Drug therapies in neonates and children during extracorporeal membrane oxygenation (ECMO); Keep your eyes open

Enno Wildschut

The studies presented in this thesis were done in collaboration between the Pediatric Intensive Care (Sophia Children's Hospital) and the department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, the Netherlands.

For more information about drug therapy during ECMO, the reader is referred to the thesis by M.J. Ahsman entitled 'Determinants of pharmacokinetic variability during extracorporeal membrane oxygenation A roadmap to rational pharmacotherapy in children.'

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Drug therapies in neonates and children during extracorporeal membrane oxygenation (ECMO); Keep your eyes open

Medicamenteuze therapie in neonaten en kinderen gedurende extracorporele membraan oxygenatie (ECMO): Houd uw ogen open

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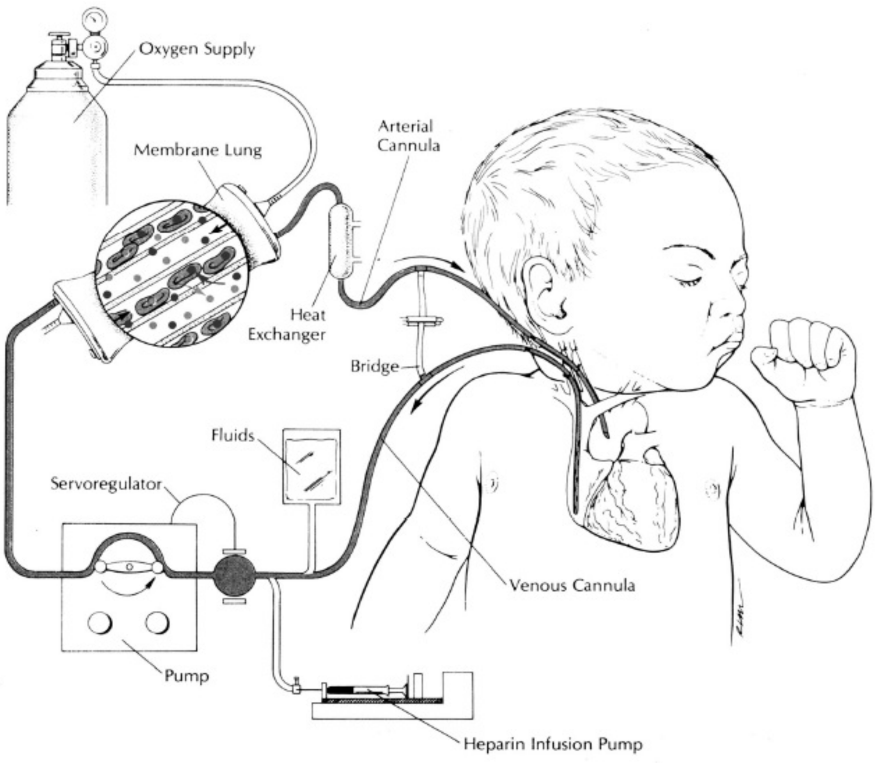
CHAPTER 1

Introduction

ECMO treatment

Extracorporeal life support (ECLS) or extra corporeal membrane oxygenation (ECMO) is a technique for providing life support in severe but potentially reversible cardio-respiratory failure in patients with an expected mortality greater than 80%.[1]
First pioneered in cardiopulmonary bypass during cardiac surgery, ECLS has been used as prolonged cardiopulmonary support in neonates since 1976.[2] It has been shown to have a survival benefit in neonates and adults.[3-4] Increasingly ECMO support is used in older children and adults. (ELSO registry report 2010)
ECMO provides extracorporeal gas exchange and circulatory support by pumping blood from the patient through an artificial circuit comprising of tubing, a pump, an oxygenator and a heater (figure 1). The oxygenator is used to oxygenate the blood and extract carbon dioxide. Blood is drawn from a venous access site, preferably a central catheter positioned in the right atrium, and returned either in the right atrium via a double lumen catheter (venovenous ECMO) for respiratory support or via the carotid artery (venoarterial ECMO) for cardiopulmonary support.

Fig. 1 schematic representation of venoarterial ECMO circuit, reproduced with permission[61]



Most ECMO centers report their data to the Extracorporeal Life Support Organization (ELSO). ECMO support is used in a variety of diagnoses. Neonatal indications include congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn (PPHN), congenital heart defects (CHD) and sepsis. The indications have not changed significantly over the last decade. Survival rates vary between different diagnoses. MAS has an excellent prognosis with short ECMO runs (131h) and 94% survival, whereas CDH has a survival rate of 51% with an average duration of ECMO of 248 hours (ELSO registry report January-2010). Pediatric diagnoses include cardiomyopathy, cardiomyositis, sepsis, viral and bacterial pneumonia and acute respiratory distress syndrome (ARDS). ECMO support is used as a bridge to recovery or organ transplant.
Although it may be life-saving in critically ill patients, ECMO treatment is associated with several complications and co-morbidity. Up until January 2010 ECMO support has been initiated in a total of 41.558 patients worldwide, including 28.004 neonates, 10.155 pediatric patients and 3399 adult patients, with an overall survival of 62 %. (table 1) (ELSO registry report January 2010) From 1992 till 2009, 435 patients received ECMO support in our center, including 361 neonates and 74 pediatric patients. (table 1)

In the ELSO database complication rates of associated ECMO centers are registered. Intracranial bleeding and nosocomial infections are the most commonly reported complications in ECMO. Surgical and pharmacological treatment of the underlying disease remains pivotal in the overall management of ECMO patients. Treatment and prevention of complications, as well as effective treatment of the primary diagnosis, are important to improve outcome in these patients. Patients on ECMO are heparinized to prevent clotting of the ECMO circuit, receive sedation and analgesia to alleviate pain and discomfort, diuretics to manage fluid overload and antibiotics or antiviral medication to treat infections.[5] Effectiveness and complications of these treatment modalities are main determinants of outcome, apart ECMO procedure itself. In other words, during ECMO the treatment team really needs to keep their eyes open!

Pharmacotherapy on ECMO

Patients on ECMO generally receive more than ten drugs per day while on ECMO.[5] Pharmacokinetic (PK) and pharmacodynamic (PD) data of widely used drugs on ECMO are sparse; concentration versus time profiles and concentration effect relationships have not systematically been evaluated. Importantly, limited studies have demonstrated altered pharmacokinetics for midazolam[6], morphine[7-8], gentamicin[9-13], vancomycin[14-17], ranitidine[18], theophylline[19] and bumetanide[20] in patients receiving

Table 1. ELSO registry summary January 2010 Updated t/m 2008

Neonatal respiratory and cardiac				
	International		Erasmus MC Rotterdam	
Diagnoses	total runs	survival(%)	total runs	survival(%)
CDH	5929	51	96	44
MAS	7584	94	143	94
PPHN/PFC	3870	78	40	78
RDS	1484	84	3	33
Sepsis	2617	75	25	72
Pneumonia	327	57	7	100
Air leak Syndrome	117	74		
Other respiratory failure	1939	63	46	74
Congenital Defect	3583	37	1	100
Cardiac arrest	55	24		
Cardiogenic shock	52	38	1	0
Cardiomyopathy	99	63	1	100
Myocarditis	49	49		
Other cardiac failure	323	41	1	100
Pediatric respiratory and cardiac				
	international		Erasmus MC Rotterdam	
Diagnoses	total runs	survival(%)	total runs	survival(%)
Viral Pneumonia	938	63	7	86
Bacterial pneumonia	500	57	2	100
Pneumocystitis pneumonia	30	50		
Aspiration pneumonia	200	66	2	100
ARDS, postop/trauma	109	62		
ARDS not postop/trauma	384	53	2	100
Acute resp. failure, non ARDS	766	51	27	81
Other respiratory failure	1527	51	21	57
Congenital Defect	3120	43	1	100
Cardiac arrest	138	43	1	0
Cardiogenic shock	97	42	3	33
Cardiomyopathy	475	57	4	100
Myocarditis	235	70		
Other cardiac failure	804	49	8	50

ECMO support. Volume of distribution as well as clearance are altered for most of these drugs, which makes it difficult to predict plasma concentrations and consequent effects in individual patients on ECMO. Adsorption of drugs by the ECMO circuits may contribute to the increased volume of distribution found in several clinical studies. This has been tested for several drugs in an *in vitro* setting.[6, 21-24] In comparison with hydrophilic drugs, lipophilic compounds seem to adhere to ECMO material to a greater extent, suggesting a relationship between the lipophilicity and drug adhesion.[22] Differences in ECMO-circuit size and construct materials may influence the extent of adsorption. Alterations over time due to a variable extent of adsorption, altered disease state, organ perfusion and function as well as maturation of organ function may all contribute to pharmacokinetic variability in differences and, consequently, variability in drug efficacy in ECMO patients.

Sedation and analgesia on ECMO

Most patients are heavily sedated to prevent either accidental decannulation or impeded ECMO flow due to movement or suboptimal cannula position. Furthermore surgical procedures such as cannulation, surgical repair of CDH, thoracic drain placement and surgical closure of the sternum in post operative cardio-surgery, necessitate adequate analgesia.

Increased sedative and analgesic requirements in neonates and children on ECMO (compared to non ECMO patients) have been reported, but international guidelines for sedation are absent, while most studies do not utilize validated sedation scores.[24-27] Midazolam and fentanyl are the most prescribed drugs for sedation and analgesia in ECMO patients, but there is much diversity between centers with regards to the drugs of choice and required levels of sedation.[28] Reported levels of sedation vary between conscious sedation where the patient is comfortable but awake and deep sedation with absent motor movement.[28]

Prolonged and high cumulative doses of morphine and midazolam have been associated with tolerance, dependency and withdrawal symptoms.[29-35] Several authors have reported opioid withdrawal syndrome in the post ECMO period.[24, 36-37] Standardized sedation protocols and daily interruption of sedation in adult ICU patients have been shown to improve short and long term outcome by reducing total sedative dose, duration of mechanical ventilation, and post traumatic stress. However these strategies have but have not been evaluated in ECMO patients.[38-39] Standardized sedation protocols using validated sedation and pain scores need to be evaluated in neonates and older children on ECMO to define uniform sedation goals. Novel protocols such as daily interruption of sedatives may decrease cumulative sedative use in ECMO patients. This may reduce incidence of withdrawal syndrome, mechanical ventilator support and possibly the duration of ECMO support.

Fluid management

Most ECMO patients have an increased inflammatory response before start of ECMO due to the underlying disease. Similarly as in cardiopulmonary bypass (CPB) for cardiac surgery, ECMO treatment in itself triggers a systemic inflammatory response (SIRS) due to high levels of circulating endotoxins, exotoxins, interleukins and leukotriens influencing the basal membranes.[40] This results in a so-called capillary leakage syndrome causing hemodynamic instability, hypoalbuminia, generalized edema[41] and consequently pulmonary edema.[42] This last phenomenon is called white-out on chest x-rays.
Management of fluid overload and generalized edema remains a challenge in ECMO patients. Pharmacological interventions, as well as hemofiltration, have been used to reduce edema and to optimize fluid management in these patients. There is evidence that hemofiltration or dialysis reduces circulating inflammatory mediators[43-45] and improves short term outcome in children after CPB.[46-48] Fluid overload is associated with worse clinical outcome in both ECMO patients and patients requiring hemodialysis.[42, 49-50] Although routine use of continuous hemofiltration may proof beneficial in reducing fluid overload and decreasing circulating inflammatory mediators, the use of hemofiltration in post cardiac surgery patients on ECMO with acute kidney failure has been associated with a higher mortality.[51-52] It is likely that the higher mortality found in these patients reflects decreased organ perfusion and organ failure more than the use of hemofiltration itself. The risks and benefits of optimizing treatment regimens with diuretics as well as the use of continuous venovenous hemofiltration have yet to be evaluated.

Infection on ECMO

In 14% of all neonates and 37% of all children with respiratory failure infection is the primary diagnosis leading to ECMO support. [ELSO database January 2010] As ECMO patients should be considered a compromised host, due to alterations in the immune system and decreased natural barriers due to indwelling cannulas and central venous lines, the prevention of nosocomial infections remains a challenge in the treatment of patients on ECMO.[53] Rates of nosocomial infections on ECMO differ between 0.6% and 26% depending on definitions.[54-57] The ELSO registry report of 2010 showed proven infection rates of 6% in neonates and 18% in pediatric patients on ECMO.
PK data for antibiotics in ECMO patients are scarce. Antibiotic use varies per center depending on local protocols and resistance patterns. Although many authors report prophylactic antibiotic use for 24 to 72 hours after cannulation effectiveness of antibiotic regimens are still unknown. To date there are no international guidelines for

antibiotic treatment during ECMO support. The most frequently reported antibiotics used in children on ECMO are; ampicilin, vancomycin, gentamicin and cephalosporin's. [54-55, 57-58] To the best of our knowledge only gentamicin and vancomycin PK have been studied in children on ECMO[9-13]. This lack of pharmacokinetic data may lead to suboptimal dosing of antibiotics and antiviral drugs. This potentially results in prolonged infection, multi drug resistant pathogens and drug related toxicity.
The generation of new pharmacokinetic data on antibiotics in ECMO patients is therefore of paramount importance, especially since nosocomial infections are associated with higher infection rates and consequent morbidity and mortality.[54, 58-59]
Diagnosing nosocomial infections and sepsis during ECMO remains a challenge. In 2005 Goldstein et al published definitions for sepsis and organ dysfunction in pediatrics.[60] These definitions were developed to facilitate clinical trials by differentiating SIRS, sepsis and septic shock based on age specific clinical and laboratorial findings. The Center for Disease Control and Prevention (CDC) criteria for nosocomial infections incorporate the same clinical parameters. Diagnosing sepsis or other infections in ECMO patients is difficult as most clinical parameters are either controlled by, or highly dependent of ECMO support. Also laboratory parameters are influenced by the ECMO circuit. These limitations potentially delay adequate treatment, or result in unnecessary and prolonged antibiotic use in these patients.[54, 57]

Aim and outline of the thesis

The overall aim of this thesis is to:

- Develop evidence based guidelines for the management of sedation, fluid overload and infections in neonates and children on ECMO and
- Optimize drug therapy in neonates and children on ECMO.

Given these universal problems in ECMO patients and the lack of evidence based guidelines a number of studies were performed to:

Part I

- Assess the extent of adsorption of drugs to several different ECMO circuits.

Part II

- Evaluate a standardized sedation protocol in ECMO patients and to identify the risk factors for increased sedative requirements.
- Study the feasibility of sedation interruption in neonates on ECMO.

Part III

- Evaluate two treatment protocols for fluid overload management in neonates on ECMO.

Part IV

- Describe infection rates and antibiotic use in neonates and older children on ECMO and identify markers for sepsis on ECMO.
- Develop evidence based dosing regimens for antibiotics and antiviral drugs administered during ECMO.

Part I

The effect of the ECMO circuit on several commonly used drugs in ECMO patients was studied in an *in vitro* model comparing used vs. new circuits; pediatric vs. neonatal circuits and centrifugal vs. roller pump circuits. The results are described in **chapter 2**.

Part II

In **chapter 3** the results of an observational study evaluating the performance of a standardized sedation protocol in neonates and children on ECMO are discussed. A standardized sedation and analgesia protocol based on validated scores was evaluated over a 2.5 year period. Risk factors for increased sedative requirements were identified. Novel strategies to reduce sedative use include daily interruption protocols. The results of an observational study evaluating feasibility of sedation interruption in 20 neonates on ECMO are described in **chapter 4**.

Part III

Two studies evaluating different strategies of fluid management in ECMO patients are discussed in chapter 5 and 6. **Chapter 5** evaluates effectiveness and safety of continuous furosemide infusions in ECMO patients, while **chapter 6** describes the results of a retrospective case-comparison study evaluating the effect of continuous venovenous hemofiltration (CVVH) on duration of ECMO, mechanical ventilation and transfusion needs.

Part IV

The results of a prospective observational study describing markers for sepsis, antibiotic use in ECMO patients and nosocomial infection rates are covered in **chapter 7**.

A prospective observational study to collect pharmacokinetic and pharmacokinetic data from neonates and children on ECMO was conducted in the Intensive Care of the Erasmus MC Sophia Children's Hospital, in collaboration with the Department of Pharmacy. By using blood samples taken during routine care and medication data from the patient data management system, drug concentrations could be determined and pharmacokinetic models created. **Chapter 8 and 9** describes pharmacokinetic data of cefotaxime and oseltamivir from this study. A population pharmacokinetic model was developed for cefotaxime and desacetylcefotaxime. Oseltamivir and its active metabolite oseltamivir carboxylate plasma levels were determined in three ECMO patients treated for H1N1 influenza during the pandemic outbreak in the fall of 2009.

The general discussion in **chapter 10** provides recommendations for treatment protocols and suggestions for future research.

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PART I

Extracorporeal membrane oxygenation: drug losses

CHAPTER 2

Determinants of drug absorption in different ECMO circuits

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PART II

Sedation and analgesia on ECMO

CHAPTER 3

Sedation and analgesia in children on extracorporeal membrane oxygenation (ECMO): are we performing well?

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CHAPTER 4

Feasibility of sedation and analgesia interruption following cannulation in neonates on extracorporeal membrane oxygenation (ECMO)

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Abstract

Introduction: In most ECMO centers patients are heavily sedated to prevent accidental decannulation and bleeding complications. In ventilated adults not on ECMO daily sedation interruption protocols improve short and long-term outcome. This study aimed at evaluating safety and feasibility of sedation interruption following cannulation in neonates on ECMO and document plasma levels of morphine, midazolam and metabolites before restart of medication.

Methods: Prospective observational study in 20 neonates (0.17-5.8 days of age) admitted for ECMO treatment. Midazolam (n=20) and morphine (n=18) infusions were discontinued within 30 minutes after cannulation. Pain and sedation were regularly assessed using COMFORT-B and Numeric Rating Scale (NRS) pain scores. Midazolam and/or morphine were restarted and titrated according to protocolized treatment algorithms. Blood samples were taken before re-introduction of midazolam and morphine to determine drug and metabolite concentrations.

Results: Median (IQR) time without any sedatives was 10.3 (5.0-24.1) hours. Median interruption duration for midazolam was 16.5 (6.6-29.6) hours and for morphine 11.2 (6.7-39.4h) hours. During this period no accidental extubations, decannulations or bleeding complications occurred. Median (IQR) overall COMFORT-B during interruption time was 9 (8-10). Median (IQR) NRS during interruption time was 1(0-2).

Midazolam, morphine and metabolite plasma levels at restart of medication were (median (IQR)): midazolam 107 (48-184) ng/ml, alfa-hydroxymidazolam 51 (23-69) ng/ml, alfa-hydroxymidazolamglucuronide 604 (406-1120) ng/ml, morphine 7 (< 5 -12) ng/ml, morphine-3-glururonide (M3G) 73 (29-80) ng/ml and morphine-6-glururonide (M6G) 16 (7-24) ng/ml.

Conclusion: This is the first study to show that interruption of sedatives and analgesics following cannulation in neonates on ECMO is safe and feasible. Interruption times are 2-3 times longer than reported for adult ICU non ECMO patients. In the present study single time interruption of sedatives and analgesics leads to lower plasma concentrations while maintaining adequate sedation. Further trials are needed to substantiate these findings and evaluate outcome benefits.

Introduction

ECMO is a type of cardio-pulmonary bypass for patients with pulmonary or circulatory failure unresponsive to conventional treatment. Most patients are heavily sedated to prevent either accidental decannulation or impeded ECMO flow due to movement or suboptimal cannula position. Although local protocols may vary midazolam, morphine and fentanyl are most frequently used in neonatal and pediatric intensive care units (PICU's) during ECMO.[1] Sedation guidelines for PICU patients are not quite satisfactory; they lack high quality evidence and exclude neonates and ECMO patients.[2-3]
ECMO support is associated with increased sedative use in neonates.[4] Prolonged and high cumulative doses of opioids and benzodiazepines have been associated with tolerance, physical dependency and consequently withdrawal syndrome in neonates and children.[5-13] Several authors have, for example, reported opioid withdrawal syndrome in the post ECMO period.[14-16] In addition, experimental animal studies suggest morphine induced neural apoptosis.[17-18]
Strategies to decrease cumulative doses and duration of continuous infusions include daily interruption, or even complete withholding, of continuous sedation.[19-24] The latter strategies both were shown to significantly reduce total cumulative doses of sedative drugs without an increase in complications. More importantly, ventilator free days, length of ICU stay and occurrence of posttraumatic stress syndrome were also significantly reduced.[19-24] Two meeting reports on daily interruption in children presented a reduction of midazolam dose in the intervention group; both studies lacked power to show an effect on mechanical ventilation or ICU stay.[25-26] Although inconclusive these studies indicate that daily interruption of sedatives in critically ill patients is feasible and safe. To our knowledge, there are no such data on neonates or children on ECMO support.
The aim of our study is therefore to evaluate safety and feasibility of initial interruption of analgesia and sedatives in neonates following cannulation for ECMO.

Methods

Study design and setting

Prospective observational cohort study.
The Erasmus MC Sophia Children's Hospital Rotterdam serves as a level III referral center. It is one of two designated pediatric ECMO centers in The Netherlands with 30 to 40 ECMO runs per year including all age groups and indications (respiratory, circulatory and cardiac). The institutional medical ethics committee review board approved the study, and informed consent was obtained from the parents or legal representatives. Criteria

for ECMO treatment were: gestational age > 34 weeks, birth weight > 2.0 kg, mechanical ventilation < 7 days, an alveolar arterial oxygen difference greater than 600 mm Hg, and an oxygenation index > 25 for more than 6 hours.

Patients

All neonates < 7 days old admitted for ECMO in one year were eligible for enrolment. Patients expected to die within 24 hours after start of ECMO were excluded. All patients received standardized anesthesia during cannulation consisting of fentanyl 5µg/kg bolus injection, morphine 50µg/kg/hr and midazolam 200µg/kg/hr continuous infusion during cannulation. On ICU admission severity of illness was assessed using the Score for Neonatal Acute Physiology Version II (SNAP II) and the Score for Neonatal Acute Physiology, Perinatal Extension,Version II (SNAPPE II scores.)

Sedation and analgesia assessment

Pain and sedation are routinely measured in our unit by the attending nurse using NRS and COMFORT-B scores.[27-28] The COMFORT-B score is a validated behavior scale for neonates and infants. It rates 6 behavioral and physiologic dimensions of distress, each scored on a subscale from 1 to 5 resulting in a overall score between 6 and 30.[28] NRS score is an analogue scale from 0-10 reflecting zero till worst pain possible.

According to study protocol, morphine and midazolam infusions were discontinued 30 -60 minutes after cannulation, if sedation was considered adequate based on COMFORT-B and NRS scores. Medication was resumed and adjusted on the guidance of COMFORT-B and NRS scores that were performed every three hours, and on indication. When the COMFORT-B was 17 or higher continuous midazolam 100µg/kg/hr was started after a loading dose of 200µg/kg. Morphine 10µg/kg/hr was started after a loading dose of 100µg/kg when NRS was 4 or higher, when sedation was ineffective with midazolam (>300µg/kg/hr), or at the discretion of the attending medical team. COMFORT-B and NRS scores were determined before medication was started.
Fentanyl was used prior to potentially painful or uncomfortable interventions, or as rescue medication when morphine or midazolam were insufficient.
Blood samples were taken 3, 6, 9, 12, 24 hours after midazolam and morphine were discontinued and before midazolam or morphine was restarted.
Restart of medication was defined as any bolus injection or restart of continuous infusion of midazolam or morphine.

