menstrual age
PNA	Post-natal age
PRIS	Propofol infusion syndrome
Q1-Q3	1st and 3rd quartile
RASS	Richmond Agitation Sedation Scale
RCT	Randomized controlled trials
SA	Sinus Node
SBS	State Behavior Scale
Sc	Sieving coefficient
SD	Standard deviation
SE	Standard error of the estimate
ScvO2	Central venous oxygen saturation
SOS	Sophia Observation Withdrawal Symptoms-scale
SVR	Systemic vascular resistance
TARG	Targeted sedation Group
TDM	Therapeutic drug monitoring
US	Undersedation;
V	Volume of distribution
VAS	Visual analogue scale
VD	Volume of distribution
VIS	Vasoactive inotropic score
WAT-1	Withdrawal Assessment Tool version-1
WT	Bodyweight

ABOUT THE AUTHOR

Niina Kleiber is a Pediatrician and Clinical Pharmacologist. She completed her medical school in Switzerland where she started her pediatric residency before joining the pediatric residency program in Sainte-Justine Hospital in Canada (Université de Montréal). She graduated as a General Pediatrician in 2011 and as a Pediatric Intensivist in 2013 (Royal College of Physicians and Surgeons of Canada). She completed her training in pediatric intensive care with a fellowship at the Royal Children's Hospital in Melbourne in 2013–2014. She became very interested with the use of intravenous clonidine as a sedative during her training in Melbourne and created two research projects that are part of this PhD. Her interest in clonidine stems from the absence of associated neurotoxicity.

From Australia, she joined the Pediatric Pharmacology Unit at the Erasmus MC Sophia Children's Hospital where she studied Clinical Pharmacology and pursed her work on sedation in the pediatric intensive care under the supervision of Professor Dick Tibboel and Saskia N. de Wildt.

In 2016, she was appointed as an Assistant Professor in General Pediatrics and Clinical Pharmacology in Sainte-Justine Hospital in Canada (Université de Montréal).

LIST OF PUBLICATIONS

Are children at risk of underdosing with oral paracetamol? results of the first pediatric oral bioavailability microtracer study
Niina Kleiber, Elisa Calvier, Miriam G. Mooij, Elke Krekels, Wouter HJ Vaes, Dick Tibboel, Catherijne A.J. Knibbe, Saskia N de Wildt
Submitted

Hemodynamic Tolerance to Intravenous Clonidine Infusion in the Pediatric Intensive Care Unit
Niina Kleiber; Joost van Rosmalen; Dick Tibboel; Saskia N. de Wildt
Submitted

Population pharmacokinetics of intravenous clonidine for sedation during paediatric extracorporeal membrane oxygenation and continuous venovenous hemofiltration.
Kleiber N, Mathôt RAA, Ahsman MJ, Wildschut ED, Tibboel D, de Wildt SN.
Br J Clin Pharmacol. 2017 Jun;83(6):1227-1239. doi: 10.1111/bcp.13235. Epub 2017 Feb 27.

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Vet NJ, Kleiber N, Ista E, de Hoog M, de Wildt SN.
Front Pediatr. 2016 Aug 24;4:89. doi: 10.3389/fped.2016.00089. eCollection 2016. Review.

Trial Recruitment in the Pediatric Intensive Care: Ask Consent Before You Start?!
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Paediatr Drugs. 2015 Feb;17(1):43-53

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Pediatr Crit Care Med. 2015 May;16(4):325-34

Drugs in the pediatric intensive care (2017) in Sharland, Turner and Barker (Ed). Neonatal and Paediatric Prescribing [provisional title] (Pages TBC).
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Pharmaceutical Press, London (in press)

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Kleiber N, Chessex P, Rouleau T, Nuyt AM, Perreault M, Lavoie JC.
Pediatr Res. 2010 Sep;68(3):188-92