Laboratory analyses

Blood samples (500 µL) were taken from a venous access port on the ECMO circuit and collected in heparinized tubes. After centrifugation (5 min, 4000 × g), the supernatant serum was stored at -80°C until analysis. Midazolam and alpha-hydroxymidazolam concentrations in serum were measured in each sample using high-performance liquid chromatography (HPLC-UV) as previously described [29]. Midazolam and alpha-hydroxymidazolam were quantified after a liquid-liquid extraction with dichloromethane. Hydroxymidazolamglucuronide was measured as alpha-hydroxymidazolam after enzymatic deglucuronidation. The limits of quantification (LOQ) were 11 and 6 mg/l for midazolam and alpha-hydroxymidazolam respectively, which corresponds to 10 mg/l for hydroxymidazolamglucuronide. Intra- and inter-assay coefficients of variation were less than 8% and 13%, respectively. Morphine serum concentrations were assessed by HPLC. Plasma 0.2 ml was mixed with 0.2 ml of 0.01 M-ammonium hydrogen carbonate (pH 9.3) and spiked with 75µl of appropriate dilutions of stock solutions of internal standards (Morphine-d3 at 37.5 ng/ml; M3G-d3 and M6G-d3 at 18.75 ng/ml). The supernatant was extracted with solid phase columns (BOND ELUT C18.1 ml and 100mg). The eluate was evaporated to dryness under nitrogen. The residue was dissolved in 75 µl of mobile phase, a mixture of acetonitrile and 10 mM of ammonium formate (pH 3.0) with formic acid (8/92, v/v) and was splitted with a ratio of 1/5 at the entrance of the mass spectrometer. A quadripole mass spectrometer (PE SCIEX API 150EX, Toronto, Ontario, Canada) equipped with a turbo ionspray interface was used for signal detection. The intra-assay for all concentrations tested was below 10%. The inter-assay variability coefficient for calibration standards and quality controls was also below 10%.

Outcome measurements

The primary aim of the study was the feasibility of sedation interruption following cannulation for ECMO in neonates; using time till restart of medication as a primary outcome measure. Secondary outcome measures were plasma concentrations of morphine, midazolam and there metabolites during the interruption period, the need for rescue medication and rate of complications defined as: extubations, decannulation and impairment of ECMO flow by 50%.

Statistical analysis

All statistical analyses were performed using Graphpad Prism version 4.03 (Graphpad Software Inc, La Jolla Ca, USA). All values are presented in median (Interquartile range) unless indicated otherwise. Differences between groups were tested for their statistical significance by Mann-Whitney non parametric test for unpaired data. A p-value <0.05 was considered significant. For correlation analyses the Spearman signed rank test was used.

Results

Patient characteristics

Twenty seven patients received ECMO support during the study period. Twenty-one met the inclusion criterion, but one of them died within 24 hours after cannulation. So the analysis included 20 patients. Median postnatal age was (range) 0.79 (0.17-5.8) days. (table 1) All patients received midazolam median (IQR) 110 (100-200) µg/kg/hr and morphine 10.9 (10-20) µg/kg/hr before cannulation. Five patients received phenobarbital for suspected convulsions before cannulation for ECMO. One patient received phenobarbital during the interruption of medication on ECMO for suspected convulsions. Twelve patients received vecuronium bromide prior to ECMO. All patients received inotropic support and antibiotics.

Table 1. Clinical characteristics

Patients (n)	20	
female/male (n)	10/10	
Mortality (%)	25%	
CDH	7	
MAS	10	
Pneumonia	1	
Sepsis	1	
Pulmonary Valve Atresia	1	
	Median(IQR)	*(Range)*
SNAP II	16 (16-23)	(26-35)
SNAPPE II	33 (16-34)	(16-54)
Oxygenation index prior to ECMO	38 (21-54)	
AaDO2 prior to ECMO (in mmHg)	599 (522-624)	
Age (days)	0.79 (0.29-3.4)	(0.17-6.8)
Length of ECMO (hours)	123 (88-218)	(53-462)
Gestational Age (weeks)	40 1/7 (38 1/7-41 4/7)	(35/ 5/7-42 3/7)
Birth Weight (kg)	3,1 (2.8-3.6)	(2.3-4.0)
Morphine dose pre-ECMO (µg/kg/hr)	10.9 (10-20)	(8.8-33)
Midazolam dose pre-ECMO (µg/kg/hr)	110 (100-200)	(50-220)

Data presented are number of patients or median values(IQR)(Range)
CDH Congenital Diaphragmatic Hernia, MAS Meconium Aspiration Syndrome, AaDO2 Arterial alveolar Oxygen Difference

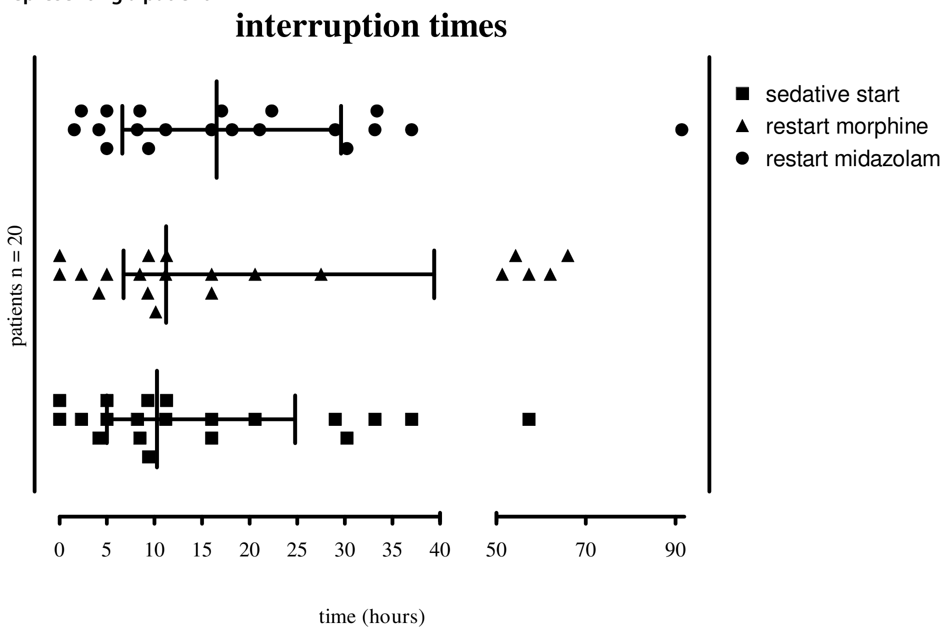
Sedation interruption

Midazolam was discontinued in all 20 patients; morphine in 18. Median interruption time for both drugs combined was 10.3 hours (IQR 5.0-24.1 h). Median interruption time for midazolam was 16.5 hours (IQR 6.6-29.6); median interruption time for morphine was 11.2 hours (IQR 6.7-39.4h). (figure 1) In six patients midazolam was reintroduced conform protocol. In seven of twenty patients (35%) (including the two patients were morphine was not discontinued) morphine was restarted before midazolam. In seven patients (35%) midazolam and morphine were restarted simultaneously.

Interruption times were shorter for patients with higher cumulative doses of midazolam or morphine (r= -0.54, p=0.013 and r= -0.58, p= 0.008), respectively. Interruption times for patients with meconium aspiration syndrome (MAS) were shorter than for patients with other diagnoses; the difference did not reach statistical significance (6.8 (3.2-15.2) hours vs. 16.0 (8.7-35.1) hours, p=0.07).

We did not find a difference in duration of interruption times (median (IQR)) between patients with and without concomitant phenobarbital use 9.8 (4.6-33) hours vs. 10.3 (3.6-24.7) hours, (p= 0.97), male and female patients 10.3 (3.7-29.6) hours vs. 9.9 (4.6-26.8) hours (p = 0.91) or survivors and non survivors 8.5 (4.2-20.5) hours,p = 0.1) vs. 16 (10.2-45) hours. There was no correlation between critical illness scores (SNAP II and SNAPPE II scores (r = 0.33, p= 0.1 and r = 0.15, p =0.7))and sedation interruption, (p=0.1).

Fig. 1 Individual interruption times of midazolam, morphine and of both sedatives. Each dot representing a patient



Safety

Cessation of analgesics and sedatives did not result in accidental decannulations or extubations during the interruption time. There were no periods with agitation resulting in impairment of ECMO flow, nor accidental bleeding.

Rescue medication

Three patients (15%) received fentanyl during the interruption period, one for perceived discomfort, manifested as unexplained hypertension, two for procedural analgesia.

Level of sedation

During midazolam and morphine interruption a median of four (IQR) (2.5-8.5) COMFORT-B and NRS Score measurements were taken per patient. Both COMFORT-B and NRS scores were low during sedation interruption (table 2). In seven patients (35%) midazolam or morphine was restarted on the guidance of a COMFORT-B score of 17 or higher. In the other 13 patients either no COMFORT-B was recorded at the moment of restart of medication (n=7), or midazolam or morphine was started despite a COMFORT-B or NRS score below the cut-off value (n=6). Reasons for start of medication in these patients were; perceived discomfort manifesting as unexplained cardiovascular or respiratory instability, or suspected discomfort in anticipation of a medical procedure. Median NRS and COMFORT-B at the restart of medication were 1 (0-2) and 17 (IQR) (11-18) respectively. Median NRS score was 0 (IQR) (0-0.5) and median COMFORT-B was 8.8 (IQR)(8-9.5).

Table 2. interruption duration, plasma levels, COMFORT-B and NRS at restart of medication

	Median	IQR	Range
Interruption duration	10:25h	5:00-24:10h	0:00-57:30h
COMFORT-B during cessation of medication	8.5	8-9	7-15
NRS	1	0-2	0-5
MDZ (n = 16)	107 ng/ml	47.7-184 ng/ml	36-750 ng/ml
1-OH_MDZ (n = 16)	51 ng/ml	23-69 ng/ml	6-109 ng/ml
1-OH-MDZ Gluc (n = 16)	604 ng/ml	406-1118 ng/ml	10-1741 ng/ml
MOR (n = 14)	7 ng/ml	<5-12 ng/ml	<5-37 ng/ml
M3G (n =15)	73 ng/ml	29-80 ng/ml	9-147 ng/ml
M6G (n =15)	16 ng/ml	7-24 ng/ml	3-37 ng/ml
COMFORT-B at restart of medication (n=13)	17	11-18	10-21

NRS Numeric Rating Scale, MDZ midazolam, 1-OH-MDZ Alfa-hydroxymidazolam, 1-OH MDZ Gluc Alfa-hydroxymidazolamglucuronide, MOR morphine, M3G Morphine-3-glucuronide, M6G Morphine-3-glucuronide

Plasma levels

During cessation of medication a total of 100 blood samples were taken. Midazolam and morphine plasma samples were collected in 16 and 15 patients respectively, during the interruption time. Results are shown in table 2 and 3. Longer interruption times were associated with lower plasma levels of morphine (r = -0.76, p = 0.0006), M3G (r = -0.55, p = 0.03), M6G (r = -0.52, p = 0.04) and alfa-hydroxymidazolamglucuronide (r = -0.57, p = 0.02). No correlation was found between interruption times vs. midazolam (r = -0.016, p=0.16) and alfa-hydroxymidazolam (r= 0.034, p= 0.89) concentrations.

Table 3. Plasma levels, COMFORT-B and NRS at median 3:09 hours (3:0-4:15), COMFORT-B and NRS after interruption of medication

		Median	IQR	Range
MDZ	(n = 16)	223 ng/ml	149-372 ng/ml	37-891 ng/ml
1-OH-MDZ	(n = 16)	66 ng/ml	48-113 ng/ml	18-141 ng/ml
1-OH-MDZ Gluc	(n = 16)	640 ng/ml	300-1220 ng/ml	159-1544 ng/ml
MOR	(n = 15)	29 ng/ml	12-36 ng/ml	8-42 ng/ml
M3G	(n = 15)	92 ng/ml	42-129 ng/ml	9-175 ng/ml
M6G	(n = 15)	21 ng/ml	10-31 ng/ml	3-43 ng/ml
COMFORT-B	(n= 16)	8	7-9	6-11
NRS	(n= 16)	0	0	0

NRS Numeric Rating Scale, MDZ midazolam, 1-OH-MDZ Alfa-hydroxymidazolam, 1-OH MDZ Gluc Alfa-hydroxymidazolamglucuronide, MOR morphine, M3G Morphine-3-glucuronide, M6G Morphine-3-glucuronide

Discussion

To our knowledge this is the first study that shows that prolonged interruption of sedatives and analgesics is feasible in neonates on ECMO. Our study also shows that this interruption leads to lower plasma concentrations of both morphine and midazolam than those previously reported in neonates on ECMO. There were no major complications associated with interruption of morphine or midazolam. Especially dislocations of ECMO cannulas or impaired ECMO flow were not reported.

On average patients remain adequately sedated for 10 hours after cessation of medication. This is much longer than reported in the adult population without ECMO.[19] Our study involved a single interruption period compared to daily interruption protocols used in adults, making it difficult to interpret the differences found in interruption times. The use of different drugs, different underlying diseases and differences in pharmacokinetics and pharmacodynamics in neonates compared to the adult ICU patients may contribute to the difference found in interruption times.

Pharmacokinetics of several drugs are altered in neonates on ECMO.[30-32] Higher volumes of distribution and decreased clearance of midazolam and morphine are reported [30, 32]. Prolonged elimination half life of these drugs could explain the long interruption times found in our study. However the plasma levels of midazolam and morphine in this study are much lower than reported previously in adequately sedated term neonates on ECMO; 103 ng/ml (IQR 41, 3-184) vs. 1400 ng/ml (range: 800–3200) ng/ml [4] for midazolam and 7, 5 ng/ml (IQR (<5-11, 5) vs. 32(7,1-50) [33] for morphine. Moreover plasma levels for both midazolam and morphine in critically ill preterm and term neonates without ECMO support are still 2-5 fold higher than our trough levels, and two fold higher than our plasma levels drawn three hours after cessation of medication.[34-39] The long interruption times can therefore not be contributed to elevated plasma levels.

Reported therapeutic morphine and midazolam plasma levels in neonates vary considerably and correlation between plasma levels and sedation scores are mostly absent due to high inter-patient variability. [4, 34, 38, 40-42] Despite this our data seem to suggest that adequate sedation can be achieved with less sedative use.

Alternatively, morphine and midazolam have active metabolites and both could significantly contribute to the sedative effects of these drugs, thereby increasing interruption times. Data on metabolites of morphine and midazolam in ECMO patients are sparse. The plasma concentrations found in this study are conform earlier studies in non ECMO neonates and children, and do not indicate altered accumulation of M6G or 1-OH-midazolam in our patients. [37, 40] Hence the interruption times found in this study can neither be contributed to altered pharmacokinetics of the drugs or their metabolites.

Potentially altered pharmacodynamics due to cannulation or ECMO treatment could play a role in the observed longer interruption times. It is therefore noteworthy that there is a negative correlation between cumulative doses of midazolam or morphine and interruption times. Patients in need of more sedation prior to ECMO treatment have shorter interruption times. Also high plasma concentrations of morphine, M3G, M6G and alfa-hydroxymidazolamglucuronide are associated with shorter interruption times. Most likely this reflects the large inter-variability and indicates no substantial difference in pharmacodynamics before and after cannulation.

The difference between our plasma levels and those presented by others may reflect differences in sedation protocols and sedation targets. Mulla et al. reported 100% effective sedation levels using validated sedation score. No reports are made regarding the percentage of necessary dose adjustments in this group.[4] Although most sedation protocols allow for decreasing sedative dose when patients are over sedated, during daily practice these dose adjustments are not always made.[40]

It could be argued that due to the study design our patients are under-sedated at the time of medication restart, and that trough levels are in effect representing inadequate drug levels in stead of the lower limit of effective plasma concentrations. Our results contradict this hypothesis.

In our study median overall COMFORT-B during the study period are low; 9 (IQR7-12). Ista et al. showed in pediatric ICU patients that a COMFORT-B below 11 indicates over sedation, whereas a COMFORT-B over 22 indicates under sedation. Low median COMFORT-B during the study period and predominant low COMFORT-B and NRS scores at time of restart of sedatives show that, if anything, sedation was reintroduced early in stead of late. [43] As with adult studies interruption of medication seems more effective in establishing appropriate sedation levels.

Critical evaluation showed a high percentage of protocol violation in this study. Either morphine was started prior to or simultaneously with midazolam (60%), or morphine was never discontinued (10%). In all but one patient NRS scores were below four indicating no need for opioids. Despite this morphine was started in all but one patient. Morphine was mostly was used as a sedative, either as a primary choice, or as an addition to midazolam, even when midazolam dose was below 300 μg/kg/hr. The attending physician was allowed to deviate from protocol based on the clinical assessment of the patient. In many neonatal ICU's morphine is the first drug of choice for sedation in ventilated (pre-) term infants. Therefore attending physicians may opt for morphine more easily than for midazolam. Secondly perceived painful procedures may have elicited the choice for morphine as a prophylactic analgesic. Due to these protocol violations it is impossible to discriminate between the sedative effects of midazolam and morphine in this study.

A second limitation lies in either missing or low COMFORT-B scores at restart of medication. In 13 patients midazolam or morphine was started despite low or absent COMFORT-B. In some instances medication was restarted due to procedures on ECMO (n=2) and scores were not performed.

In others, failure to perform scores may reflect the high workload for ICU nurses in treating these patients. Furthermore it may indicate a perceived failure of the COMFORT-B were the clinical assessment of the nurses are not reflected in higher COMFORT-B. In nine patients nurses indicated that the patient was uncomfortable or more awake than deemed necessary. Ista et al. showed in children on our ICU that interpretation of the COMFORT-B between 11 and 22 is difficult and may necessitate an additional score.[43]

Finally, fear of accidental decannulation or ECMO system failures may precipitate earlier restart of sedatives by both physicians and nurses. Therefore the observed interruption duration may be an underestimation, if the protocol would have been followed more faithfully.

Conclusions

Interruption of sedatives and analgesics is feasible and safe in neonates on ECMO without an increased risk of complications. Interruption times are 2-3 times longer than reported in the adult ICU patients. Single time interruption of sedatives and analgesics results in lower drug exposure while maintaining adequate sedation. Further trials are needed to substantiate these findings and evaluate outcome benefits such as a reduction in time on ECMO, mechanical ventilation and incidence of abstinence symptoms.

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PART III

Fluid management on ECMO

CHAPTER 5

An exploratory study with an adaptive continuous intravenous furosemide regimen in neonates treated with extracorporeal membrane oxygenation.

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Abstract

Introduction: Loop diuretics are the most frequently used diuretics in patients treated with extracorporeal membrane oxygenation (ECMO). In patients after cardiopulmonary bypass (CPB) surgery, the use of continuous furosemide infusion is increasingly documented. Because ECMO and CPB are 'comparable' procedures, continuous furosemide infusion is used in newborns on ECMO. We report the use of continuous intravenous furosemide in neonates treated with ECMO.
Methods: This was a retrospective observational study in neonates treated with continuous intravenous furosemide during ECMO.
Results: Thirty-one patients were included in the study. A median of 25 (9 - 149) hours after the start of ECMO, continuous furosemide therapy was started at a median rate of 0.08 (0.02 – 0.17) mg/kg per hr. The continuous furosemide dose was not changed in the individual patient. Seven patients received a furosemide bolus prior to, and five patients received additional loop diuretics during, the continuous infusion.
Urine production before continuous furosemide therapy was not significantly different between patients who received a furosemide bolus prior to the infusion and those who did not receive this bolus. (P = 0.29) Although a positive effect of the 'loading' bolus was observed in urine output in the first 24 hours, there was no statistical significant difference in urine output (P = 0.20) or in time to reach a urine output of 6 ml/kg per hour between patients. After 24 hours urine production remained median 6.2 ml/kg per hour irrespective of furosemide boluses. The forced diuresis was tolerated well, illustrated by stable hemodynamic parameters and a decrease in ECMO flow and vasopressor score over the observation period.
Conclusions: This is the first report on continuous intravenous furosemide therapy in newborns treated with ECMO. The used furosemide regimens used in this study varied widely in continuous and intermittent doses. However, all regimens achieved adequate urine output. An advantage of continuous, over intermittent, intravenous furosemide could not be documented. Furosemide dosing regimens should be developed for neonates treated with ECMO. In addition therapeutic drug monitoring studies are required to prevent furosemide toxicity since so far no data are available on serum furosemide levels in neonates treated with ECMO.

Introduction

Extracorporeal membrane oxygenation (ECMO) is performed in newborns for a variety of diagnoses such as meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), persistent pulmonary hypertension of the newborn (PPHN) and sepsis/pneumonia.[1] The ECMO circuit, like the cardiopulmonary bypass circuit (CPB), triggers an important inflammatory reaction and is clinically associated with the so-called capillary leakage syndrome, resulting in intravascular hypovolemia and renal hypoperfusion.[2] Hence the ECMO patient becomes usually increasingly edematous in the initial phase and diuretics are often used to enhance the diuresis to mobilize the fluid excess. Loop diuretics, generally given as intravenous bolus, are the most frequently used diuretics in patients treated with ECMO.[3]

Since the observation that continuous intravenous furosemide might be superior (especially in hemodynamic unstable patients) to intermittent administration in infants after cardiac surgery the use of continuous furosemide infusion is increasingly documented in patients after CPB surgery.[4-8] Although there are no data available evaluating the use of continuous intravenous furosemide in newborns during venoarterial (VA) ECMO, in our unit continuous furosemide infusion is used increasingly in newborns treated with ECMO because ECMO and CPB are 'comparable' procedures.

Although the dosing schedule is largely empirical in this group of patients with varying renal function and altered pharmacokinetics (PK), the current practice is to start with low furosemide infusion rate (0.05 - 0.1 mg/kg/hr).[3, 9]

We retrospectively studied the use of continuous intravenous furosemide in neonates treated with VA ECMO, over a two year period. In addition in neonates who did not receive continuous intravenous furosemide during VA ECMO, urine production, cardiovascular status and furosemide dose were evaluated.

Materials and methods

The study was performed at the pediatric surgical intensive care unit (ICU) of the Sophia Children's Hospital of Erasmus Medical Centre in Rotterdam, the Netherlands. This ICU serves as one of the two designated ECMO centers in the Netherlands. The medical records of all neonates, who received ECMO treatment between October 2002 and October 2004, were screened for the use of continuous intravenous furosemide during ECMO treatment and consequently studied by means of chart review in combination with data available in the electronic patient data management system.

Demographic and clinical data recorded included gestational and postpartum age, gender, weight, diagnosis, ECMO flow and duration of ECMO treatment, time (after starting

ECMO) continuous furosemide infusion was started, dose and duration of continuous intravenous furosemide, additional loop diuretics, inotropic support and fluid intake. The following variables were measured before and at regular time intervals during the study for a maximum of 72 hours: urine-output, heart rate, mean arterial blood pressure and serum albumin, creatinine and urea levels.
Continuous intravenous furosemide was started at the time the patient was hemodynamically stable. The patient was considered hemodynamically stable if there was no need for ongoing fluid resuscitation and/or increase in inotropic support. The amount of inotropic support was measured by the vasopressor score.[10-11]
During continuous intravenous furosemide therapy serum electrolyte levels (sodium, potassium, calcium and magnesium) were closely monitored and supplements were given if necessary.

Statistical analysis

All data are represented as median (range) unless indicated otherwise.
Wilcoxon two-sample tests were used for comparison between the different furosemide regimens.

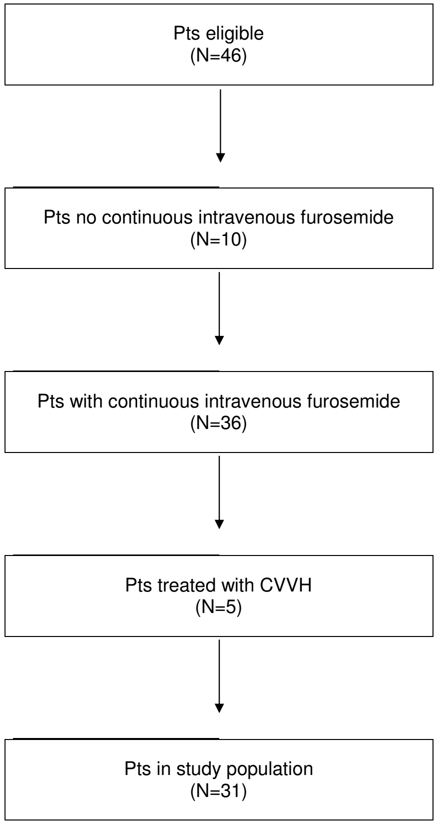
Results

Patients with continuous intravenous furosemide during VA ECMO

General

Forty-six patients in whom VA ECMO was performed were eligible for the study. Ten patients were excluded from the study because they did not receive continuous intravenous furosemide during ECMO. Thirty-six patients were enrolled in the study. Five patients were excluded from analysis since they were treated with continuous venovenous hemofiltration (CVVH). Three patients were treated with CVVH because of acute renal failure (median creatinine 90 µmol/l and urea 22.7 mmol/l) and two patients were treated from the start of ECMO with CVVH (trial). Thirty-one patients were analyzed (figure 1).
The study population consisted of 12 female and 19 male patients. Median gestational age was 40 (35 - 43) weeks. On admission median postpartum age was 1 (0 - 16) days and median weight was 3.5 (2.3 - 5.2) kg. ECMO was performed for MAS in 10 patients, for CDH in 13 patients, for sepsis/pneumonia in five patients, for PPHN in two patients and for cardiomyopathy in one patient. ECMO was started median 4 (0 - 46) hours after admission. All patients were weaned from ECMO after median 127 (44 - 339) hours. The median

Figure 1 study flow chart



admission time in the ICU was 11 (3 - 186) days. Due to recurrent and therapy resistant pulmonary hypertension five patients with CDH died before discharge form the ICU.

Furosemide regimen

Prior to the start of continuous intravenous furosemide seven patients received a furosemide bolus IV (dose 1 [0.4 - 2.4] mg/kg). Continuous intravenous furosemide therapy was started median 25 (9 - 149) hours after the start of ECMO at a median rate of 0.08 (0.02 - 0.17) mg/kg/hr. The continuous furosemide dose in the patients who received a bolus prior to the infusion was 0.08 (0.04 - 0.13) mg/kg/hr; in the patients who did not receive a bolus, the dose was 0.08 (0.02 - 0.17) mg/kg/hr. The furosemide dose was not changed in the individual patient during the study period. The total administered continuous furosemide dose over 24 hours was median 1.92 (0.48 - 4.08) mg/kg.
During the study period five patients received additional loop diuretics, four patients received a total median furosemide dose of 7 (5.6 – 10.8) mg/kg and one received a total bumetanide dose of 0.1 mg/kg. The total administrated continuous and intermittent

Table 1

	Furosemide	regimen			
Furosemide	before	0-24 hrs	24-48 hrs	48-72 hrs	0-72 hrs
Furosemide bolus IV					
Patients (N)	7	4	2	1	4
Dose (mg/kg.24hrs)	1.0 (0.4 - 2.4)	1.1(1.0 - 3.6)	3.3(1.0 - 3.6)	3.6	
Dose (mg/kg.72hrs)					7(5.6 - 10.8)
Bumetanide bolus IV					
Patients (N)			1		1
Dose (mg/kg.24hrs)			0.1		
Dose (mg/kg.72hrs)					0.1
continuous IV Furosemide					
Patients (N)		31	25	23	
dose (mg/kg/hr)		0.08(0.02 - 0.17)	0.08(0.02 - 0.17)	0.08(0.02 - 0.17)	

data are represented as median (range)

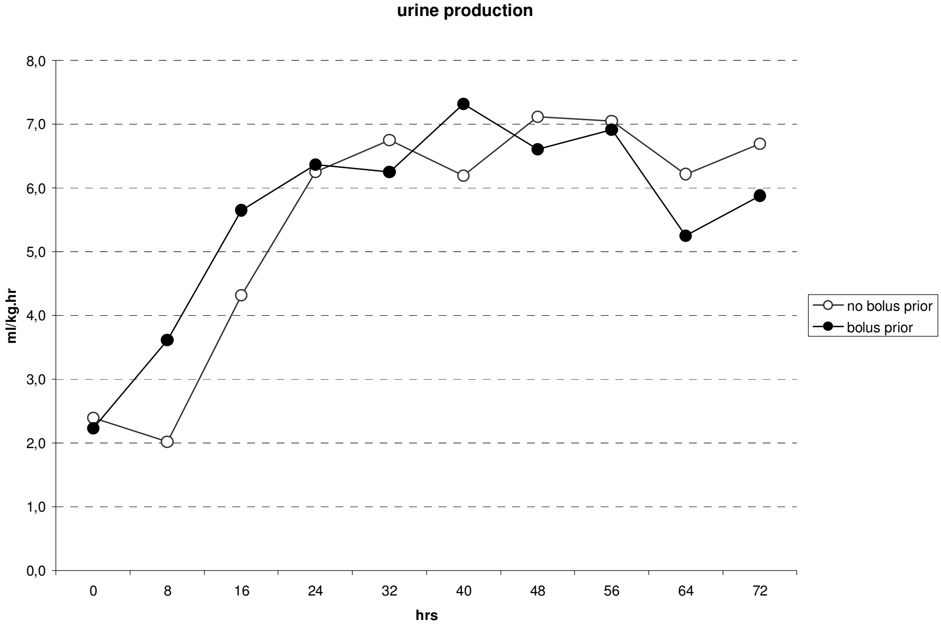
intravenous furosemide doses on the first, second and third days of the study was 1.92 (0.48 – 6.6), 1.92 (0.96-6.6) and 2.0 (0.5-6.6) mg/kg per 24 hrs, respectively. The furosemide regimen is depicted in table 1.In 10 patients continuous furosemide infusions were discontinued a median 2 (0 - 144) hours before cannulation and in 21 patients it was discontinued a median of 25 (4 - 623) hours after decannulation. The duration of the continuous furosemide infusion during ECMO was median 98 (21 - 294) hours, which is in accordance with median 80% (29% - 95%) of the ECMO time.

Furosemide effects

In the patients (n = 7) who received a furosemide bolus prior to the continuous infusion, median urine production before the start of continuous infusion was 2.2 ml/kg/h hour; in the patients (n = 24) who did not receive this furosemide bolus, it was 2.4 ml/kg/h, ($p = 0.29$). Median urine production increased to 3.6, 5.7 and 6.4 ml/kg/h respectively after 8, 16 and 24 hours of furosemide infusion in the patients (n = 7) who received a furosemide bolus prior to the continuous infusion; in the patients (n = 24) who did not receive a furosemide bolus, urine production values were 2.0, 4.3 and 6.3 ml/kg/h, respectively, ($p = 0.10$). The time that a urine production of 6 ml/kg/h was reached in the patients with and without bolus prior to the continuous infusion was not significantly different, ($p = 0.20$).

Median urine production remained 6.2 ml/kg/h after 24 hours of continuous furosemide infusion in all patients irrespective of a bolus prior to the continuous furosemide infusion. The urine production is shown in figure 2.

Figure 2 The line with closed circles depicts the median urine production of the patients (N=7) who received a furosemide bolus prior to the continuous infusion. The line with open circles depicts the median urine production of the patients (N=24) who did not receive a furosemide bolus prior to the continuous infusion.



Fluid balances, calculated over eight hour intervals, was median +79.4 ml before the start of continuous furosemide infusion in the patients who received a furosemide bolus prior and +98.0 ml in the patients who did not receive this bolus. Median fluid balances in the patients who received a furosemide bolus were +76.9 ml, -21 ml and -10.5 ml, respectively after 8, 16 and 24 hours of continuous furosemide therapy. In the patients who did not receive a furosemide bolus prior to the furosemide infusion the median fluid balances after 8, 16 and 24 hours of continuous furosemide therapy were +106.4 ml, +28.2 ml and +12.0 ml, respectively.

ECMO regimen

The priming volume of the ECMO circuit was approximately 350 ml, the solution consisted of albumin and packed red blood cells, and the initial median ECMO flow was 130 (82-185) ml/kg/min, equaling 80% of the total cardiac output.

Median ECMO flow at the start of the continuous furosemide and after at 8, 24, 48 and 72 hours of continuous furosemide were 87 (31-147) ml/kg/min, 86 (15-144) ml/kg/min, 76 (13-153) ml/kg/min, 50 (14-95) ml/kg/min and 59 (14-90) ml/kg/min. The ECMO flow in the CDH patients was not significantly different.

Cardiovascular effects

Median mean arterial pressure and heart rate at the start of ECMO and at the start of the furosemide treatment were 50 (38 - 78) mm HG and 167 (102 – 237) beats per minute and 51 (37 - 74) mm HG and 138 (88 - 198) beats per minute, respectively. Median blood pressure and heart rate after 8, 24, 48 and 72 hours of furosemide treatment were 52 (38 - 72) and 134 (109 - 171) beats per minute, 52 (37 - 127) mm HG and 140 (107 - 185) beats per minute, 54 (40 - 80) mm HG and 143 (94 - 196) beats per minute, and 51 (40 - 65) mm HG and 145 (98 - 189) beats per minute, respectively. All cardiovascular parameters were within the normal range for age. [12-13] All patients remained cardiovascular stable during the administration of continuous intravenous furosemide and the inotropic support was gradually decreased during the observation period illustrated by the vasopressor score. The number of patients requiring inotropic support was decreased during the study from 25/31 (81%) to 16/31 (52%). Median vasopressor score at start ECMO was 11 (0-196) and at the start of the continuous furosemide infusion 5 (0 - 170), respectively. Median vasopressor scores after at 8, 24, 48 and 72 hours of continuous furosemide were 5 (0 - 170), 5 (0 - 170), 5 (0 - 170) and 5 (0 - 30) respectively. Inotropic support was significantly higher in the CDH patients. Median vasopressor score of the CDH patients at start ECMO at the start of continuous furosemide infusion and after 8, 24, 48 and 72 hours of continuous furosemide infusion were 33 (0 - 170), and 20 (0 - 170), 20 (0 -170), 20 (0 - 170), 17 (0 - 170) and 12.5 (0 - 30), respectively.

Renal function

Median serum creatinine levels at start ECMO and at start continuous intravenous furosemide infusion were respectively 55 (14-90) μmol/l and 52 (14 - 90) μmol/l. Median serum creatinine levels after 24, 48 and 72 hours of continuous intravenous furosemide treatment were 50 (19 - 79) μmol/l, 49 (20 - 79) μmol/l and 43 (22 - 66) μmol/l, respectively. Median serum urea levels at start ECMO and at start of continuous intravenous furosemide were 3.1 (1-9.7) mmol/l and 2.8 (1.3 – 6.5) mmol/l. After 24, 48 and 72 hours of furosemide infusion, median serum urea levels were 4.0 (1.5 - 23) mmol/l, 4.4(1.5 - 8.6) mmol/l and 5.4 (1.3 – 11.6) mmol/l, respectively. Median serum albumin levels at start ECMO and at start furosemide infusion were 16 (4-27) g/l and 27 (16 - 36) g/l. During continuous intravenous furosemide treatment, median serum albumin levels were 27 (21 - 36) g/l, 29 (16 - 41) g/l and 30 (24 - 40) g/l after respectively 24, 48 and 72 hours, respectively.

Patients who did not receive continuous intravenous furosemide during VA ECMO

General

Ten patients did not receive continuous intravenous furosemide during ECMO. Two patients were excluded from this evaluation because they were treated with CVVH. One patient was treated with CVVH because of acute renal failure (creatinine 74 µmol/l and urea 4.8 mmol/l) and the other patient was treated from the start of ECMO with CVVH (trial). Eight patients were evaluated.

This group consisted of five female and three male patients. Median gestational age was 40 (36 - 42) weeks. On admission median postpartum age was 1 (0 - 6) days and median weight was 3.3 (1.9 – 3.7) kg. ECMO was performed for MAS in three patients, for CDH in two patients, for sepsis in two patients and in one patient for pulmonary hypertension after pneumonectomy due to congenital cystic adenomatoid malformation of the lung. ECMO was started median 0 (0 - 198) hours after admission. Seven patients were weaned from ECMO after median 98 (8 - 275) hours. The median admission stay in the ICU was 6 (0 - 22) days. One patient with sepsis died on ECMO.

Furosemide regimen

Only four patients received intermittent intravenous furosemide. One patient received the first bolus 32 hours before the start of ECMO, and the other two patients started with intermittent furosemide after 18 and 159 hours, respectively, after the start of ECMO. The furosemide dose doses before ECMO and on the first, second and third days after start of ECMO were 1.84 mg/kg per 24 hrs, and 1 mg/kg per 24 hrs, 5 mg/kg per 24 hrs and 5 mg/kg per 24 hrs., and 1 mg/kg per 24 hrs in the patient who started furosemide after 159 hrs on ECMO.

Urine production-fluid balance

Median urine production after 24, 48 and 72 hours on ECMO were 4.4 ml/kg/h, 5.4 ml/kg/h and 5.6 ml/kg/h. Median fluid balance after 24, 48 and 72 hours on ECMO were +173 ml, +34 ml and +11.9 ml.

ECMO regimen

The priming volume of the ECMO circuit was approximately 350 ml and the solution consisted of albumin and packed red blood cells, and the initial median ECMO flow was 146 (111-161) ml/kg/min, equaling 80% of the total cardiac output. Median ECMO flow rates after 24, 48 and 72 hours on ECMO were 135 (56-189) ml/kg/min, 116 (80-126) ml/kg/min and 116 (80-126) ml/kg/min.

Cardiovascular effects

Median mean arterial blood pressure and heart rate at the start of ECMO and after 24, 48 and 72 hours on ECMO were 45 (30-79) mm Hg and 148 (112-291) beats per minute, 48 (43-56) mm Hg and 146 (93-171) beats per minute, 47 (42-55) mm Hg and 130 (107-162) beats per minute, and 51 (48-56) mm Hg and 124 (114-180) beats per minute, respectively. At the start of ECMO and after 24, 48 and 72 hours on ECMO a total of eight, five, four and four patients received inotropic support. Median vasopressor scores at the start of ECMO and after 24, 48 and 72 hours on ECMO were 23 (2-85), 5 (0-42) and 5 (0-40), respectively.

Renal function

Median serum creatinine levels at the start of ECMO and after 24, 48, and 72 hours on ECMO were 47 (21–121), 45 (24–55), 47 (24–87), and 38 (25–85) μmol/l, respectively. Median serum urea levels at the start of ECMO and after 24, 48, and 72 hours on ECMO were 2.9 (0.9–10.0), 2.3 (0.9–9.3), 2.4 (1.5–8.5), and 3.5 (1.7–6.5) mmol/l, respectively. Median serum albumin levels at the start of ECMO and after 24, 48, and 72 hours on ECMO were 24 (21–35), 27 (24–30), 28 (26–30), and 27 (24–32) g/l, respectively.

Discussion

Diuretics, especially loop diuretics are the mainstay in the enhancement of diuresis in patients treated with ECMO. Contrary to the extensive pharmacokinetic/pharmacodynamic (PK/PD) research on (loop) diuretics in preterm and term neonates, very limited research has been performed on (loop) diuretics in neonates treated with ECMO.[3, 14]
Wells and colleagues[3] studied the PK/PD of bumetanide in 11 term neonates treated with ECMO and reported that the steady state volume of distribution and the elimination half-life were greater than comparable values reported in previous studies of bumetanide disposition in premature and term neonates without ECMO while the plasma clearance was similar for both groups. Although significant diuresis, natriuresis and kaliuresis were observed with 0.1 mg/kg, the duration of the effects was less than expected given by the prolonged renal elimination.
Since the observation that continuous intravenous furosemide might be superior (especially in hemodynamic unstable patients) to intermittent administration in infants and children after CPB surgery continuous furosemide infusions have been increasingly used in patients after cardiac surgery.[4-7] Trials, assessing efficacy and safety of continuous versus intermittent intravenous furosemide in pediatric patients after CPB surgery revealed that the total furosemide dose administered by continuous infusion was generally less than the dose by intermittent administration.[5-8] No significant dif-

Table 2 Furosemide trials

Furosemide	Singh prospective RCT 24 hours (1992)	Luciani prospective RCT 24 hours (1997)	Klinge prospective RCT 72 hours (1997)			Van der Vorst prospective observational study 72 hours(2001)		
Intermittent								
Patients	12	15	23					
Continuous								
Patients	8	11	23			12		
Intermittent								
Age	1.44(±1.4)yr	3.7(±3.4)m	2.4(± 2.1)yr					
Continuous						13(0-33)wk*		
Age	2.3(±2.2)yr	1.8(±2.5)m	3.4(±3.1)yr					
P-value	NS	0.1	NS					
Study day			1	2	3	1		
intermittent dose mg/kg/hr	6.23(±0.62)	6.8(±1.2)	1.6(±0.6)	0.9(±0.5)	1.0(±0.5)			
continuous dose mg/kg/hr	4.9(±1.78)	2.5(±0.3)	2.1(±0.7)	1.7(±0.6)	1.7(±1.0)	2.2(±0.4)	4.2(±1.1)	3.6(±1.3)
P-value	0.045	0.001	0.014	0.0003	0.014			
intermittent UO (ml/kg/hr	3.53(±4.1)	3.3(±1.1)	3.1(±0.8)	2.9(±1.1)	2.9(±1.0)			
continuous UO (ml/kg/hr	3.36(±1.79)	2.5(±1.1)	2.7(±0.8)	2.9(±0.9)	3.6(±1.1)	2.4(0.6-5.2)*	5.8(3.5-9.1)*	5.4(3.6-7.4)*
P-value	NS	0.05	NS	NS	NS			
intermittent UO/variance	13.07(±14.56)	3.8(±2.1)						
intermittent UO/variance maximal			15.8(± 3.7)					
intermittent UO/variance minimal			0.3(± 0.2)					
continuous UO/variance	2.19(±1.92)	1.9 (±1.6)						
continuous UO/variance maximal			9.4(±4.1)					
continuous UO/variance minimal			0.5(±0.3)					
P-value	0.045	0.02	< 0.0001					

* median (range). Data given as mean (standard deviation) unless indicated otherwise, NS not significant, RCT randomized controlled trial, UO urine output

ference was observed in the main pharmacodynamic outcome parameter; urine production. However significant less variance in urine output was observed in the patients who received a continuous infusion. (Overview in table 2) Studies in critically ill adult patients showed as well that there was no difference in urine production with continuous versus intermittent intravenous furosemide administration. However the diuresis was more controlled with less hemodynamic and electrolyte variations during continuous furosemide infusion.[4, 15-18]

Because ECMO and CPB are 'comparable' procedures, continuous furosemide infusion is increasingly used in newborns treated with ECMO. In our unit continuous intravenous furosemide therapy was used in 78% of the neonates treated with ECMO.

The dosing schedule of continuous intravenous furosemide in neonates treated with ECMO is largely empirical because of the variable renal function and altered pharmacokinetics.[3, 9] This is supported by our observation that the continuous intravenous furosemide dose varied widely from 0.02 - 0.17 mg/kg/hr and that 12/31 (39 %) patients received additional loop diuretics. Although, the urine output was satisfactory in the patients studied, the use of additional loop diuretics suggests that the applied infusion rates were not optimal. Therefore dosing regimens for continuous intravenous furosemide therapy in infants treated with ECMO should be developed. Since ECMO and CPB are 'comparable' procedures the developed PK/PD model for infants after cardiac surgery might also be applicable for patients treated with ECMO.[8, 19]

To obtain an acceptable fluid balance (approximately zero) with maintenance fluid of 120 to 140 ml/kg per 24 hours, the target urine production is set at 6 ml/kg/h in our institution. In all patients studied the desirable urine output of approximately 6 ml/kg/h was achieved within 24 hours of continuous intravenous furosemide infusion and remained at the desired level thereafter, however the used furosemide regimens varied widely. The increased urine production was not correlated with the ECMO flow and the vasopressor score, while both were reduced during the observation period.

Due to the retrospective nature of our observational study data on urinary furosemide and sodium excretion were not routinely available to differentiate between increased urine production by furosemide therapy or by clinical improvement.

All patients received continuous intravenous furosemide at a median rate of 0.08 (0.02 – 0.17) mg/kg/hr and 12 patients received additional loop diuretics prior and/or during the continuous infusion. This illustrates that different regimens are used in the same group of patients and produced similar urinary output. This is in line with the observation in patients post CPB surgery with intermittent versus continuous administration of furosemide.[5-7] In the patients who received a 'loading' bolus a positive effect was observed in the urine output (figure 2), but no statistical significant difference was reached in urine output in the first 24 hours or in the time to reach a urine output of 6 ml/kg/h, which might be explained by the inter-individual variability and the difference in group size. In previous studies by our group in infants post CPB surgery, we suggested that continuous intravenous furosemide therapy would be more effective if initially started at a relatively high infusion rate and preferably preceded by a loading bolus.[8,19] With the developed PK/PD model for infants after cardiac surgery we simulated various furosemide regimens and observed the effect of a furosemide 'loading' bolus on urine production as well as on the time to reach the predefined urine output.[19]

The enhanced diuresis was well tolerated, illustrated by the stable hemodynamic parameters and a decrease in ECMO flow and vasopressor score over the observation period. Moreover the number of patients requiring inotropic support decreased during the study period.

Renal function of the studied patients was within the normal range for age, i.e. there were no signs of pre-renal failure before or during furosemide treatment. The observed increase in serum urea levels is most probably due the extreme high rates of whole-body protein breakdown observed in critically ill infants on ECMO.[20-21]

The total administered furosemide dose, continuous and intermittent was median 1.92 (0.48 – 6.6) mg/kg per 24 hours in our study population. This dose is relatively low compared to the continuous intravenous furosemide dose used in infants and children post CPB surgery.[5-8] In infants post CPB surgery, who received continuous intravenous furosemide at a rate of 9.6 mg/kg per 24 hours no toxic serum furosemide levels (> 50 μg/ml) were observed.[8, 22] A drawback of our retrospective observational study is that serum furosemide levels were not routinely recorded to monitor furosemide toxicity. Because all patients are less than five years of age, we have no routinely recorded to monitor furosemide toxicity. Audiography is performed at the age of five years according to the nationwide standardized evaluation of ECMO patients in The Netherlands to evaluate hearing loss as a sign of furosemide toxicity (among other causes). An indirect proof of the absence of hearing loss in our patients is the absence of significant delays in language development evaluated at the age of one and two years.[23] Moreover no data are available on serum furosemide levels in newborns treated with ECMO in the literature.[8] Therefore therapeutic drug monitoring studies are now performed in our centre to prevent furosemide toxicity.