ECTS FOR PHD OF NIINA KLEIBER

Courses	Date	Location	ECTS
Litterature research: Endnote and other database	May 2014	Rotterdam	0.3
Pharmacology Day Leiden-Rotterdam	May 2014	Rotterdam	0.3
Course on R	19–92 May 2014	Rotterdam	1.4
Course on NONMEM CHDR	29–91 October 2014	Leiden	2.5
Metrum institute online course :			
• Essentials of Population PK-PD Modeling and Simulation (MI210)	Feb-March 2015	Rotterdam	1
Pharmacology course of NIH	Weekly from April 2014 to April 2015	Rotterdam	2
Biostatistical Methods I: Basic Principles (CC02)	September October 2015	NIHES Rotterdam	5.7
Toxicology meeting	Monthly for 2 years	Rotterdam	1
PhD Education Day (Monique van Dijk)	February – June 2015	Rotterdam	0.2
METC course	January to May 2015	Rotterdam	0.3
Seminars and Workshops			
Workshop on ECMO at 7th World Congress on Pediatric Intensive and Critical Care	3 May 2014	Istanbul	0.3
Seminars Leiden Rotterdam on PK-PD modelling	May 2014	Rotterdam	0.3
Research Integrity Meeting : Challenges, Commitments, Culture	18th of June 2015	Rotterdam	0.3
Journal club on NONMEM at AMC in Amsterdam	Monthly from April 2014 to December 2015	Amsterdam	1
General Pharmacology meetings	Weekly from April 2014 to December 2015	Rotterdam	2
PhD Day 2015: Surviving your PhD!	June 4, 2015	Rotterdam	0.2
Symposium on Pediatric Pharmacology	8 September 2015	Rotterdam	0.1
PGx workshops 2015	4 th November	Leiden	0.2
Symposium QTc-interactions	8 September 2015	Rotterdam	0.1
Pediatric Pharmacology meeting	Weekly from April 2014 to December 2015	MC Sophia Rotterdam	2
Conferences and Presentations			
7th World Congress on Pediatric Intensive and Critical Care : - Oral Presentation on hemodynamic tolerance of clonidine after heart surgery	4–4 May 2014	Istanbul	2
Oral presentation on research project on effect of sedatives on microcirculation in the PICU	October 2014	MC Sophia Rotterdam	1
35th International Symposium on Intensive Care and Emergency Medicine	17–70 March 2015	Brussels	1
The 26th Annual Meeting of the European Society of Paediatric and Neonatal Intensive Care : Poster presentation	10–03th of June 2015	Vilnius	0.5
Sophia Research Day	26th of June 2015	Rotterdam	0.3

	Date	Location	ECTS
Pharmacology Day Leiden-Rotterdam Presentation : Population pharmacokinetics of clonidine on ECMO	29th of June 2015	Leiden	1.3
Presentation at Pediatric Pharmacology meeting - Effect of sedative on microcirculation and vascular function	7 October 2014	Rotterdam	1
7th European Paediatric Formulation Initiative (EuPFI) Workshop and Conference	16–67 September 2015	Antwerp	1
FIGON Dutch Medicine Day Poster presentation	5–5 October 2015	Ede	1
Oral Presentation at the 6th Congress of the European Academy of Paediatric Societies – EAPS 2016 : - Sedation with clonidine during pediatric ECMO: A population pharmacokinetic model	October 21–15, 2016	Geneva	1
Grand Rounds Presentation: Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial, Lancet 2016	February 2017	Montreal	0.2
Poster Presentation at ASCPT meeting 2017 - Children at risk of underdosing with oral acetaminophen (APAP)? results of a pediatric oral bioavailability microdosing study	March 15–58th 2017	Washington	1
POSTER presentation at the Canadian Paediatric Society 94th Annual Conference, May 31 - June 3	1st of June 2017	Vancouver	1
Teaching			
Pharmacogenetics presentations on clinical cases	May 2015	Rotterdam	1
Pharmacology of the PICU (to fellow in Clinical Pharmacology)	Août 2015	Rotterdam	1
Student supervision on research projects: - Counterfeit antiepileptic drugs in Bénin - Topical sirolimus in vascular anomalies - Case-report on valproic acid toxicity in a child with tuberous sclerosis complex - Case-report: Serotonin syndrome or neuroleptic malignant syndrome in a child treated with metoclopramide?	February 2017 until now	Montreal	4
Course on Pharmacokinetics (PHL6060) – steady-state, absorption, distribution, metabolism and elimination Master degree student in Pharmacology Université de Montréal, Department of Pharmacology	February 2017	Montreal	3

Total ECTS: 42.5

DANKWOORD

Dear Professor Tibboel, Dear Dick, I am really thankful for the exchanges of ideas, your support and your input. What you taught me is extremely precious for my career. I also thank you for listening to "my crazy ideas" and support me as you did. My time in Rotterdam would not have been the same without your broad and clever view and your nice attitude.

Dear Professor de Wildt, Dear Saskia, a few years ago I contacted you from Melbourne to join the Clinical Pharmacology training in Rotterdam. A few weeks after I arrived, you suggested that I should join the PhD program. I asked for a period of reflection, as this was not the initial plan. You answered: "You will do a PhD, I even discussed it with Dick". And that was the end of the period of reflection. The amount of what I learned since is priceless. You taught me how to get the best from the "already best I could do". Thank you for that!

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