Unfortunately we can not demonstrate the advantage of continuous furosemide above intermittent intravenous furosemide in our patients. Only eight patients who did not receive continuous intravenous furosemide were eligible for comparison. Urine production of these patients was median 4.4 ml/kg/h after 24 hours on ECMO, approximately the median time that continuous IV furosemide was started in the study population. Since their diuresis was considered sufficient (continuous) furosemide therapy was not started.

Conclusion

To the best of our knowledge this, is the first report on continuous intravenous furosemide in neonates treated with ECMO and it shows that continuous furosemide is frequently used. However, the furosemide regimens used in this study varied widely in continuous and additional intermittent doses. All regimens achieved adequate urine output within 24 hours and no statistical significant difference was observed following a loading bolus. The patients tolerated the forced diuresis well and no adverse effects were observed, however furosemide toxicity was not evaluated as part of this protocol. Although the urine output was satisfactory, the used furosemide regimens might not be optimal regimens for newborns treated with ECMO and therefore dosing regimens should be developed.

For obvious reasons, our retrospective observational study will not answer the question of whether continuous intravenous furosemide is the preferred way of administration of furosemide in neonates treated with ECMO.

Currently a prospective study is conducted in our unit to evaluate a continuous furosemide regimen, 0.2 mg/kg/hr, based on the PK/PD model developed for infants post CPB surgery for a predefined urine output of approximately 6 ml/kg per hour. During the continuous furosemide infusion serum furosemide levels are monitored at regular intervals to evaluate furosemide toxicity in newborns treated with ECMO.

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CHAPTER 6

Hemofiltration in newborns treated with extracorporeal membrane oxygenation, a case-comparison study

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Abstract

Introduction: Extracorporeal membrane oxygenation (ECMO) is a supportive cardiopulmonary bypass (CPB) technique for patients with acute reversible cardiovascular or respiratory failure. Favorable effects of hemofiltration during CPB instigated the use of this technique in infants on ECMO. The current study aimed at comparing clinical outcomes of newborns on ECMO with and without continuous hemofiltration.

Materials and Methods: Demographic data of newborns treated with hemofiltration during ECMO were compared to those of patients treated without hemofiltration in a retrospective 1:3 case – comparison study.

Primary outcome parameters were time on ECMO, time till extubation after decannulation, mortality, and potential cost reduction. Secondary outcome parameters were: total and mean fluid balance, urine output in mL/kg/d, dosage of vasopressors, blood products and fluid bolus infusions, serum creatinine, urea and albumin levels.

Results: Fifteen patients with hemofiltration (hemofitlration group) were compared to 46 patients without hemofiltration (control group).

Time on ECMO was significantly shorter in the hemofiltration-group: 98 (48-187) hours versus 126 (24-403) hours in the control group (p=0.02). Time from decannulation till extubation was shorter as well: 2.5 (0-6.4) vs. 4.8 (0-121.5) days (p=0.04). The calculated cost reduction was €5000, - per ECMO run. There were no significant differences in mortality. Patients in the hemofiltration group needed fewer blood transfusions: 0.9 ml/kg/d (0.2-2.7) versus 1.8 ml/kg/d (0.8-2.9) in the control group (p<0.001). Consequently the number of blood units used was significantly lower in the hemofiltration group (p<0.001). There was no significant difference in inotropic support or other fluid resuscitation.

Conclusion: Adding continuous hemofiltration to the ECMO circuit in newborns improves outcome by significantly reducing time on ECMO and on mechanical ventilation, due to better fluid management and a possible reduction of capillary leakage syndrome. Fewer blood transfusions are needed. All in all, overall costs per ECMO run will be lower.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a supportive cardiopulmonary bypass (CPB) technique for patients with acute reversible cardiovascular or respiratory failure. Many ECMO candidates have an increased inflammatory response with capillary leakage before start of ECMO due to asphyxia, hypoxia and shock. ECMO treatment in itself will trigger or aggravate a systemic inflammatory response (SIRS), resulting in a so-called capillary leakage syndrome.[1] High levels of circulating endotoxins, exotoxins, interleukins and leukotriens influence the basal membranes.[2] Moreover the ECMO system activates leucocytes, thrombocytes and the complement system.[3, 4] This leads not only to water and small molecules leakage through the capillary membrane, but also to leakage of relatively large molecules, including albumin. Permeation of circulating albumin from the blood compartment into the extra cellular space often results in generalized edema. The blood pressure will fall due to extravasation of water and proteins, necessitating administration of oncotic agents and/or vasopressor drugs. Low blood pressure and tissue edema will potentially cause deficient tissue perfusion and oxygenation leading to multi-organ failure, of which lung and kidney failure are the most prominent.

As early as twenty years ago Zobel et al. described that hemofiltration rapidly corrected hypervolemia and pulmonary edema in nine critically ill children with multi-organ failure.[5] *In vitro* and in vivo studies meanwhile have shown that hemofiltration counteracts SIRS by decreasing inflammatory mediators.[6-8] Later studies focused on hemofiltration as a method to prevent multi-organ failure due to capillary leakage syndrome in children during cardiac surgery on CPB.[9] Journois et al. reported that hemofiltration resulted in the removal of water and inflammatory proteins from the blood, and consequently in less pulmonary edema and improved pulmonary function. Time on mechanical ventilation could be shortened therefore, and the postoperative alveolar-arterial oxygen gradient improved.[10, 11] Hemofiltration is also associated with faster recovery of left ventricular function of the heart, better diastolic compliance, better contractility and less myocardial edema as recorded by trans-esophageal echocardiography during CPB.[12, 13]

Kelly et al. reported that pulmonary edema increases time on ECMO.[14] The potentially favorable effects of hemofiltration during CPB instigated the use of hemofiltration in infants on ECMO in our center since August 2004. It was intended to prevent and diminish the capillary leakage syndrome, and thus to shorten time on ECMO, time on ventilatory support, to lower numbers of blood transfusions, and consequently to reduce overall mortality and costs in this group.

Therefore, since October 2004, in all patients receiving ECMO a hemofilter was incorporated in the ECMO system independent of kidney function. Initially the hemofilter was incorporated after cannulation due to logistic procedures.

The current case-comparison study aimed to evaluate the potential benefit of hemofiltration in ECMO patients by comparing clinical parameters in patients on ECMO with and without continuous hemofiltration.

Materials and Methods

Setting

The intensive care unit (ICU) of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands is a large tertiary facility. It is one of the two designated ECMO centers in the Netherlands with 30-40 ECMO runs annually, including newborns and children up to 18 years of age. The referral area for ECMO has eight million inhabitants with ± 90,000 newborns annually.

Study design

Retrospective case-comparison study. Demographic data of all newborns (< 28 days post partum) on ECMO treated with hemofiltration between October 2004 and October 2006 were compared to those treated without hemofiltration in the previous two years (October 2002-October 2004) in a 1:3 case–comparison study. Cases and controls were matched for age, weight, diagnosis and ECMO-mode. Inclusion criteria were: in need of ECMO treatment, younger than 28 days, and the addition of hemofiltration in the treatment group. To evaluate the effects of CVVH during ECMO versus the control group, only those patients receiving CVVH within three hours after start of ECMO were included. We excluded patients treated with furosemide in the hemofiltration group to eliminate possible confounding effects of additional diuretic treatment on fluid management. Controls constituted of a series of consecutive patients taken from the previous 2 years. Controls were matched for age, weight, diagnosis and ECMO-mode.

ECMO, hemofiltration and fluid management

The ECMO circuit was primed with 180 mL of a mixture of packed red blood cells, albumin, 100 mL balanced electrolyte solution saline-adenine-glucose-mannitol (SAGM) and 500 units heparin. The ECMO flow at start was set between 120 and 150 mL/kg/min. Post pump pressure was between 200 and 400 mmHg.

The filter (Multiflow 60, Hospal, Lyon, France) was placed parallel to the ECMO circuit, distal to the ECMO roller pump. Pressure was measured proximal and distal to the filter. The pressure difference was kept constant at 40 mmHg.

In the filtration group, the predilution flow rate of the filtration fluid (HF-BIC32, Dirinco, Rosmalen, The Netherlands) was as default 50 mL/kg/hour. Transfusions with erythrocytes and platelets were administered isovolemically by ultrafiltrating as much fluid from the patient as the administered blood product. Ultrafiltration was targeted to achieve a normal or negative fluid balance depending on the clinical condition of the patient while maintaining normal hemodynamic parameters. During SIRS and the resulting capillary leakage syndrome this could not always be achieved. In the control group, patients were treated with either continuous or intermittent furosemide infusions to achieve the above mentioned targets as reported earlier by our group.[15] Transfusion of blood products in this group were performed by isovolemic exchange with whole blood drawn from the ECMO system in an equal amount to the transfused volume thereby maintaining normal hemodynamic parameters. With some exceptions the primary ECMO mode was venoarterial.

Data collection and analysis

The following data were retrieved from our Patient Data Management System: physiological parameters, medication, infusions, urinary output, CVVH, ECMO and ventilator settings, fluid balance, laboratory tests and interventions. These data were collected every hour on the hour. Primary outcome measurements were: time on ECMO in hours, time between decannulation and extubation in days and overall mortality. Secondary outcome parameters were: total and mean fluid balance, urine output in mL/kg/d, total doses of vasopressors, blood products and fluid bolus infusions, serum creatinine, urea and albumin levels, and overall costs. Fluid balance was assessed as mean net fluid balance per ECMO day, by measuring total fluid input and output and dividing the difference by the time on ECMO. The difference between predilution and filtration flow rate was included.

The amount of inotropic support was calculated, as reported previously, by the so-called vasopressor score: [dopamine dose (μg/kg/min) x 1] + [dobutamin dose (μg/kg/min) x 1] + [noradrenalin (μg/kg/min) x 100] + [adrenalin (μg/kg/min) x 100].[16, 17]

Statistics

All data are presented as median (range) unless indicated otherwise. Differences between the groups were tested for their statistical significance by Mann-Whitney non-parametric test for unpaired data, the Pearson's Chi Square test and the Fisher's Exact test, according to the character of the variable. A p-value <0.05 was considered significant.

Informed consent

Due to the design of the study (a retrospective case-record evaluation) approval by the medical ethical committee, and the need for informed consent was waived according to Dutch law.

Results

Patient profiles

Fifteen patients with hemofiltration (hemofiltration group) were compared to 46 patients without hemofiltration (control group). Patient characteristics are shown in table 1. Median postpartum age on admission was 2.2 (0.9-6.7) days in the hemofiltration-group and 1.7 (0.5-18) days in the control group. Median weight was 3.5 (2.5-5) kg in the hemofiltration-group and 3.3 (1.9-5) kg in the control group.

PRISM III (Pediatric Risk of Mortality) scores were calculated retrospectively at the time of admission on our ICU. Most patients were cannulated within 24 hours of admission. PELOD (Pediatric Logistic Organ Dysfunction) score, Oxygenation Index (OI) and AaDO2 (Alveolar-arterial Oxygen Gradient) were taken within 6 hours of cannulation.

Although there are more CDH patients in the control group there are no significant differences in PRISM, PELOD, OI and AaDO2 reflecting a similar severity of illness before ECMO.

Congenital diaphragmatic hernia and meconium aspiration syndrome were the most frequent indications for ECMO therapy. Other diagnoses were respiratory distress syndrome, viral or bacterial pneumonia, congenital cystic adenomatoid malformation of the lung, persistent pulmonary hypertension, post cardiac surgery, and sepsis.

In both groups, two children with isolated pulmonary disease were treated with venovenous ECMO. All other patients, 13 (87%) in the hemofiltration-group and 44 (96%) in the control group respectively, were treated with venoarterial ECMO.

Three patients in the hemofiltration-group and four patients in the control group underwent surgery during ECMO, i.e. closure of a diaphragmatic defect (n=5), thoracotomy due to congenital cystic adenomatoid malformation of the lung (n=1) or correction of a transposition of the great vessels (n=1) for which post cardiac surgery ECMO was needed. Furosemide was administered to 40 children in the control group.

Outcome

Time on ECMO was significantly shorter in the hemofiltration group: 98 (48-187) hours versus 126 (24-403) hours in the control group (p=0.02). Time from decannulation till extubation was shorter as well: 2.5 (0-6.4) days versus 4.8 (0-121.5) days (p=0.04). Mortality rate was similar in both groups, 3/15 in the hemofiltration group and 7/46 in the control group (p=0.61). Fluid balance per day on ECMO was significantly lower in the hemofiltration group compared to the control group (p<0.001).

Patients in the hemofiltration group needed fewer blood transfusions than controls 0.9 (0.2-2.7) ml/kg/d versus 1.8 (0.8-2.9) ml/kg/d, (p<0.001). Consequently the number of used blood units was significantly lower in the hemofiltration group (p<0.001). No statistically significant difference was observed between the two groups with respect to

Table 1 Patient profiles

		Control group (n=46)	HF-group (n=15)	
		n (%)	n(%)	p-Value
Gender	Female	21 (46)	5 (33)	
	Male	25 (54)	10 (67)	0.44*
Scores	OI	37 (14-90)	35 (17-51)	0.29**
	AaDO2	628(492-694)	633 (551-651)	0.93**
	PELOD	20 (1-30)	20 (10-20)	0.82**
	PRISM III	25 (14-39)	20 (14-40)	0.18**
Start ECMO	Oct 2002 - Aug 2004	38 (83)	0(0)	
	Aug 2004- July 2006	8 (17)	15 (100)	-
Diagnosis	CDH	16 (35)	3 (20)	
	MAS	16 (35)	5 (33)	
	Respiratory diseases	7 (15)	2(13)	
	Sepsis	4 (9)	2 (14)	
	Idiopathic PPHN	2 (4)	2 (13)	
	Post cardiac surgery	1 (2)	1 (7)	0.73***
Surgery	No Surgery	42(91)	12 (80)	
	CDH closure	3 (7)	2 (13)	
	Great vessel surgery	1 (2)	1 (7)	0.24***
ECMO mode	Veno-arterial	44 (96)	13 (87)	
	Veno-venous	2 (4)	2 (13)	0.22***
		median (min-max)	median (min-max)	
Body weight (kg)		3.3 (1.9-5)	3.5 (2.5-5)	0.31**
Age (days)		1.7 (0.5-18)	2.2 (0.9-6.7)	0.28**

* Pearson's Chi square test, ** Mann-Whitney U test, *** Fisher exact test, CDH congenital diaphragmatic hernia, MAS meconium aspiration syndrome, OI oxygenation index, AaDO2 Alveolar-arterial oxygen tension gradient, ECMO extracorporeal membrane oxygenation, PRISM23 Pediatric Risk of Mortality 3, PIM2 Pediatric Index of Mortality, PELOD Pediatric logistic organ dysfunction

volume and number of units of platelet and colloid transfusions. Used colloid solutions included fresh frozen plasma, pasteurized plasma solution and human albumin. Maximal creatinine values were above normal range in both groups, and tended to be lower in the hemofiltration group (p=0.17). Maximal urea level was significantly lower in the hemofiltration group (p=0.01). No significant difference was noted between the two groups with respect to the lowest albumin value. Doses of vasopressor did not differ significantly between the groups.(table 2)

Table 2 Outcome

	Control group	HF-group	Mann-Whitney U-test
	median (min-max)	median (min-max)	P-value
Time on ECMO (hours)	126 (24-403)	98 (48-187)	0.02
Time till extubation after decannulation (days)	4.8 (0-121.5)	2.5 (0-6.4)	0.04
Fluid balance (mL/kg/d)	40 (-53-214)	-29 (-75-60)	<0.001
Urine (mL/kg/d)	121 (28-292)	54 (11-94)	0.38
Filtration flow rate in (L/kg/d)	-	1.2 (0.6-1.4)	-
Filtration flow rate out (L/kg/d)	-	1.3 (0.6-1.7)	-
Blood loss (mL/kg/d)	57 (8-135)	12 (6-30)	<0.001
Erythrocyt transfusion (mL/kg/d)	39 (0-73)	16 (0-35)	<0.001
Platelet transfusion (mL/kg/d)	37 (0-65)	29 (11-63)	0.11
Colloïds (mL/kg/d)	6 (0-37)	4 (0-30)	0.25
Pasteurized plasma (mL/kg/d)	18 (0-98)	20 (2-69)	0.79
units erythrocytes (units/d)	1.8 (0.8-2.9)	0.9 (0.2-2.7)	<0.001
units thrombocytes (units/d)	0.9 (0.2-1.9)	0.7 (0.2-2)	0.3
furosemide (mg/kg/d)	1.2 (0-2.6)	-	-
Bumetanide (mg/kg/dg)	0 (0-0.27)	-	-
maximum serum creatinin (mcmol/l)	58 (14-91)	49 (28-105)	0.17
maximum serum urea (mmol/l)	6 (1-42)	4 (2-13)	0.01
minimum serum albumin	21 (2-30)	23 (13-28)	0.15
Vasopressor score	7 (0-56)	5 (0-41)	0.83
mortality rate	7 (16)*	3 (21)*,**	0.61
day of death after decannulation	3.4 (0-11,4)	1.5 (-0.5 - 6.4)	0.56

* n (%), ** One patient died on ECMO, HF hemofiltration

Costs

Although the need for additional support was higher in the initial phase of CVVH on ECMO personnel costs did not differ between both groups. ECMO nurses were continuously available for the priming of the system, and integrated the hemofilter in the ECMO circuit. They took care of both the ECMO circuit (with or without hemofilter) and the patient. A median patient in the control group needed 28 hours more on ECMO and 55 hours more on mechanical ventilation. The total costs per day on ECMO, including costs for personnel, materials, and overhead, were calculated at €4328,-.
The mean total costs per day for treatment on an ICU ward with mechanical ventilation in our institution amount to € 1480,-. A median extra 5.4 units of blood were needed per patient in the control group, representing €964,-.

In the hemofiltration group extra costs were generated by 1 or 2 filters (€90, - each) and a median of one 5-liter bag of substitution fluid (€15,-).
The profit gained by adding hemofiltration to the ECMO circuit thus amounted to more than €5000,-

Discussion

In 2008 Hoover et al. showed that the use of CVVH in pediatric patients on ECMO is associated with improved fluid balance and caloric intake and less diuretics than in case-matched ECMO controls.[18] We report the first study in newborns that shows that hemofiltration during ECMO improves clinical outcome. This is expressed by a shorter duration of ECMO treatment, and of mechanical ventilation post ECMO. Moreover, the use of hemofiltration resulted in fewer blood transfusions in this group. The calculated cost reduction for each hemofiltrated patient was more than €5000,-. Although adding hemofiltration to an ECMO circuit may result in the need for additional support, in our centre our ECMO staff is trained to manage the CVVH treatment negating additional trained nursing support. Adding a treatment to an already complex patient may result in treatment errors. This is always an issue in an intensive care setting and difficult to express in money. This said we did not have any complications in administering CVVH during ECMO in the study.
Capillary leakage syndrome is a frequent complication of CPB and ECMO leading to generalized edema, hypotension and ultimately multi-organ failure. Several studies reported that the use of hemofiltration during and after CPB resulted in less edema and shorter post-operative ventilation.[9-13] Before start of ECMO, due to asphyxia, hypoxia and shock, many ECMO candidates already have an increased inflammatory response with capillary leakage. In an effort to maintain a normal blood pressure patients are treated with inotropic support, but unfortunately also with ample fluid suppletion. This therapy may result in an increase of generalized edema and subsequently pulmonary edema. ECMO treatment aggravates this inflammatory syndrome.[1]
The higher need for blood transfusions in the control group is most likely due to the possibility of isovolemic transfusion of blood and platelet transfusions via the hemofilter in the hemofiltration group. This may in itself have a beneficial effect on multi-organ failure. Bjerke et al. reported that restricting blood transfusions in newborns on ECMO decreased ECMO run time by 15%.[19] Tran et al. studied factors associated with multi-organ failure in patients with critical trauma. One such factor was the number of blood transfusions received.[20] This relation may be due to a nonspecific host response to transfusions, resulting in progressive multi-organ failure. As the multi-organ failure score is one of the major predictors of death on the ICU, blood transfusions contribute

to worse clinical outcome. Modern strategies to deplete red-cell transfusions of leukocytes may, however, decrease this risk, as recently indicated in critically ill children by Lacroix et al.[21]. Nevertheless, restrictive blood transfusion strategy is recommended in children whose condition is stable.

We did not demonstrate a favorable effect of hemofiltration on multi-organ failure or capillary leakage; expressed as better renal function, lower vasopressor score or less need for fluid resuscitation. Creatinine levels were slightly elevated in both groups[22], and tended to be lower in the hemofiltrated group. The slightly lower level of serum creatinine and urea in the filtrated group will, at least partially, be explained by the convective clearance effect of hemofiltration. There was no statistical difference in other volume suppletions or inotropic support. This study was not designed to evaluate the effect of hemofiltration on SIRS. Due to the retrospective nature of our study, levels of inflammatory mediators were obtained from plasma, urine or filtrate were not available.

We did not find a statistically significant change in mortality rate, but patient numbers in this study are too small to draw conclusions on this aspect of the results. The total mortality rate of 10 in a population of 61 patients (16%) is fairly low, in comparison to both the mortality rate of 53 in a population of 188 patients (28%) in the previous 10 years of ECMO treatment and the overall mortality of 24% in the ELSO (Extracorporeal Life Support Organization) registry in newborns treated with ECMO for respiratory failure. Addition of hemofiltration increased fluid extraction during ECMO in our study, expressed by a better overall fluid balance, in contrast to treatment with diuretics.

Limitations of our study

In this case-comparison study patients were matched for most confounding factors. Due to the relative small sample size we were not possible to perfectly match cases and controls, resulting in a higher percentage of CDH patients in the control group. We acknowledge that patients with CDH have a higher overall mortality and morbidity, especially compared to patients with MAS. This also applies to patients with idiopathic pulmonary hypertension, constituting 13 % of the cases. However, no significant differences in baseline characteristics (table 1) between the groups exist. Both severity of illness expressed by PELOD and PRISMIII scores as well as severity of respiratory failure expressed by OI and AaDO2 did not differ significantly.

Secondly the groups were treated in different time periods; patients in the hemofiltration group were treated two years later than patients in the control group. As ECMO hemofiltration was introduced not until August 2004, the hemofiltration group in this single-center, retrospective study consists of only 15 patients. No significant changes in indications for treatment on ECMO took place over the years and patients were treated by the same team without major infrastructural changes in our ECMO setting.

Furthermore, no data were collected to detect decrease in inflammatory mediators. Therefore it is not possible to evaluate the potential favorable effects of hemofiltration on SIRS, i.e. through a mechanism that lowers the inflammatory mediator response. An ongoing randomized controlled trial in our institution is expected to yield more information enabling to optimize the value of hemofiltration during ECMO.

Conclusion

Adding continuous hemofiltration to the ECMO circuit in newborns improves short-term outcome by significantly reducing time on ECMO and on mechanical ventilation and by a possible reduction of SIRS and capillary leakage syndrome. Furthermore, significantly fewer blood transfusions are needed. Hemofiltration during ECMO decreases costs per ECMO run by € 5000. Given the fact that 30 patients per year receive ECMO treatment in our institution, a €150.000 cost reduction per year could be accomplished.

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PART IV

Infectious diseases on ECMO

CHAPTER 7

Bacterial Infections on ECMO: a diagnostic and therapeutic challenge

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CHAPTER 8

Pharmacokinetics of Cefotaxime and Desacetylcefotaxime in Infants during Extracorporeal Membrane Oxygenation

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Abstract

Extracorporeal membrane oxygenation (ECMO) is used to temporarily sustain cardiac and respiratory function in critically ill infants, but can cause pharmacokinetic changes necessitating dose modifications. Cefotaxime (CTX) is used to prevent and treat infections during ECMO, but the current dose regimen is based on pharmacokinetic data in non-ECMO patients. The objective of this study was to validate the standard dose regimen of 50 mg/kg b.i.d. (postnatal age (PNA) < 1 wk), 50 mg/kg t.i.d. (PNA 1-4 wks) and 37.5 mg/kg q.i.d. (PNA > 4 wks). We included 37 neonates on ECMO, with a median PNA (range) of 3.3 (0.67-199) days and a body weight of 3.5 (2.0-6.2) kg at onset of ECMO. Median (range) ECMO duration was 108 (16-374) hours. Plasma samples were taken during routine care and pharmacokinetic analysis of CTX and its active metabolite desacetylcefotaxime (DACT) was done using nonlinear mixed-effects modeling (NONMEM). A 1-compartment pharmacokinetic model for CTX and DACT adequately described the data. During ECMO, CL_{CTX} was 0.36 L/h (range 0.19-0.75), V_{CTX} was 1.82 L (0.73-3.02), CL_{DACT} was 1.46 L/h (0.48-5.93) and V_{DACT} was 11.0 L (2.32-28.0). Elimination half lives for CTX and DACT were 3.5 h (1.6-6.8) and 5.4 h (0.8-14). Peak CTX concentration was 98.0 (33.2-286) mg/l. DACT concentration varied between 0 and 38.2 mg/l, with a median of 10 mg/l in the first 12 hours post dose. Overall, CTX concentrations were above a MIC of 8 mg/l over the entire dose interval. Only one out of the 37 patients had a sub-MIC for over 50% of the dose interval. In conclusion, the standard cefotaxime dose regimen provides sufficiently long periods of supra-MIC to provide adequate treatment of infants on ECMO.

Introduction

Extracorporeal Membrane Oxygenation (ECMO) is used as a standardized last resort to support critically ill infants who can no longer maintain sufficient cardiac and respiratory function with conventional life support techniques.[1-2] Over a period of maximally three weeks, blood flow is continuously diverted via a venous cannula into an extracorporeal circuit, oxygenated via a membrane and returned to the general circulation via a venous or arterial cannula. A hemofilter can be added to the circuit to supplement insufficient renal function. Standard pharmacological treatment includes high doses of antibiotics for the treatment of pre-existing or nosocomial infections, which are facilitated by the direct microbial access to the patients general circulation via cannulas and circuit components.[3] One of the antibiotics commonly used in neonates on ECMO is cefotaxime (CTX), which possesses antimicrobial activity against many of the pathogens commonly involved in neonatal and ECMO-related infections, such as E. coli, Klebsiella Pneumoniae, Enterobacter and Staphylococcus spp.. [4] In adults, cefotaxime can be excreted unchanged via the renal system, but also after hepatic conversion into its active metabolite desacetylcefotaxime (DACT, for 15-25% of a dose).[5] There appears to be an inverse correlation between renal function and elimination half-life, particularly for DACT.[6]

In the absence of specific pharmacokinetic data, our current cefotaxime dose regimen is the same for both ECMO and non-ECMO patients. In general however, ECMO is associated with altered pharmacokinetics for a variety of drugs, probably due to an increase in circulatory volume, a disease-related clearance reduction or adsorption of drugs to membranes and other circuit components.[7] We designed this study to evaluate the pharmacokinetics of cefotaxime and desacetylcefotaxime during ECMO and validate our dose regimen.

Materials and Methods

All neonates about to receive ECMO treatment at the Erasmus MC-Sophia Children's Hospital from December 2006 to June 2009 were eligible. The local institutional ethics review board approved this study. Parental informed consent was obtained for blood sampling and use of clinical data. Criteria for ECMO treatment were: gestational age > 34 weeks, birth weight > 2.0 kg, mechanical ventilation < 7 days, an alveolar arterial oxygen difference more than 600 mm Hg, and an oxygenation index > 25. Concomitant drugs were given in accordance with the departmental treatment protocol and doses were adapted to each neonate's clinical condition. The most recent weight available prior to ECMO was used for dose calculation and pharmacokinetic analysis. Drug administrations, laboratory results and real-time parameters such as ECMO flow were recorded in a patient data management system.

ECMO

The ECMO circuit consisted of extracorporeal cannulas (Medtronic, Kerkrade, the Netherlands), PVC tubing (Bentley Bypass 70 tubing, Baxter, The Netherlands), a silicone rubber membrane oxygenator (Pediatric Extended Membrane Oxygenator, Medtronic), and Heat Exchanger (Heat Exchanger Monitoring adapter and Luer-lock, Medtronic). Priming volume was estimated at 350 mL. A continuous venovenous hemofiltration (CVVH)-filter (Multiflow 60, Hospal, Lyon, France) was placed parallel to the ECMO circuit, distal to the ECMO roller pump. Pressure was measured proximal and distal to the filter; the difference was kept constant at 40 mmHg.

Cefotaxime administration

Cefotaxime was given intravenously as a bolus injection (max. 3 minutes). Dose regimens have been standardized hospital-wide to vary with postnatal age from 50 mg/kg b.i.d. (PNA < 1 wk) and 50 mg/kg t.i.d. (PNA 1-4 wks) to 37.5 mg/kg q.i.d. (PNA > 4 wks) [8] for ECMO and non-ECMO-patients alike, but doctors could deviate from protocol at their own discretion. Doses were rounded off to the nearest 5 mg to allow reliable administration of prescribed CTX doses. Nurses validated physician-prescribed medication orders and recorded actual injection times in the data management system as part of their standard care routine. CTX was administered via an extracorporeal line after the oxygenator, just before blood was returned to the patient's circulation.

Blood sampling and assay

Blood was collected during routine laboratory rounds three times daily. When possible, additional samples were taken one hour before and 0, 1 and 3 hours after cannulation to characterize early pharmacokinetic changes. Sampling continued for a maximum of 24 h after decannulation. Blood (max. 1 ml) was taken from a venous pre-oxygenator access point dedicated to sample withdrawal on the ECMO circuit and collected in ethylenediaminetetraacetic acid (EDTA)-decoagulation vials, which were stored at 4-7°C until further processing. After centrifugation (5 min, 4000 × g), the supernatant serum was stored at -80°C until assay. Sampling times and duration of storage at 4-7°C were recorded. CTX and DACT concentrations were quantified via liquid chromatography-mass spectrometry (LC-MS) as previously described.[9] Limits of quantification were 0.2 mg/l for both CTX and DACT. Intra- and inter-assay coefficients of variation were < 15%.

Blood culture

Blood cultures are performed daily at our institution. Samples were taken from a venous access port and sent in for microbiological surveillance.

PK model development

CTX and DACT models were developed sequentially using nonlinear mixed-effects modeling software (NONMEM VI 2.0, Globomax LLC, Ellicott City, MD). NONMEM allows the estimation of typical population pharmacokinetic parameters, and their respective inter- and intra-individual variability in combination with the estimation of residual random variability. The first-order conditional estimation (FOCE) method, with interaction between the inter-individual and random effects, was used throughout method development. Differential equations were used with NONMEM's ADVAN 6 subroutine to describe the population PK of CTX and DACT. After selection of an appropriate base model, inter-individual random effects were evaluated on clearance (CL) and volumes of distribution (V) with an exponential model. Covariance between CL and V was modeled using an omega block function. Residual variability was described with a proportional error model; the proportional variance coefficient was separately estimated for samples taken within one hour post-dose to account for expected variable discrepancies between the actual and the recorded dose time. Post-sampling degradation was incorporated into the error model by calculating the concentration at the time of sampling using the degradation rate constant in EDTA-decoagulated whole blood from literature (k_{deg}=0.0132, $t_{1/2}$ = 52 h,[9]); the median correction of observed CTX concentrations was +15.7%. Covariate effects on CL or V were incorporated into the model as previously described[10] and their statistical significance was assessed in a stepwise inclusion and exclusion procedure [11]. The tested covariates include gestational age (GA), postnatal age (PNA), body weight (WT), time after dose (t_{dose}), time after start or end of extra-corporeal circulation (t_{EC} and t_{END}), ECMO on/off, ECMO-flow (Q_{ECMO}), CVVH-flow (Q_{CVVH}), indication, the number of ECMO runs, ECMO-modality (venovenous or venoarterial), sex, body temperature, urine output, fluid balance, serum albumin, serum creatinine and concomitant use of vasopressive medication (norepinephrine, dopamine, dobutamine or epinephine). After selection of appropriate covariates, remaining inter-occasion variability was tested on CL and V for CTX and DACT in which occasions were defined as t_{EC} periods of 48 h; pre- and post-ECMO observations were considered separate occasions.

PK model performance

Evaluation of models was based on improvements in the minimum value of objective function (OFV), standard error of parameter estimates and goodness-of-fit plots generated via the Xpose software package (v 4.0.4, Dr. M. Karlsson, University of Uppsala, Sweden)[12] within R (v 2.8.1, The R Foundation for statistical computing, www.R-project.

org). Additional plots were prepared using GraphPad Prism 4.03 (GraphPad Software Inc, La Jolla, CA). Goodness-of-fit plots included, among others, plots of measured drug concentrations vs. population (PRED) or individual (IPRED) predictions, conditional weighted residuals (CWRES) [13] vs. time or other covariates and plots of observed concentrations (dependent variable or DV), PRED and IPRED vs. time. Bayesian IPRED concentrations were obtained via NONMEM's *posthoc* option. Statistical significance of a potential model improvement was determined via the log-likelihood ratio test for nested models, using the OFV produced by NONMEM. A decrease in OFV of 3.84 ($p = 0.05$, χ^2 distribution, one degree of freedom) was considered statistically significant. A stricter criterion ($p = 0.01$, $\Delta OFV = 6.63$) was used in the backward elimination procedure for covariate effects: if deletion of a covariate did not result in a significant worsening of the objective function, the covariate was removed from the model. The resulting model was considered the final model. Shrinkage was calculated to assess whether the estimated η and ε parameter distributions match those of the original data assuming normal distribution.[14] Stability and performance of the final model were checked using an internal validation procedure via the bootstrap resampling technique, in which 1200 bootstrap data sets were generated by random sampling with replacement.[15] We used the Wings for NONMEM software package (v6.12 March 2007, Dr N. Holford, Auckland, New Zealand). Model validity was assessed by calculating median values and the 2.5^{th} and 97.5^{th} percentiles of parameter distribution generated by the bootstrap, and comparing them with the original estimates. The bootstrap was also used to calculate standard errors for each estimate.

Dose regimen evaluation

The fraction of a dose interval during which the cefotaxime concentration exceeds the MIC of susceptible micro-organisms ($t_{>MIC}$, as % of dose interval over 24 h) is considered an appropriate measure of efficacy [16-17]. Based on bacteriological screening results of our ECMO patients and literature on pathogens involved in pediatric meningitis[4], the main pathogens include Escherichia, Staphylococcus, Klebsiella, Serratia and Enterobacter species. Reported MIC values (MIC distributions of wild type microorganisms, via www.Eucast.org) are at or below 4 µg/mL (S. aureus). Assuming a worst case scenario of up to 40% protein binding[18], the maximal MIC value in plasma is around 8 µg/ml. Using the individual parameter estimates derived from the final PK model, concentration-time curves were constructed for each individual by simulating the predicted concentration over intervals of 0.2 h. We calculated $t_{>MIC}$ over 24 h for each individual patient and compared the median values for each dose regimen; we considered the antimicrobial effect to be optimal at a $t_{>MIC}$ of at least 50%.[16]

Results

Data

We included 37 patients with a total of 392 samples (median per patient: 10, range 1-17). Pre-ECMO samples were available for 8 individuals (1 each); post-ECMO samples were available for 13 individuals (on average 2.1 each). See table 1 for patient characteristics. CTX and DACT were successfully quantified in all samples, with 4 (CTX, 1.0%) and 3 (DACT, 0.8%) concentrations below the quantification limit (BQL). DACT concentrations were converted to CTX equivalents using a molecular weight ratio of 455.5/413.4 (Mw_{CTX}/Mw_{DACT}).

Table 1 Patient characteristics[a]

General	
Sex	18 M / 19 F
Primary Diagnosis	Meconium aspiration syndrome, n=17 (46%) Congenital diaphragmatic hernia, n=8 (22%) Pulmonary hypertension (other causes), n=5 (14%) Congenital heart defects, n=4 (11%) Other (sepsis, viral infections, etc.), n=3 (7%)
Body weight (kg)	3.5 (2.0-6.2)
Gestation (weeks)	37 (34-42)
Postnatal age at start ECMO (days)	3.3 (0.67-199)
Survival	25 Y / 12 N
Cefotaxime	
Dose (i.v.)	50 mg/kg b.i.d., n=24 (65%) 50 mg/kg t.i.d., n=7 (19%) 37.5 mg/kg q.i.d., n=3 (8%) 25 mg/kg b.i.d., n=2 (5%) 37.5 mg/kg t.i.d., n=1 (3%)
Serum chemistry	
Albumin (g/L)	31 (21-40)
Serum creatinine (µmol/L)	32 (19-69)
ASAT (IU/L)	44 (14-369)
ALAT (IU/L)	10 (0.5-40)
ECMO	
ECMO modality	Venovenous (VV), n=22 (54%) Venoarterial (VA), n=19 (46%) Four patients had 2 ECMO runs each: 3 VV + VA, 1 VA + VV
Median ECMO flow (mL/kg/min)	308 (50-530)
Duration of ECMO (h)	108 (16-374)
Continuous venovenous hemofiltration	30 Y / 7 N
CVVH flow (mL/min)	193 (100-350)
Body temperature	2 hypothermic (24°C) / 35 normothermic (36°C)

[a] Parameters expressed as median (range) or n (%). ASAT = aspartate amino transferase; ALAT = alanine aminotransferase; CVVH = continuous venovenous haemofiltration.

Blood culture

Thirty-four patients had negative blood cultures throughout their ECMO run during CTX administration. Two patients had one positive culture at day 8 and 10 of ECMO respectively, but both had negative cultures beforehand and at least two days thereafter; it is unclear whether these were false-positive cultures or transient infections. One patient had positive cultures at days 11 and 13, in which an enterococcus could be isolated.

PK model development

A 1-compartment model with first-order elimination for both CTX and DACT best fit the data; additional compartments improved goodness-of-fit plots nor the OFV. BQL concentrations were removed from the dataset; deletion did not change CL and V parameter estimates for the base model. Proportional residual error terms improved the model whereas an additional error did not. There was a structural deviation in CWRES vs. t_{dose} plots indicating lower than expected concentrations in the first hour after CTX infusion. A separate proportional residual error for samples with $t_{dose} < 1$ h reduced this deviation. Alternatively, first-order absorption and lag-time models were tested but they did not significantly improve fit, probably because only a fraction of the concentrations was over predicted. No other covariates were correlated with this deviation. Inter-individual variability was successfully estimated for CL and V for both compounds. Covariance between CL and V significantly improved minimization and stability; correlation varied from 70.6% (CL_{DACT}~V_{DACT}) to 90.8% (V_{CTX}~V_{DACT}). Inter-occasion variability (occasions of 48 h) was tested only after trends with t_{EC} or other time-varying covariates proved non-significant and improved fit with a significant ($p<0.001$) reduction in OFV. An increase in CL_{CTX} and CL_{DACT} upon cannulation, which could be seen in eight patients based on one pre-ECMO sample each, could not be modeled with statistical significance. Allometric scaling[19] was tested before other covariates, but this did not reduce the OFV. The covariate inclusion procedure suggested that the following covariates might be correlated to V or CL and improve the OFV upon inclusion ($p<0.05$): GA, Q_{CVVH}, WT, PNA, vasopressor use and t_{END} (CL_{CTX}); fluid balance and serum creatinine (V_{CTX}); sex, duration of pregnancy, WT, Q_{ECMO}, t_{END} and Q_{CVVH} (CL_{DACT}); t_{END} (V_{DACT}). After stepwise exclusion, the only significant remaining effects were WT (CL_{CTX}), Q_{CVVH} (CL_{DACT}) and t_{END} (CL_{CTX} and CL_{DACT}), but drops in unexplained inter-individual variability were small: -2.7% (WT~CL_{CTX}), -8.1% (Q_{CVVH}~CL_{DACT}), -0.5% (t_{END}~CL_{CTX}), -4.2% (t_{END}~CL_{DACT}). None of the covariates reduced inter-individual variability for V_{CTX} or V_{DACT}. See table 2 for parameter estimates of the final model. See appendix 1 for the differential equations used in the final model, including covariate effects.

Table 2 Parameter estimates[a]

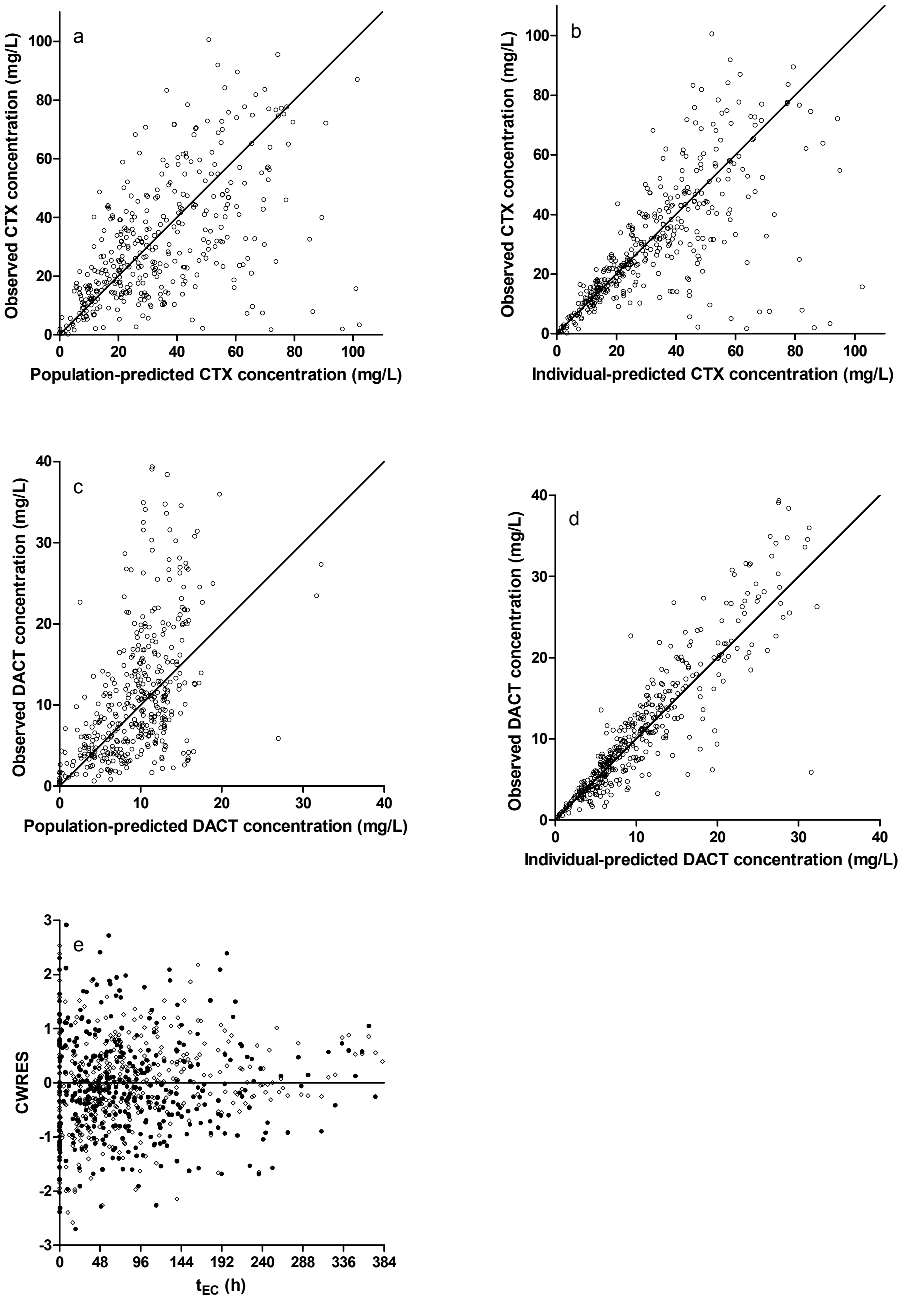
	Unit	CTX		DACT		Remarks
		Estimate (CV %)	Bootstrap median (95% CI)	Estimate (CV %)	Bootstrap median (95% CI)	
Population parameters						
V	L	1.82 (8.2%)	1.86 (1.60-2.20)	11.0 (14.0%)	11.0 (7.90-14.0)	
CL	L/h	0.36 (7.9%)	0.36 (0.30-0.41)	1.46 (11.5%)	1.42 (1.10-1.77)	
Covariate effects						
WT	-	0.56 (43.7%)	0.55 (0.02-1.00)	-	-	$CL = CL_{pop} \cdot (WT/3.5)^{WT}$
$CVVH$	-	-	-	0.72 (35.8%)	0.69 (0.10-1.10)	$CL = CL_{pop} \cdot (Q_{CVVH}/193)^{CVVH}$ without CVVH, $CL = CL_{pop}$
t_{END}	-	0.16 (80.8%)	0.16 (0.002-0.48)	0.53 (53.7%)	0.51 (0.18-1.20)	$CL = CL_{pop} \cdot (t_{END}/100)^{t_{END}}$ when $t_{END} = 0$, $CL = CL_{pop}$
Interindividual variability						
V	%	35.4 (24.2%)	35.9 (16.7-51.5)	59.8 (19.7%)	60.8 (39.4-84.2)	
Cl	%	36.1 (21.5%)	34.8 (24.1-53.1)	51.4 (18.6%)	53.3 (39.7-76.1)	
Interoccasion variability						
V	%	25.0 (20.7%)	24.5 (15.7-35.8)	25.0 (20.7%)	24.5 (15.7-35.8)	Calculated over periods of 48 h on ECMO
Cl	%	25.0 (20.7%)	24.5 (15.7-35.8)	25.0 (20.7%)	24.5 (15.7-35.8)	Calculated over periods of 48 h on ECMO
Residual variability						
Proportional (t_{dose}<1 h)	%	69.4 (25.4%)	68.3 (44.9-90.7)	69.4 (25.4%)	68.3 (44.9-90.7)	
Proportional t_{dose}>1 h)	%	32.7 (8.2%)	32.3 (27.4-37.6)	32.7 (8.2%)	32.3 (27.4-37.6)	

[a] CTX = cefotaxime; DACT = desacetylcefotaxime; CV = coefficient of variation; V = volume of distribution; CL = clearance; WT = body weight in kg; Q_{CVVH} = CVVH flow; t_{END} = time after decannulation in h; t_{dose} = time after last dose. Cl and V estimates for DACT were calculated assuming a conversion fraction ($F_{DACT/CTX}$) of 1.

PK model performance

See figure 1 for the goodness-of-fit plots. In certain individuals, DACT was structurally underestimated (see figure 1c) but there was no significant trend with any covariate; inter-individual variability on PK parameters corrected this pattern (figure 1d). There was no trend in CWRES vs. t_{EC}. All parameter estimates were within the 95% confidence interval calculated using bootstrap data (table 2). The higher coefficients of variation

Figure 1 Goodness-of-fit plots for the final model. Observed cefotaxime (CTX) concentration vs. population predicted (a) and individual-predicted (b) concentration. Similar plots are displayed for desacetylcefotaxime (DACT) (c and d). There is no apparent pattern in conditional weighted residuals (CWRES) vs. time after start of ECMO (t_{EC}) for CTX (closed circles) or DACT (open circles, e).

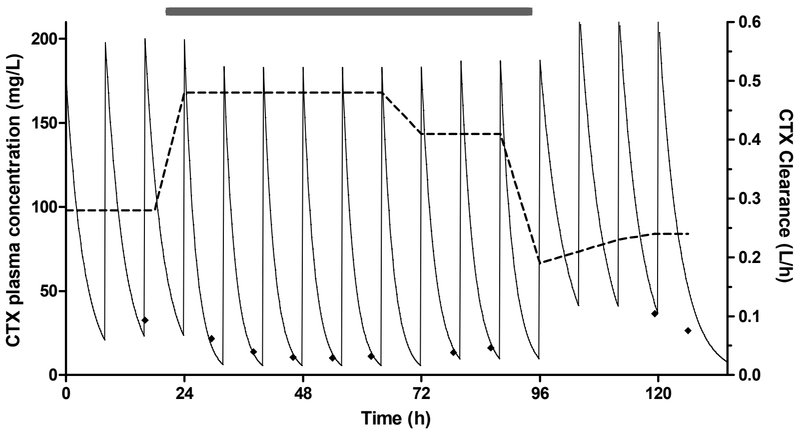


for the covariate effects show that their estimation is difficult in this dataset, probably due to the small sample size and high residual variability. Shrinkage was calculated for inter-individual variability (η) on CL_{CTX} (5.2%), V_{CTX} (4.7%), CL_{DACT} (6.4%), V_{DACT} (4.4%) and the residual variability (ε, 2.2%) using Perl-speaks-NONMEM.[20]

CTX and DACT pharmacokinetics

See table 2 for parameter estimates. During ECMO, median CL_{CTX} = 0.36 L/h (0.19-0.75), V_{CTX} = 1.82 l (0.73-3.02), CL_{DACT} = 1.46 l/h (0.48-5.93) and V_{DACT} = 11.0 l (2.32-28.0). Over the weight range of 2-6.2 kg, median CL_{CTX} varies from 0.26-0.50 L/h. The elimination half-life is 3.5 h (CTX, 1.6-6.8) and 5.4 h (DACT, 0.8-14). In the individuals for which pre or post-ECMO samples are available, CTX and DACT clearance appear to increase upon cannulation (median CL_{CTX} = 0.30 to 0.36 L/h, CL_{DACT} = 1.37 to 1.46 L/h). After decannulation, CL_{CTX} and CL_{DACT} drop almost instantaneously but recover steadily over the following 72 h (from 0.22 to 0.40 l/h and from 0.18 to 1.38 l/h). See figure 2 for plasma concentrations and clearance estimates for one of the studied individuals.

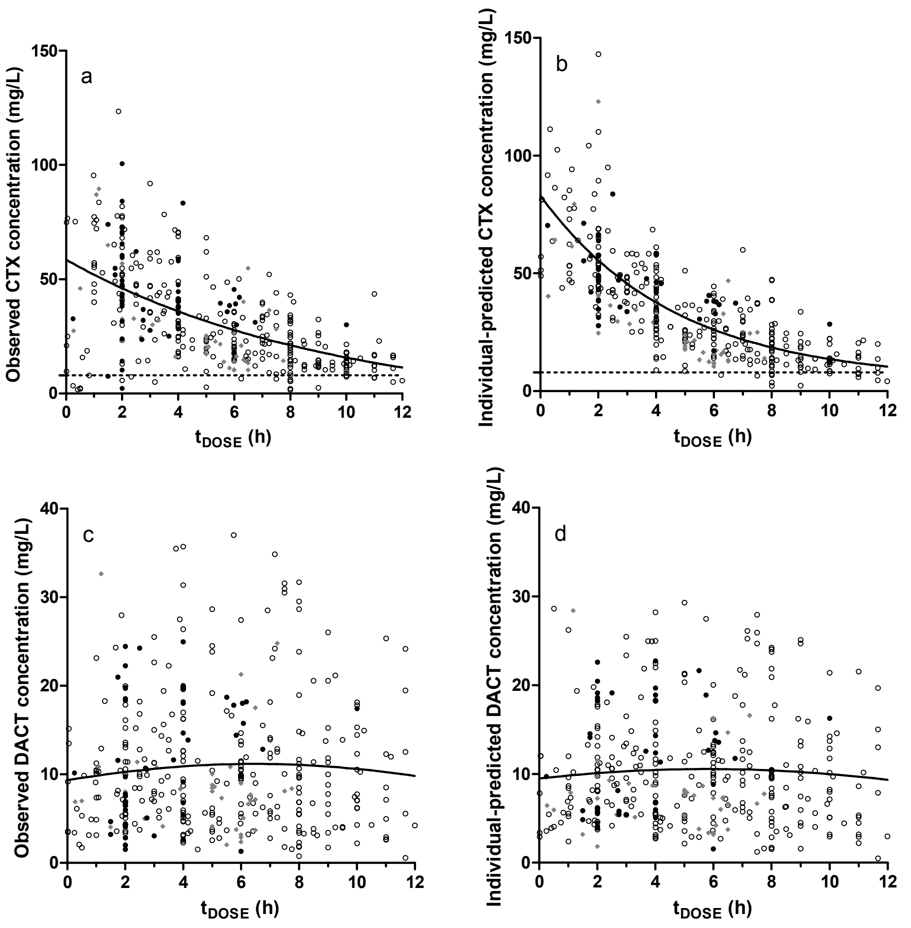
Figure 2 Characteristic concentration-time curve for one of the subjects (with a dose of 50 mg/kg t.i.d.) with a number of samples pre- and post-ECMO. Displayed are the Bayesian estimated CTX plasma concentration profile (continuous curve) with the observed concentrations (diamonds, both left axis) and CTX clearance (intermittent curve, right axis). The duration of ECMO-treatment is indicated by the grey box.



Dose regimen

Individual *posthoc* estimates of CTAX plasma concentration at intervals of 0.2 h over the entire observation period were used to calculate the $t_{>MIC}$ for each patient. Peak CTX concentrations were 98.0 mg/L (33.2-286). DACT concentrations varied between 0 and 38.2 mg/L, with a median of 10 mg/L in the first 12 h post dose. The median $t_{>MIC}$ (calculated for CTX only) was 100%. Thirty-six out of 37 patients had a $t_{>MIC}$ over 50% for all their CTX doses. The remaining patient (PNA < 1 wk) had declining plasma concentrations even after a new dose; it is possible that one or more doses were skipped due to medical procedures at dose time, inadvertent dose registration without actually having given the dose, or other unknown reasons. This caused this individuals $t_{>MIC}$ to drop to 49%. See figure 3 for the individual-predicted CTX and DACT concentrations over a dose interval of 12 h. With the exception of the aforementioned patient, concentrations in all three age categories (PNA < 1 wk with *n* = 26; 1-4 wks with *n* = 7, and > 4 wks with *n* = 4) were above the MIC

Figure 3 Observed and individual-predicted concentrations versus dose-time for cefotaxime (CTX, a & b) and desacetylcefotaxime (DACT, c & d). In plots a and b the target MIC is indicated by the intermittent line. Data points are marked to stratify data by postnatal age (PNA): < 1 wk (open circles), 1-4 wks (grey diamonds), > 4 wks (closed circles). The solid lines represent a naive pooling fit of all data for CTX (nonlinear first-order decline curve) and DACT (course LOWESS curve).



over a period of at least six hours. In general, the patients with a PNA of 1-4 wks were at the bottom of the concentration-time curve, but their dose interval is only eight hours.

Discussion

In the present study, the standard dose regimens provided sufficient $t_{>MIC}$ values for antibiotic efficacy during ECMO, which is reflected in the low number of positive blood cultures. The patient with the lowest $t_{>MIC}$ (49%) had negative cultures throughout his ECMO run while the patients with positive cultures had $t_{>MIC}$ of 90% or higher, but this could be caused by resistance or lack of efficacy of other concomitant antibiotics. The CTX clearance estimate we found in ECMO patients (0.36 l/h) is similar to those for non-ECMO treated full-term neonates, which vary from 0.20-0.55 l/h.[21-23] The distribution volume however is larger than in non-ECMO patients (1.82 l vs. 0.68-1.14 l)[22-23], which could be caused by hemodilution or capillary leakage of protein-bound drug into the extravascular compartment, especially in the early phase of ECMO (24h-36 h after cannulation). This increase is consistent with studies on the pharmacokinetics of vancomycin[24] and theofylline[25] during ECMO. There were no signs of the rapid increase of V following cannulation that has been described for midazolam.[10, 26] Unfortunately we only had few samples before and after ECMO, but patients for which we do have some samples show an interesting clearance pattern upon which we might formulate a hypothesis on the physiological processes involved. It would seem that these critically ill patients have a reduced clearance before cannulation. Many of them have vasopressor drugs with prolonged periods of circulatory shock and profound effects on renal function. As soon as ECMO is initiated, clearance rises to that of a non-ECMO treated patient, possibly due to the continuous hemofiltration and improved organ perfusion the extracorporeal circulation provides. After decannulation, clearance drops again (as the patient is still critically ill) but slowly increases due to maturation or improved disease state. This pattern is visible for both CTX and DACT.

$T_{>MIC}$ was sufficiently high despite the increased distribution volume, which suggests that cefotaxime is dosed higher than strictly necessary in non-ECMO patients. This need not be a problem with drugs that are as safe as cephalosporins are considered to be. [27-28] Our standard dose regimen is based on studies in neonatal and pediatric patients that have identified the influence of gestational age[29], body weight[29], postnatal age[21] and renal function[30] on CTX pharmacokinetics. Although creatinine clearance is a clinically relevant predictor of renal CTX clearance in non-ECMO patients[30], we had no measure of creatinine clearance due to the young age of most patients and the underlying disease state.[31] Serum creatinine was measured, but there was no correlation with CTX clearance after body weight had been added to the model. Interestingly, gestational age and postnatal age did not predict CL or V; other factors such as disease state, protein binding, organ perfusion, etc. might be responsible. A study in 107 neonates[21] showed that clearance increases dramatically with PNA during the first week after birth, but there was no sign of this development in our dataset. It's possible that critical illness in our ECMO patients, with the use of drugs influencing renal perfusion (i.e. high doses of norepinephrin and dopamine) has lead to a low baseline renal clearance that is artificially supplemented by CVVH; the median Q_{CVVH} per individual did not vary much. Although we were able to identify several variables with a statistically significant effect on CTX and DACT pharmacokinetics, the percentage of variability explained is max. 8.1%, which illustrates our limited understanding of ECMO-related sources of PK variability. Considering the sufficiently high $t_{>MIC}$ values in all patients, we probably do not need to adjust the dosage based on these covariates.

DACT concentrations are highly variable as indicated by figure 3c and d. The contribution to the antibacterial effect varies with the microbial species involved, which makes it difficult to make a general assessment of efficacy.[32] DACT concentrations are similar to those in other studies[21, 33]; there does not seem to be an increased risk of DACT accumulation, as has been suggested for hydrophilic metabolites during ECMO.[10] The concentrations may have been slightly overestimated because of the increased CTX hydrolysis that can occur following hemolysis caused by contact with circuit surfaces or storage in plasma tubes.[32]

Since most samples were taken during routine care, the dataset contained a large number of samples for each patient, spread out over the full duration of ECMO. This allows a reliable characterization of time-effects on PK parameters. A potential drawback of this method, as opposed to dose and sample registration by dedicated researchers or their assistants, is additional variability due to inter-observer differences in registration. We expected a maximum discrepancy of 30 min between actual and recorded dose times based on a comparison of observed work routines of individual nurses. A high residual variability in the first hour post-dose is probably caused by inter-nurse variability in the time between CTX injection and medication order validation. Since this phenomenon appeared to be randomly distributed over individuals, doses, t_{EC}, etc, we estimated a separate residual variability, which in effect entails less influence on the final model compared to the samples taken at later dose-times. This also affects the median curve of individual predictions compared to the same curve in the original observations (figure 3a vs. 3b). Data that were recorded during standard clinical practice should therefore be used with caution, but a balanced dataset without blood withdrawal at non-routine sampling times offers important advantages.

Conclusion

The standard cefotaxime dose regimen provides sufficiently high $t_{>MIC}$ in ECMO infants. The CTX distribution volume is higher in ECMO vs. non-ECMO patients (1.82 vs. 0.68-1.14 L), whereas CTX clearance is similar. A dose regimen of 50 mg/kg b.i.d. (PNA < 1 wk), 50 mg/kg t.i.d. (PNA 1-4 wks) or 37.5 mg/kg q.i.d. (PNA > 4 wks) can be used to effectively treat these patients.

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Appendix 1

Equations final PK model cefotaxime and desacetylcefotaxime

Cefotaxime (CTX):

$$CL_{CTX,ij} = \left(CL_{CTX,pop} \times \left(\frac{WT}{3.5}\right)^{\theta_{WT}} \times \left(\frac{t_{END}}{100}\right)^{\theta_{TEND}} \right) \times e^{(\eta_{IIV,i} + \eta_{IOV,j})}$$

Eq. A1

in which $CL_{CTX,ij}$ is the CTX clearance for individual i at the jth occasion, $CL_{CTX,pop}$ is the population average CL for patients with a median weight (3.5 kg), WT is body weight, t_{END} is time after ECMO-decannulation, $\eta_{IIV,i}$ is the inter-individual variability for individual i, and $\eta_{IOV,j}$ is the accompanying inter-occasion variability (in periods of 48 h during ECMO). When $t_{END}=0$ (i.e. before and during ECMO), the accompanying covariate effect is removed from the equation.

$$V_{CTX,ij} = V_{CTX,pop} \times e^{\eta_{IIV,i}}$$

Eq. A2

in which $V_{CTX,ij}$ is the CTX distribution volume for individual i at the jth occasion, $V_{CTX,pop}$ is the population average and $\eta_{IIV,i}$ is the inter-individual variability for individual i.

Desacetylcefotaxime (DACT):

$$CL_{DACT,ij} = \left(CL_{DACT,pop} \times \left(\frac{t_{END}}{100}\right)^{\theta_{TEND}} \times \left(\frac{Q_{CVVH}}{193}\right)^{\theta_{CVVH}} \right) \times e^{(\eta_{IIV,i} + \eta_{IOV,j})}$$

Eq. A3

in which $CL_{DACT,ij}$ is the DACT clearance for individual i at the jth occasion, $CL_{DACT,pop}$ is the population average, t_{END} is time after ECMO-decannulation, Q_{CVVH} is the CVVH flow, $\eta_{IIV,i}$ is the inter-individual variability for individual i, and $\eta_{IOV,j}$ is the accompanying inter-occasion variability (in periods of 48 h during ECMO). When $t_{END}=0$ or $Q_{CVVH}=0$, the accompanying covariate effects are removed from the equation.

$$V_{DACT,ij} = V_{DACT,pop} \times e^{\eta_{IIV,i}}$$

Eq. A4

in which $V_{DACT,ij}$ is the DACT distribution volume for individual i at the jth occasion, $V_{DACT,pop}$ is the population average and $\eta_{IIV,i}$ is the inter-individual variability for individual i.

Differential Equations

$$\frac{dCTX}{dt} = D - \frac{CL_{CTX}}{V_{CTX}} \times AMT_{CMT1}$$

Eq. A5

in which dCTX/dt is the rate of CTX transit, D is the administered dose, CL_{CTX} is CTX clearance, V_{CTX} is the apparent distribution volume and AMT_{CMT1} is the amount of CTX present in compartment 1 at any one time.

$$\frac{dDACT}{dt} = \left(\frac{CL_{CTX}}{V_{CTX}} \times AMT_{CMT1}\right) - \left(\frac{CL_{DACT}}{V_{DACT}} \times AMT_{CMT2}\right)$$

Eq. A6

in which dDACT/dt is the rate of DACT transit, CL_{CTX} is CTX clearance, V_{CTX} is the apparent distribution volume, CL_{DACT} is DACT clearance, V_{DACT} is the apparent distribution volume, AMT_{CMT1} is the amount of CTX present in compartment 1 and AMT_{CMT2} is the amount of DACT present in compartment 2 at any one time, assuming that all CTX is converted to DACT.

CHAPTER 9

Plasma levels of oseltamivir and oseltamivir carboxylate in critically ill children on extracorporeal membrane oxygenation support

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Abstract

Background: To evaluate the effect of extracorporeal membrane oxygenation (ECMO) support on pharmacokinetics of oseltamivir and oseltamivir carboxylate in children.
Methods: Steady state 0-12 hour pharmacokinetic sampling was performed in new influenza A (H1N1) infected children treated with oseltamivir while on ECMO support. Cmax, Cmin and aerea under the curve $(AUC)_{0\text{-}12h}$ were calculated. The age-specific oseltamivir dosage was doubled to counter expected decreased plasma drug concentrations due to increased volume of distribution on ECMO support.
Principal Findings: Three patients were enrolled aged 15, 6 and 14 years in this pharmacokinetic case series. For two children the oseltamivir carboxylate plasma concentrations were higher than those found in children and adults not on ECMO. These increased plasma concentrations related to the increased oseltamivir dosage and decreased kidney function. In one patient suboptimal plasma concentrations coincided with a decreased gastric motility.
Conclusion: Oseltamivir pharmacokinetics are not significantly influenced by ECMO support. Caution is required in case of naso-gastric administration and decreased gastric motility

Introduction

Currently the first influenza pandemic of this century is almost at its end. The new variant influenza A (H1N1) virus appears to be relatively mild compared to its pandemic predecessors.[1] Still, a life threatening disease pattern not characteristic for seasonal influenza has been identified in often young patients infected with new variant influenza A (H1N1). The clinical picture of this severe illness is one of Acute Respiratory Distress Syndrome (ARDS), sometimes associated with septicemia-like symptoms. While relatively rare, these cases impose a burden on intensive care units.[2-4]

The optimal treatment for children and adolescents with influenza associated ARDS has not yet been established. Based on recent data, mostly obtained in adults, the use of extra corporeal membrane oxygenation (ECMO) support in combination with the use of neuraminidase inhibitors appears to be a feasible option.[3] ECMO support is associated with altered pharmacokinetics for several drugs. This is due to the increment of the total circulation volume and adherence to plastic tubing and membranes.[5] Suboptimal plasma concentrations of neuraminidase inhibitors may be associated with reduced antiviral effectiveness of the drug and the development of viral drug resistance.[6] The aim of this study is to evaluate the effect of ECMO support on plasma concentrations of oseltamivir and oseltamivir carboxylate in children.

Methods and design

This is a prospective analysis of pharmacokinetic data from new influenza A (H1N1) infected children (0-18 years) treated with oseltamivir that required ECMO support (Medtronic Sh. 70 USP class VI 3/8 x 3/32 superTygon®, Medtronic, Minneapolis, USA). As routine protocol the age-specific oseltamivir dosage was doubled to counter expected decreased plasma drug concentrations due to ECMO support. This resulted in the following oseltamivir dosing regimen: <15 kg: 60 mg/day q12h, 15-23 kg: 90 mg/day q12h, 23-40kg: 120 mg/day q12h and >40 kg: 150 mg/day q12h. Medication was administered though nasogastric or duodenal tube. According to our hospital based ECMO protocol continuous venovenous hemofiltration (CVVH) (Multiflow 100 Hospal, Lyon, France) was performed.

Twenty-four hours after initiation of ECMO support blood samples were obtained from the ECMO system in BD Hemocard™ EDTA/NaF tubes. Sampling was performed at 0-1-2-4-6-12 hours after oral administration of oseltamivir suspension 15mg/ml (patient 1) and 12mg/ml (patient 2 and 3). After sampling and centrifugation, the supernatant serum was stored at -80°C and shipped in batch. Plasma concentrations for oseltamivir and oseltamivir carboxylate were determined by PRA, Bio-analytical Laboratory Assen, The Netherlands by a commercial validated HPLC assy.

Medical data was collected using a patient data management system. Written informed consent was obtained from parent or care takers prior to enrolment. The study was approved by the Erasmus MC medical ethics review board.

Results

Three patients were enrolled (1 girl, 2 boys) aged 6, 14 and 15 years in this pharmacokinetic case series. A total of 17 samples (6, 6 and 5 samples each) were available for analysis. None of the patients had a medical history that could influence the oseltamivir pharmacokinetics. All patients required ECMO due to ARDS. Patient one and two received enteral feeding and tamiflu suspension via a duodenal tube. Patient three had severe gastro-enteric bleeding and decreased gastric motility with gastric residue as a result of septicemia accompanied with diffuse intravascular coagulopathy and heparinization on ECMO. Medication in this patient was administered via a gastric tube. Patient one and three had decreased renal function expressed by increased creatinine concentrations

Table 1. Baseline characteristics of patients

Patient	**1**	**2**	**3**
Age (years)	15	6	14
Dosage (Q12h)	150	120	150
Dosage (Q12h/kg)	3	4	2,7#
Sex	F	M	M
Creatinine (μmol/l)	88	32	100
Formulation and route of administration	Suspension, Duodenal tube	Suspension, Duodenal tube	Suspension, Gastric tube
Oseltamivir			
Cmax (ng/ml)	92,4	41,4	3,4
Cmin (ng/ml)	1,9	0	0
AUC_{0-12h} (ngxh/ml)	232,9	87,4	25
Oseltamivir carboxylase			
Cmax (ng/ml)	1300	548	224
Cmin (ng/ml)	736	236	77,2
AUC_{0-12h} (μgxh/ml)	10642	3211	978,1

Weight estimated, due to critical illness and later death impossible to weigh.
Cmin minimal concentration, Cmax maximal concentration, AUC area under the curve

at the time of sampling (see table1). ECMO flow rates and hemofiltration rates were not adjusted during sampling.

The results of the pharmacokinetics concentrations of oseltamivir and oseltamivir carboxylate are presented in table 1 and figures 1 and 2. In patient three suboptimal plasma concentrations were observed for both the parent drug and oseltamivir carboxylate. These coincided with a decreased gastric mobility and nasogastric medication administration. For none of the patients adverse medication reactions were reported.

Figure 1

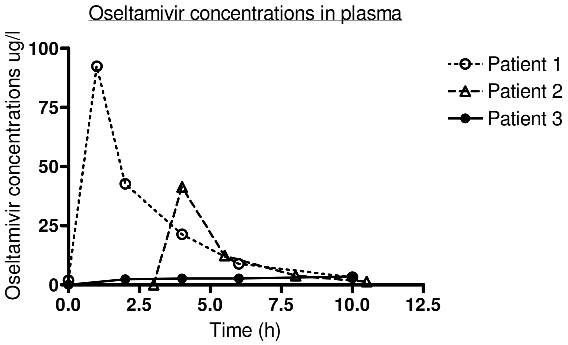
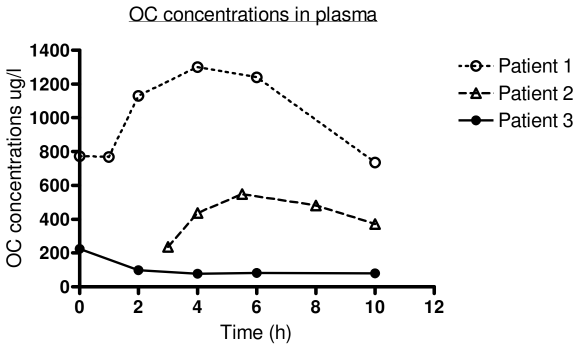


Figure 2



Discussion

In this pharmacokinetic case study high plasma concentrations for oseltamivir carboxylate were achieved in two out of three patients. Both patients had plasma concentrations that were almost two fold higher compared to historical controls in children aged 3-5 years and 13-18 receiving 2 mg/kg oseltamivir.[7, 8] The elevated plasma concentrations found in our study reflect in part the higher dosing used in our patients. In addition, the (mild) renal impairment seen in patient one may also have led to an increase in plasma oseltamivir carboxylate concentrations. In a study by He et al. this has also been shown in adults with mild to severe renal failure.[9]

The plasma concentrations found in this case series show a marked variance. This was previously also seen in non critically ill children.[7, 8] Age related changes in the clearance of oseltamivir carboxylate may be an additional explanation.[7] Patient three clearly had suboptimal serum concentrations of both oseltamivir and oseltamivir carboxylate. In this patient the absorption of oseltamivir was severely impaired due to gastric bleeding and decreased gastric motility. In critically ill adults two studies report that oseltamivir can be safely used and is adequately absorbed following nasogastric administration.[10, 11] Our finding warrants caution in patients with severe gastrointestinal problems, not only in ECMO patients but in all critically ill patients with gastrointestinal problems. We propose that in these patients, conversion to inhaled or when available intravenous medication (i.e. zanamivir) is indicated.

Although the study is limited by its size it is the first study to show that adequate plasma concentration of oseltamivir and oseltamivir carbocylate can be achieved in critically ill patients on ECMO. The differences found in plasma concentrations in our patients fall within normal inter-patient variability and can also be attributed to organ function and drug absorption. Based on this data ECMO does not seem to influence pharmacokinetics of oseltamivir and oseltamivir carboxylate, negating the need to increase dose in patients on ECMO.

Conclusion

Oseltamivir pharmacokinetics are not significantly influenced by ECMO support. An increase in oseltamivir dosage is therefore not necessary while treating patients on ECMO. Caution is required in case of nasogastric administration and decreased gastric mobility. In these patients another route of antiviral medication should be considered.

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CHAPTER 10

General discussion

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) support is an established life saving therapy in neonatal respiratory and cardiac failure[1] and is also widely used in pediatric and adult patients with respiratory and/or circulatory failure.[2-8] The primary use of ECMO support is to provide gas exchange and cardiovascular support while preventing barotrauma, volutrauma, biotrauma and oxygen toxicity associated with mechanical ventilation and insure sufficient oxygen delivery to tissues to prevent multiple organ failure.

Survival after ECMO support varies depending on the primary diagnosis; ranging from 94% for meconium aspiration syndrome (MAS) to 24% for cardiac arrest in neonatal ECMO. In pediatric patients reported survival ranges between 42% and 70%. (ELSO registry, 2010) Overall survival after ECMO support is 62%, and mortality is primarily associated with pre-ECMO conditions and complications on ECMO such as bleeding, renal failure and infections.[9-13] Prolonged ECMO support is associated with poor outcome[13] and with increased complications; especially nosocomial infections.[14-23]

Pharmacotherapy during ECMO

Improvement of outcome could be accomplished by effective treatment of the primary diagnoses leading to ECMO, as well as by a reduction of adverse effects of ECMO such as intracranial hemorrhage, edema, nosocomial infections and opioid or benzodiazepine withdrawal symptoms. Pharmacotherapy plays an important role. Patients on ECMO receive 10 or more drugs per day; for treatment of persistent pulmonary hypertension, bacterial or viral infections, circulatory failure, fluid overload and distress.[24]

Pharmacokinetic (PK) and pharmacodynamic (PD) studies in neonates and older children on ECMO are sparse and most results are limited by small sample size. The available studies have demonstrated altered PK for midazolam[25], morphine[26-27], gentamicin[28-32], vancomycin[33-36], ranitidine[37], theophyline[38] and bumetanide[39] (table 1). Volume of distribution as well as clearance are altered for most of these drugs making it difficult to predict plasma concentrations and consequent effects in neonates and older children on ECMO.

Differences in ECMO techniques and variability in the patient population as well as restrictions on blood sampling in the neonatal and pediatric population pose challenges to pharmacological research in this patient group. Disease state, SIRS and capillary leakage, increased circulating volume due to the ECMO circuit and decreased organ perfusion all contribute to changes in pharmacokinetics. So far, the influence of pharmacogenetics has not been assessed, but genetic variation in the enzymes involved in metabolism and elimination might explain some of the variability found in PK. Timing of DNA-sampling is difficult however: blood sampling should occur before cannulation since patients receive large amounts of donor blood products to prime the circuit and to maintain hamatocrit. Alternative methods such as DNA samples via buccal swaps should be used to obtain these data.

To improve pharmacotherapy in ECMO patients both PK and PD studies are necessary to establish adequate dosing regimens of sedatives, analgesics, antibiotics, diuretics and antiviral drugs. Understanding PK and identifying co-variables that influence PK and PD will enable clinicians to predict effect and effectiveness of both frequently used drugs as well as newer drugs not previously studied. This knowledge will aid to prevent under and over dosing as well as reduce adverse events.

This thesis presents the results of a number of clinical studies evaluating pharmacokinetic and pharmacodynamic aspects of drug therapy in neonatal and pediatric patients on ECMO support.
Several aspects of PK/PD of drugs used during ECMO support were evaluated *in vitro* as well as in a large prospective observational study including almost 80 neonates and children on venovenous (VV) and venoarterial (VA) ECMO. The results of these studies are discussed in this thesis and in the thesis of Maurice Ahsman entitled: Determinants of pharmacokinetic variability during extracorporeal membrane oxygenation: A roadmap to rational pharmacotherapy in children, Erasmus MC, 2010.
First the effect of different ECMO circuits on drug disposition was studied in an *in vitro* setting. Secondly, with the use of liquid chromatography-mass spectrometry (LC-MS) and NONMEM analysis, pharmacokinetic data for several drugs could be obtained with limited blood sampling. Some of the methods used to validate LC-MS for quantification of drugs, as well as population pharmacokinetic data on sildenafil and midazolam are described in the thesis of Maurice Ahsman. Finally, we characterized pharmacodynamic endpoints for sedation and analgesia, evaluated fluid management regimens and antibiotic therapies on ECMO. The results are described in this thesis.

Extracorporeal membrane oxygenation: drug losses

Adsorption of drugs to the material of the ECMO systems may contribute to the reported altered pharmacokinetics. Adsorption rates have been tested for several drugs.[25, 40-43] *In vitro* tests show significant adsorption, especially of lipophilic drugs, to different ECMO circuits. We have shown a clear relationship between lipophilicity, expressed as Log P values (where more positive log P values represent higher lipophilicity), and adsorption in an *in vitro* setting (chapter 2). Especially fentanyl and midazolam showed equal or higher adsorption to the ECMO circuit than previously reported.[40, 44-46] Different methods and materials could in part explain the observed differences. We have shown that adsorption in a centrifugal ECMO circuit with a microporous membrane was significantly lower compared to the combination of a silicone membrane and a roller-pump circuit. Since adsorption was not influenced by circuit or membrane size in roller-pump silicone membrane circuits as shown in chapter 2, this effect is most likely due to the different oxygenator. This finding confirms earlier reports of drug adsorption in cardiopulmonary bypass oxygenators.[47] Secondly our circuits included a hemofilter which have been shown to adsorb drug such as vancomycin, amikacin and levofloxacin in addition to filtration.[48-49] This could have contributed to the higher extent of adsorption observed in our ECMO circuits.

Translating *in vitro* results to clinical practice remains difficult. There is a large discrepancy between drug adsorption observed in our *in vitro* tests and the increased volume of distribution observed in our pharmacokinetic study in neonates on ECMO.[50] Whether this is due to rapid distribution in body fat tissues or whether continuous infusion rates are higher than adsorption rates in our ECMO circuits remains uncertain. Another contributing factor could be the addition of the hemofilter which was absent in out clinical study.

The *in vitro* results with rapid adsorption within minutes after injection indicate that highly lipophilic drugs should not be administered via the ECMO circuit. Mulla and colleagues showed significant increased midazolam dosages of continuous infusions in patients who received infusions directly into the ECMO circuit, especially in the first 24 hours. *In vitro* studies with continuous infusions to establish adsorption rates and saturation rates, as well as wash out experiments that compare different components of both new and used circuits might increase our understanding in the dynamics of circuit adsorption.

These studies will enable us to better predict pharmacokinetic effects of drugs in ECMO patients and possibly incorporate these effects into PK population models.

In conclusion, ECMO circuits affect drug availability by adsorption to components of the ECMO circuit. The relationship between log P values and adsorption will enable clinicians to estimate the extent of adsorption of different drugs, based on their chemical properties. Future studies need to address maximum adsorption rates and need to try to incorporate *in vitro* data into pharmacokinetic models.

Sedation and analgesia on ECMO

Continuous sedation is widely used during ECMO to reduce oxygen consumption and to minimize agitation to prevent impaired ECMO flow or even decannulation. However prolonged use of sedatives and analgesics is associated with several complications. In adults deep sedation or neuromuscular paralysis decreases or negates spontaneous ventilation, which decreases sputum clearance and consequently increases the risk of ventilation associated pneumonia.[51] Several studies have shown that a reduction of sedative use in the adult Intensive Care Unit (ICU) setting, via daily sedation interruption protocols or no continuous sedation protocols, reduces duration of mechanical ventilation and ICU stay.[52-53] Two meeting reports on daily interruption in children presented a reduction of midazolam dose in the intervention group although both studies lacked power to show an effect on mechanical ventilation or ICU stay.[54-55] Furthermore, continuous midazolam and lorazepam infusions have been associated with an increased risk of delirium in adult ICU patients.[56-57]
In children prolonged sedative use and high cumulative dosing is associated with dependency and withdrawal syndrome.[43, 58-73] Especially ECMO patients seem to be at risk for developing withdrawal symptoms necessitating prolonged weaning of opioids and sedatives. [74] In addition, pentobarbital use in pediatric patients is associated with hemodynamic complications, withdrawal symptoms and neurological sequelae.[75]
Furthermore, animal studies in rats and mice that received morphine, midazolam, propofol or high doses of ketamine in the newborn period found increased neuroapoptosis in these animals.[76-78] These observations suggest that a reduction in sedative exposure may improve short and long term outcome in neonates and children. Although unknown if these findings can be extrapolated to humans, it further stimulates the use of sedation protocols that minimize sedative use while maintaining adequate sedation levels.

Increased sedative requirements have been described in ECMO patients, although evaluation of sedatives and analgesia use with regular validated scores is lacking.[63, 79-83] In addition there are no international guidelines for sedation on ECMO defining optimal sedation targets. In chapter 3 we describe the use of a standardized sedation protocol on ECMO. Half of all patients needed three or more drugs to achieve sedation targets including nine percent of patients treated with continuous pentobarbital infusions for sedation. Additional medication was started within the first 48-72 hours after cannulation for ECMO, suggesting that increased volume of distribution as well as pre-ECMO conditions may play an important role in sedation needs during ECMO. Most children aged 1-23 months received additional medication besides midazolam and morphine. Furthermore increased sedative use was associated with duration of pre

ECMO ICU stay, and a higher sedative dose prior ECMO. Interestingly Pediatric Risk of Mortality Scores (PRISM2) scores and vasopressor scores, indicating disease severity, were higher in patients who required less sedatives. Decreased metabolism associated with a more severe disease state could result in higher plasma concentrations of both midazolam and morphine explaining decreased sedative needs. However we found no difference in plasma concentrations in the first 72 hours on ECMO in patients with and without additional medication. (unpublished data)
Pharmacodynamic aspects probably play an important role in the increased sedative needs in ECMO patients. Disease state might also influence pharmacodynamics of sedatives with critically ill patients needing less sedation. Whether psychological factors, especially in toddlers and infants, play a role in the achieving satisfactory sedation remains unknown. Conscious sedation with an awake but comfortable patient may be more difficult to achieve in this age group leading to deeper sedation levels. Finally patients with additional medication had longer ECMO runs, although increased sedative needs occurred mostly in the first 72 hours. Whether this is due to the primary diagnosis, disease state on ECMO, or the increased sedative use, remains unsure and needs to be studied prospectively in a randomized controlled trial.

Although there is limited pharmacokinetic data on morphine and midazolam in neonates on ECMO, no data are available in older children on ECMO. Also there are no pharmacokinetic data on clonidine or ketamine-S in ECMO patients of any age. Dosing of these drugs is titrated to effect, but the therapeutic window in ECMO patients is unknown. In our study population the addition of clonidine sufficed in 24 patients, whereas ketamine-S continuous infusions alone were effective in only one patient. In non ECMO ICU patients, clonidine has been shown to reduce midazolam requirements and is well tolerated in doses up to 2µg/kg/hr.[84] However pharmacokinetic population models indicate that in children 1-6 years a maintenance dose of clonidine of 0.3µg/kg/hr, after an initial loading dose and higher infusion rates for three hours, achieves plasma concentrations of 1µg/l which are associated with effective sedation in adults.[85] Our median clonidine dose was 0.3µg/kg/hr. However clonidine is a highly lipophylic drug and clearance is mostly dependent on renal function. Hence, both clearance and volume of distribution of clonidine could be significantly altered in ECMO patients. Pharmacokinetic studies need to be performed in ECMO patients to establish evidence based dosing regimens and determine optimal dosing in randomized controlled trials evaluating midazolam vs. clonidine continuous infusions.
In 65% of all patients, morphine was given despite low NRS scores suggesting that morphine was not used as analgesic, but predominantly as a sedative in our study population. Since cannulation for ECMO is considered a minor surgical procedure non-opioid analgesics such as paracetamol might suffice to achieve adequate pain relief. This ap-

proach may reduce opioid use and its related adverse events. Therefore we have recently started a randomized controlled comparing intravenous paracemamol and morphine for analgesia in ECMO patients.

Despite overall low sedation and pain scores which should warrant dose reduction medication doses were rarely reduced by the attending medical team. Data in adults suggest however that limiting sedatives and analgesics may influence duration of mechanical ventilation, withdrawal symptoms and other long term outcome. A solution for this problem may be daily interruption of continuous sedation. In chapter four, we have shown that interruption of sedatives is feasible in neonates on ECMO. Furthermore trough levels of midazolam and morphine in this patient group were much lower than previously reported in neonates on ECMO as well as in non ECMO neonates. This indicates that sedation interruption has the potential to reduce overall sedative use. Although patients with additional sedatives and analgesics had a longer duration of ECMO this could be due to the primary diagnosis more than medication use but it warrants further study.

In previous studies correlation between plasma concentrations of midazolam and level of sedation have been poor with large inter and intra-patient variability.[86-89] Oversedation and a reluctance to reduce analgesics and sedatives in critically ill patients further limits interpretation of plasma concentrations. Dosing regimens based solely on pharmacokinetic data can therefore overestimate dosing requirements. Future randomized controlled trials need to evaluate daily interruption or no continuous sedation protocols in both neonates and older children on ECMO. These studies should focus on both short term clinical outcome parameters; withdrawal, delirium, total duration of ECMO and total mechanical ventilation and long term neurological and psychological outcome.

The role of delirium in Pediatric Intensive Care Units (PICU) is an emergent topic of interest. In adult ICUs delirium is reported in 20-80% of all ICU patients.[90] Both midazolam and lorazepam are associated with increased risk for delirium in the adult ICU population.[56-57] Moreover, in the adult ICU delirium is associated with higher mortality.[91-92] Unrecognized hyperactive delirium may also in part explain excess sedative needs in ICU patients. Failure to diagnose delirium delays or withholds effective treatment and increases sedative use unnecessarily. In the PICU, reported delirium rates range between 3-18%.[93] However diagnosing pediatric delirium in the ICU setting is difficult, especially since 80% of children in the Dutch PICU's are below two years of age. To date no effective diagnostic tool is available, although diagnostic criteria are being proposed by several authors.[94-95] Future studies need to incorporate these diagnostic tools for delirium in PICU patients to address the incidence of delirium and the effect of its treatment on sedation scores and outcome. Within this context pharmacokinetics, efficacy and safety of antipsychotic drugs such as haloperidol need to be evaluated in pediatric patients on ECMO.

In conclusion, a standardized and validated sedation and analgesia protocol leads to overall low COMFORT-B and NRS pain scores in patients on ECMO. Midazolam and morphine continuous infusions below 300µg/kg/hr and 30µg/kg/hr resulted in adequate sedation in half of our patients while with the addition of clonidine as a tertiary sedative 82% of all patients were adequately sedated. Patients aged 1-23 month had a higher risk for inadequate sedation. Pharmacokinetic data of midazolam, morphine and clonidine are necessary to evaluate optimal dosing in this patient group.

There should be more attention to reduction of sedatives and analgesia in the presence of low scores. Interruption of sedatives and analgesics is feasible and safe in neonates on ECMO without an increased risk of complications. Single time interruption of sedatives and analgesics result in lower drug exposure while maintaining adequate sedation. Randomized controlled trials are needed to substantiate these findings and evaluate outcome benefits such as a reduction in time on ECMO, mechanical ventilation and incidence of abstinence symptoms.

Fluid management on ECMO

Fluid overload, SIRS and consequent capillary leakage remains a challenge in ECMO patients. Fluid overload and capillary leakage increases pulmonary edema, possibly worsens ARDS and results in longer ECMO runs and extended period of mechanical ventilation. Fluid overload of more than 10% and failure to return to normal (dry) weight are associated with worse outcome.[9] Several authors report renal failure prior to, or during ECMO, as a risk factor for mortality.[9, 22, 96] Therefore, adequate reduction and prevention of fluid overload in ECMO appears to be an important factor in outcome.

Strategies to diminish fluid overload include diuretics and dialysis or hemofiltration. In chapter 5 we describe a pharmacodynamic study of furosemide dosing in ECMO patients. We show that continuous furosemide administration is well tolerated in ECMO patients and leads to stable and adequate diuresis. In a follow up study continuous infusions furosemide of 4mg/kg/d resulted in plasma concentrations below toxic levels. [97] However dosing regimens of continuous furosemide infusions need to be evaluated prospectively.

Cardiopulmonary bypass, ECMO and septic shock trigger a systemic inflammatory response syndrome (SIRS) leading to capillary leakage and edema. In theory hemofiltration during ECMO should reduce SIRS and consequent capillary leakage as well as increase effective fluid management. Hemofiltration has been used to decrease circulating cytokines in SIRS, septic shock and post cardiopulmonary bypass patients, improving short term outcome.[98-99] Renal replacement strategies have also been used on ECMO, especially in patients with renal failure during ECMO. In chapter 6 we describe a case-comparison study demonstrating that the routine use of hemofiltration incorporated in the ECMO circuit is viable and significantly decreases ECMO duration, time on mechanical ventilation and number of blood transfusions. Others have shown similar benefits in using CVVH as a standard adjuvant therapy in ECMO instead of rescue therapy with renal failure.[100-101] In contrast low survival rates reported with renal replacement therapy in the ELSO registry and literature[102] are probably based on patients with severe renal failure due to circulatory failure prior to, or during ECMO, and do not reflect survival in the routine use of CVVH.

Blood transfusions in critically ill children have been associated with prolonged ICU stay and higher mortality.[103-104] Using hemofiltration, the volume of the transfused blood products can be extracted during the transfusion.This is thought to optimize the benefit of transfusions while maintaining a negative or stable volume balance, and reduce the total amount of transfusions needed. The reduction of blood product transfusions could be contributing to the beneficial effects of hemofiltration found in our study.

However despite positive short-term effects of hemofiltration on ECMO, no effect on mortality has been established, possibly due to the small sample size of the studies.

Furthermore there is an ongoing debate on CVVH techniques.[101] Incorporating a hemofilter in an ECMO system is simple and effective but dialysate flow and volume extraction regulated via infuser pumps may not be as reliable as using standard hemofiltration systems, risking rapid fluid depletion compared to separate dialysate pumps. We found a two percent difference between described and actual infusion and extraction rates of our infuser pumps (unpublished data). In a three kilogram newborn on ECMO with a 50ml/kg/h filtration flow this results in a 3 ml/h extra fluid loss. Ricci et al found similar differences in actual net ultra-filtration in neonates and children during renal replacement therapy.[105] Further studies need to focus on different pumps used and need to determine optimal flow rates to eliminate cytokines.

Using standardized CVVH eliminates creatinine as a reliable marker for endogenous kidney function. Most patients on ECMO have a decreased urine output in the first few days on ECMO, but we also found a trend towards a decreased urine output in the dialysis group compared to patients without CVVH. Hence Acute Kidney Injury (AKI) may be masked by routine CVVH use. Several factors may predispose for AKI. There are reports of increased hemolysis with added hemofiltration on ECMO, possibly increasing the risk of AKI.[106] Secondly, aggressive fluid extraction may result in hypovolemia and pre-renal kidney failure, while high flux hemofiltration in children reduces levels of pro-BNP[107], thereby decreasing the ability to regulate volume overload.[108] New biomarkers such as Neutrophil Gelatinase Associated Lipocalin (NGAL) and cystatin C may help evaluate

kidney function on ECMO and guide filtration rates while identifying patients with acute renal failure. Use of non invasive techniques to measure tissue or organ perfusion such as Near Infrared Spectroscopy (NIRS) may also aid to evaluate renal perfusion.[109-110]
Finally, the addition of a hemofilter influences pharmacokinetics of renally cleared drugs in different ways. Both drug characteristics as well as filter characteristics determine if a drug is filtrated by dialysis. High volume of distribution, lipophilicity, molecular weight and high protein binding reduce free plasma concentrations, thereby limiting the ability to be filtrated by the hemofilter. Filter material, filter size and filter pore size influence both adsorption and filtration of drugs by the hemofilter.[111-112]
Decreased endogenous renal function may decrease tubular excretion and lead to higher plasma concentrations for drugs cleared by active excretion, whereas increased clearance compared to pre-ECMO conditions may be found in drugs with an elimination based on glomerular filtration. Drugs that are partly reabsorbed such as fluconazole may have higher clearance rates on high flux hemofiltration compared to normal renal clearance.[113]
Several antibiotics are cleared using CVVH and can be partially predicted, but there is wide inter-patient variability necessitating therapeutic drug monitoring for drugs with a small therapeutic window (such as vancomycin) that are predominantly cleared via the kidney.[113-114] In our studies clearance of cefotaxime and sildenafil increased on ECMO compared to pre- and post-ECMO conditions, possibly due to increased organ perfusion as well as the added CVVH. Future pharmacokinetic studies need to address the effect of hemofiltration during ECMO on pharmacokinetics of renally cleared drugs. Collecting urine and dialysate while measuring plasma concentrations of drugs and metabolites will enable to researches to assess the relative contribution to clearance of kidney and CVVH. Combining biomarkers and pharmacokinetic studies may identify more reliable markers for renal clearance in patients on ECMO with CVVH.
In summary, both intermittent as well as continuous furosemide infusions lead to stable diuresis in ECMO patients. Prophylactic hemofiltration in ECMO patients is superior to diuretics in maintaining fluid balance and reduces time on ECMO and on mechanical ventilation. Future studies should focus on monitoring endogenous renal function, long term renal function and effect of hemofiltration on pharmacokinetics.

Infectious diseases on ECMO

In chapter 7, we describe antibiotic use and outcome in patients with nosocomial infections in a study population of 47 neonates and 31 pediatric patients during ECMO support. Infections remain a significant problem in neonates and children on ECMO with 37% of patients with a proven infection prior to, or during ECMO support and an additional 15% of patients with suspected infection. Nosocomial blood stream infection (BSI) rates in our population varied from 14% or 23 BSI/1000 ECMO days to 9% or 13 BSI/1000 ECMO days depending on definitions. Although nosocomial rates in our center are comparable to reported infection rates in the literature, interpretation of the data is difficult due to the different criteria used. Even using Center of Disease Control (CDC) criteria for nosocomial BSI, infection rates are still 5-10 times higher compared to central line related BSI in non ECMO critically ill children.[16, 115] Moreover nosocomial infections are associated with higher mortality, although most patients die due to the underlying disease.

More interestingly a high number of patients received antibiotics despite negative cultures, or antibiotics were changed due to persistent bacteriemia. A total of 21 different antibiotics were prescribed during the study period, whereas empirically started antibiotics were only discontinued in nine patients. Of all the antibiotics given only 20% have been studied in the neonatal or pediatric population on ECMO (table 1).

Several factors contribute to the high antibiotic use in ECMO patients. There is a lack of reliable diagnostic tools to identify sepsis.[21, 116] We showed that C reactive Protein (CRP) does not discriminate between suspected and proven sepsis. However high levels of CRP do result in prolonged antibiotic use since it was the most important reason for antibiotic change in our patients. Procalcitonin (PCT), a new biomarker for sepsis, is a useful tool for detecting early sepsis and evaluating efficacy of antibiotics in pediatric patients.[117] PCT is elevated in post operative cardiac patients after cardiopulmonary bypass, which questions its use in ECMO patients as a marker for sepsis.[118] However serial measurements might be useful in determining early sepsis. PCT seems to have a high sensitivity, meaning that low PCT values exclude sepsis, thereby negating the use of prolonged antibiotics.[118]

Secondly the use of surveillance cultures may induce unnecessary antibiotic use. Single time positive blood cultures with skin contaminants occurred in four of our patients; in three patients there was no clinical suspicion of infection. In spite of consequent persistent negative blood cultures as well as absence of clinical signs of infection all three patients received therapeutic antibiotics. We conclude that surveillance cultures lead to high costs and overtreatment of patients on ECMO. Therefore we advise to abandon standard surveillance cultures and only perform cultures on indication.

Finally prevention strategies have been shown to reduce nosocomial infection rates in ECMO patients.[14] This may be the most important aspect of reduction of nosocomial infections and antibiotic use in all ICU patients. Education as well as implementation and monitoring of hygienic preventive measures may have a large impact on nosocmial infections.

Table 1 drugs used during ECMO

Antibiotics	n	PK studies
Amoxycilline		-
amoxycilline-clavulic acid		-
Azitromycin		-
Benzylpenicillin		-
Cefazoline		-
Cefotaxime	37/neonate/ infant	[125]
Ceftazidime		-
Ceftriaxon		-
Cefuroxim		-
Ciproxin		-
Claritromycin		-
Cotrimoxazol		-
Erythromycin		-
Flucloxacilline		-
Gentamicin	29/neonate	[28]
Gentamicin	18/infant	[29]
Gentamicin	17/neonate/ infant	[30]
Gentamicin	15/neonate	[31]
Gentamicin	10/neonate	[32]
Linozolid		-
Meropenem		-
piperacillin_tazobactam		-
Rifampicine		-
ticarcillin-clavulanic acid	2/child	[131]
Tobramycin		-
Vancomycin	6/neonate	[132]
Vancomycin	12/infant	[35]
Vancomycin	15/neonate	[33]
Vancomycin	45neonate/ infant/child	[34]

Antimycotics	N	PK studies
Caspofungin	2/adult	[122]
Caspofungin	1/adult	[123]
Fluconazol		
Metronidazol		
Voriconazol	2/adult	[122]
Voriconazol	1/child	[126]
Voriconazol	1/adult	[124]

Antiviral	N	PK studies
Lamivudine		
Oseltamivir	3/child	Wildschut et al
Ribavirin	1/neonate	[128]
Zidovudine		

vaso-active	N	PK studies
Amiodarone	1/neonate	[130]
bosentan		
Captopril		
digoxine		
enalapril		
Labetalol Hcl		
Nifedipine retard		
Sildenafil	23/neonate	Ahsman et al.

Diuretics	n	PK studies
Bumetanide	11/nneonate	[39]
Furosemide	7/neonate	[97]
hydrochloorthiazide		
spironolacton		

sedatives and analgesics	n	PK studies	Miscellaneous	n	PK studies
clonidine			Ranitidine	13/neonate	[37]
fentanyl	12/infant	[124]	dexamethason		
Ibuprofen				domperidon	
ketamine-S			esomeprazol		
midazolam	20/neonate	[25, 79]	heparine		
midazolam	20/neonate	[50]	hydrocortison		
morphine	11neonate/ infant	[27]	octreotide		
morphine	7/neonate/ infant	[43]	Omeprazol		
morphine	14/neonate	[26, 127]	phenytoine		
paracetamol				prednisolon	
pentobarbital			rocuronium bromide		
phenobarbital	1/neonate	[129]	Theophyline	75neonate/child	[38]
propofol			valproic Acid		
			vecuronium Bromide		

Medication given to 78 neonatal and pediatric ECMO patients described in chapter 3 and 7 of this thesis
n/ number of patients included in study, [number] reference to studies,

Besides the use of preventive measurements there is an urgent need for PK data on antibiotics.

Twenty-four percent of our patients had an ongoing sepsis on ECMO despite adequate antibiotics. These ongoing infections may have been related to sub-therapeutic drug concentrations. Plasma concentrations of most antibiotics are not known and need to be established to effectively treat infections. Efficacy of antibiotics whose effectiveness depends on peak concentrations such as aminoglycosides may be reduced by increased volume of distribution whereas the risk of adverse events related to trough levels may be increased due to reduced clearance. Antibiotics whose effectiveness depends on time above MIC such as cefalosporins and vancomycin may be affected by differences in drug clearance as well as volume of distribution. Both the risk of under treatment as well as toxicity needs to be considered while dosing antibiotics on ECMO. PK models predicting plasma concentrations for antibiotics need to be developed to guide antibiotic dosing regimens in ECMO patients. Using NONMEM and sparse sampling, we were able to describe cefotaxime pharmacokinetics in neonates and young children. Reassuringly, for all but one patients plasma concentrations of cefotaxime were above MIC indication effective plasma concentrations despite an increased volume of distribution. However there was considerable variability in plasma concentrations of both cefotaxime and the metabolite. The altered pharmacokinetics found in patients on ECMO as well as the inter-patient variability did not influence dose requirements; mainly due to the large therapeutic window of cefotaxime. The only covariates with a statistically significant correlation were body weight and time after decannulation (CTX clearance), and hemofiltration flow and time after decannulation (DACT clearance). These results do not offer predictive determinants or new clues into mechanisms of PK changes, especially considering the large unexplained inter-patient variability. In a few individuals for which samples were available pre- and post-ECMO, we could see a temporarily increased clearance during ECMO leading to lower plasma concentrations compared to pre- and post-ECMO concentrations. We were unable to model this increase with statistical significance, but it indicates that ECMO support or the addition of CVVH temporarily improves metabolism and excretion. The instantaneous improvement at the time of cannulation suggests that improved perfusion, clearance due to the hemofiltration or adsorption could be the underlying mechanisms. This is supported by the sudden clearance drop after decannulation, since this entails cessation of artificially improved organ perfusion and oxygenation as well as removal of clearance and adsorption due to hemofiltration and ECMO circuit.

In the recent H1N1 influenza pandemic ECMO support was successfully instigated in children and adults diagnosed with influenza, with survival rates of 70%.[119-121] Oseltamivir is the drug of choice in H1N1 new influenza, where alternatives such as inhaled zanamivir or intravenous zanamivir have not been evaluated in critically ill children. Three patients with H1N1 new influenza supported with ECMO were enrolled in our pharmacokinetic study. Although limited in size we showed that adequate plasma levels could be achieved in ECMO patients and that the influence of the ECMO circuit is limited. One patient with profuse gastric retentions and hematemesis failed to achieve adequate plasma concentrations of oseltamivir and oseltamivir carboxylate. This is interesting, because the drug is administered orally and is thus dependent on adequate oral absorption to reach therapeutic plasma concentrations. The patients studied were critically ill, which may lead to decreased gut transit times, but also decreased intestinal transporter and metabolism. Hence, prediction of plasma levels of orally administered drugs may be even more difficult than in drugs administered intravenously to ECMO patients. Based on these studies dosing conform guidelines for non ECMO patients can be recommended. Future pharmacokinetic studies need to target additional antibiotics such as meropenem and linezolid to obtain dosing regimens for ECMO patients.

In conclusion, we have shown that bacterial infections are an important problem in ECMO patients. Reducing unnecessary antibiotic use in this population may reduce the emergence of multi resistant pathogens, especially since there is a potential for sub-therapeutic plasma concentrations in these patients. There is an urgent need for reliable biomarkers for identifying bacterial infections and evaluate response to therapy.

Furthermore there should be a priority to evaluate PK of the most frequently used antibiotic, antifungal and antiviral drugs to guide dosing. In light of this need, we developed a population PK model for cefotaxime and evaluated oseltamivir, confirming adequacy of the current dosing protocols based on non ECMO patients.

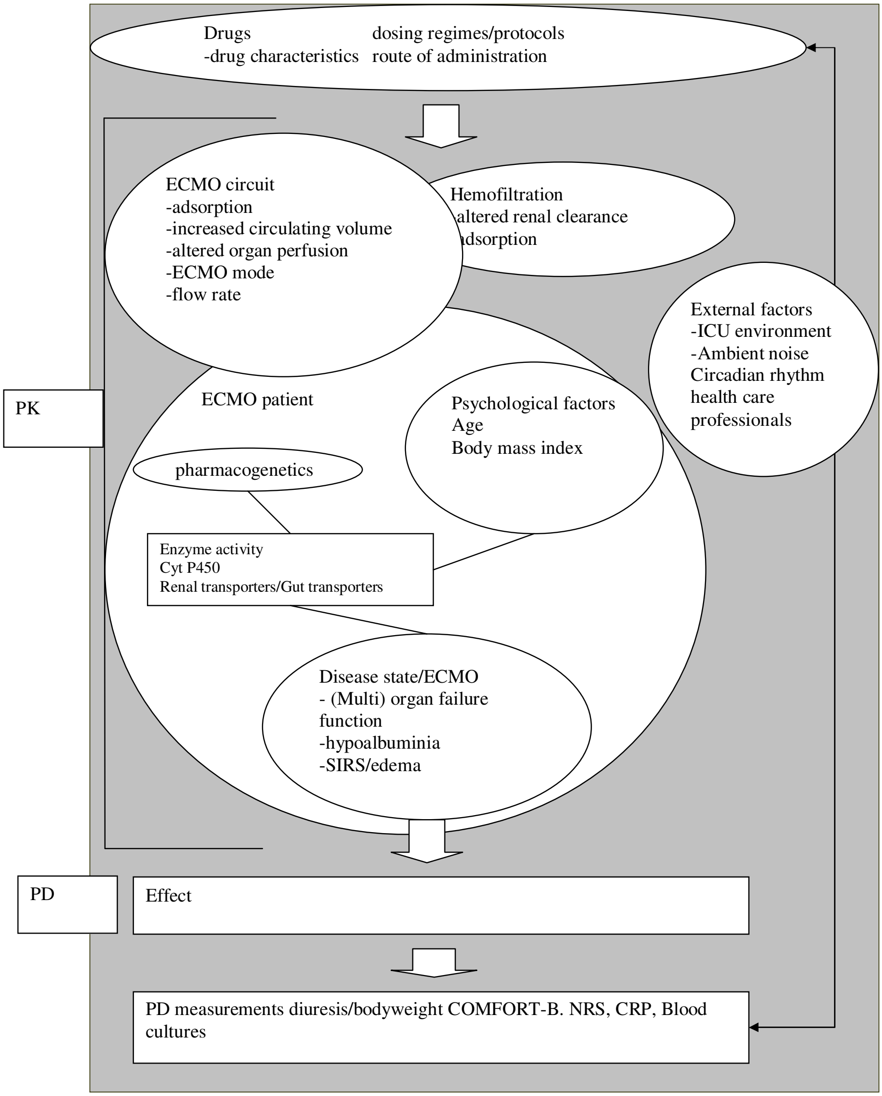
Developing evidence based guidelines: recommendations and future perspectives

Evidence based drug dosing regimens for pediatric patients on ECMO are still lacking for many regularly used drugs due to absent PK and PD data. Table 1 gives an overview of known PK studies done in ECMO patients, compared to drugs used in our study population described in chapter two and eight.

By combining PK and PD studies we aimed to develop dosing regimens for several drugs. Developing standardized PD parameters and endpoints is invaluable in interpreting PK data. A myriad of co-variables influence PK and PD in ECMO patients (figure 1). Difference in desired levels of sedation, the use of multiple drugs and poor relationship between sedation scores and plasma concentrations make it difficult to use PK data of sedatives and analgesic as a guideline for dosing regimens. Although the combination of midazolam, morphine and clonidine in the context of a standardized and validated sedation and analgesia protocol leads to overall low COMFORT-B and NRS pain scores in most patients on ECMO, pharmacokinetic data of these drugs in children on ECMO, especially outside the newborn period, is lacking. PK studies, especially in older children are necessary to evaluate optimal dosing regimens. Randomized controlled trials such as morphine vs. intravenous paracetamol and midazolam vs. clonidine are needed to compare the effect of different sedatives and analgesics in ECMO patients and analyze possible reduction of overall sedative and analgesic use. Daily interruption of sedatives should be evaluated in randomized controlled trials to substantiate our findings and evaluate outcome benefits such as a reduction in time on ECMO, mechanical ventilation and incidence of abstinence symptoms. Incorporating assessment for delirium in ICU patients should be addressed in children both on and of ECMO to identify possible adverse effects of sedatives as well identify untreated delirium resulting in inappropriate sedative use.

The effect of prophylactic hemofiltration on kidney function and pharmacokinetics of renally cleared drugs remains unknown in pediatric ECMO patients. Future studies need to focus on endogenous kidney function, incidence of AKI and the influence of hemofiltration on PK in ECMO patients.

Figure 1 Determinants of pharmacodynamics and pharmacokinetics of srugs in ECMO patients.



Infectious diseases are still a major problem in patients on ECMO. Uniform documentation using CDC criteria will help in comparing nosocomial infection rates between different ECMO centers as well as evaluate antibiotic treatment protocols and prevention strategies.

Reliable biomarkers for sepsis on ECMO are lacking resulting in wide and prolonged use of antibiotics as well as the use of costly daily surveillance cultures. Establishing clear diagnostic parameters for sepsis should be a priority. Most importantly PK data of antibiotics and antifungal and antifungal drugs should be generated to develop population models or at least provide data from limited case series to validate or change current dosing regimens.

Finally the implementation of new techniques and technologies in ECMO circuits will influence PK and PD of drugs. Reduction in ECMO size will decrease circulating volume and the need for blood transfusions. This might reduce SIRS and consequent capillary leakage. The use of specialized coated tubing or oxygenators will potentially decrease coagulation risks, thereby reducing the need for anticoagulation and bleeding complications. These coatings will possibly influence drug adsorption, thereby effecting volume of distribution. All these factors will influence PK of drugs by altered protein binding, reduction of edema and inflammatory mediators and consequent effect on transporters and Cyp450 metabolism. Addition of a hemofilter to the ECMO circuit and the use of hollow fiber membranes with decreased adsorption of lipophilic drugs compared to silicone membranes will have an effect on volume of distribution and PK.

By analyzing samples presently in our biobank, we may be able to obtain enough samples to model the pharmacokinetics of more drugs and their metabolites, so that proper dose regimens can be constructed. Ultimately, combining data sets or conducting multi-center trials will be needed to increase the number of samples. This will enable the development of population models for less frequently used drugs as well as identify more of the above mentioned co-variables to explain inter-patient variability.
The power of PK studies in these patients could also be enhanced by combining data from critically ill and relatively healthy non-ECMO patients. To help identify factors that underlie PK changes, studies into fluid dynamics, organ perfusion, capillary function and microcirculation might be useful. A recent study by Top et al. showed depressed microcirculatory parameters prior to ECMO in neonates with respiratory failure with clear improvement after ECMO.[122] These novel techniques may improve our understanding of PK in critically ill patients, but it is still a long way before we might use them in (mechanistic) population PK analyses. Developing new biomarkers such as cystatin C and NGAL for diagnosing AKI and NIRS to evaluate organ perfusion might increase valuable parameters that could be incorporated in pharmacokinetic studies.
Studies into the mechanisms of PK changes due to maturation, disease progression or the extracorporeal circulation can help our understanding of the behavior of individual drugs. The combination of routine sparse sampling, drug assay via LC-MS and a PK analysis using NONMEM allow the study of drug behavior in vulnerable patients without harm to the individual subject. Combining PK sparse sampling with randomized controlled trials with clear PD outcome measurements will help us to enhance our understanding of drug therapy in patients on ECMO. Hopefully this, in combination with a good

cooperation between pediatricians, pharmacists and clinical pharmacologists, leads to more evidence-based dose regimens for pediatric and neonatal ECMO patients. There is no one size fits all dosing algorithm for all ECMO patients. ECMO support in critically ill neonates and children will always be highly dynamic with rapid changes occurring frequently. Medical professional taking care of these patients should be aware of the PK changes occurring in there patients but most importantly; they need to keep their eyes open and look at their patient.

Major findings and treatment recommendations

- High loss of Lipophilic drugs occur in silicone membrane oxygenators and drug such as fentanyl and midazolam should be administered directly to the patient.

- A standardized sedation protocol using validated sedation and pain scores should be used to guide sedative and analgesic treatment.
- Increased sedative need should be expected in the first 48 hours
- Special attention most be given to decreasing sedatives and analgesics when possible.
- Daily interruption of sedatives is feasible in neonates on ECMO resulting in overall low plasma concentrations of midazolam and morphine

- Continuous furosemide infusions lead to stable diuresis without hemodynamic complications if hemofiltration is not an option.
- Prophylactic hemofiltration should be added to all ECMO circuits

- Infectious diseases are a major health care issue in ECMO patients.
- The use of surveillance cultures should be avoided since it leads to over diagnosing and unnecessary antibiotic use.
- Cefotaxime and oseltamivir can be dosed according to normal age specific dosing regimens

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CHAPTER 11

Summary

Summary

ECMO support is an established life saving therapy for potentially reversible respiratory and/or cardiac failure in patients when conventional treatment fails. Survival after ECMO support varies highly depending on the primary diagnosis. Mortality is primarily associated with pre-ECMO conditions and complications on ECMO such as bleeding, renal failure and infections. Improvement of outcome may be accomplished by effective treatment of the primary diagnoses leading to ECMO, as well a reduction of adverse effects of ECMO. Adequate drug therapy is important in reaching these goals.
In contrast, pharmacokinetic (PK) and pharmacodynamic (PD) studies in neonates and older children on ECMO are sparse, and are limited by small sample size. The available studies have demonstrated altered pharmacokinetics with increased volume of distribution as well as decreased clearance for several drugs.

This thesis presents the results of several clinical studies evaluating pharmacokinetics and pharmacodynamics of drug therapy in neonatal and pediatric patients on ECMO support.

Chapter 1 describes the technique of ECMO support and its effect on drug disposition. Furthermore it discusses the challenges in treating neonates and older children on ECMO; the difficulties in management of sedation and analgesia, fluid management and infections leading to the studies in this thesis are presented.

Part I deals with the effect of the ECMO circuit on drug disposition.
In **chapter 2** we describe an *in vitro* experiment testing potential determinants of drug adsorption to several ECMO circuits. Drug adsorption is correlated to the lipophilicity (log P value) of individual drugs. This effect is strongest for circuits with a silicone membrane oxygenator; a sigmoidal function adequately describes the correlation between log P value and drug recovery. Drug loss is smaller in circuits with a centrifugal pump, probably due to shorter tubing length and the polypropylene hollow-fiber membrane, which is especially poignant for lipophilic drugs such as midazolam or fentanyl. These drug losses can partly explain an increase in volume of distribution that is commonly seen during ECMO. As a consequence, dose recommendations for lipophilic drugs based on studies with one type of oxygenator are probably not valid for another. In addition, drugs should preferably be injected into patients instead of the extracorporeal circuit. Due to its lower drug loss and faster equilibration, morphine is the preferred opioid over fentanyl. The oxygenator size (pediatric vs. neonatal) or previous use of circuits have little influence on drug loss

Part II includes two pharmacodynamic studies of sedative and analgesic effects in neonates and older children during ECMO.

In **chapter 3** we describe the use of a standardized sedation and analgesia protocol incorporating COMFORT-B and Numeric Rating Scale (NRS) pain scores in 47 neonates and 28 older children on ECMO. The aim of this study was to evaluate protocolized sedative and analgesic use in neonatal and pediatric ECMO patients. A secondary aim was to identify potential risk factors that predict higher dose requirements of sedatives and additional sedatives and analgesics use in ECMO patients. Overall low COMFORT-B and NRS pain scores were achieved in patients on ECMO using a standard sedation and analgesia protocol. Almost half of the patients needed additional medication besides midazolam and morphine to achieve adequate sedation within first 48 hours of ECMO. Patients aged 1-23 month, with longer ICU stay prior to ECMO and higher initial sedative medication represented a higher risk for inadequate sedation. Patients with higher sedative requirements had longer ECMO runs. After addition of additional drugs early in the ECMO run, we observed low scores without concomitant dose reduction. This failure by the medical team to decrease sedatives and analgesics may have contributed to longer ECMO runs. Strategies to reduce sedatives and analgesics such as daily interruption of sedatives need to be evaluated in randomized controlled trials.

In **chapter 4** we assessed feasibility of sedation interruption in neonates on ECMO. In 20 neonates continuous infusions of midazolam and morphine were discontinued within 30 minutes after cannulation. Sedatives or analgesics were restarted based on high COMFORT-B or NRS pain scores. Trough levels at time of restart of medication were taken in an attempt to determine minimal effective concentrations. Midazolam was discontinued in all patients, whereas morphine was discontinued in 18 patients. Median (IQR) time without any sedatives was 10.3 hours (5.0-24.1 h). During this period no accidental extubations, decannulations or bleeding complications occurred. Midazolam, morphine and metabolite plasma levels at restart of medication were lower than previously reported in sedated neonates on ECMO. Interruption times found are 2-3 times longer than reported for adult ICU non ECMO patients. Further randomized controlled trials are needed to substantiate these findings and evaluate outcome benefits such as a reduction in time on ECMO, mechanical ventilation and incidence of abstinence symptoms.

Part III evaluates two treatment protocols for fluid overload management in neonates on ECMO.

Chapter 5 covers the results of a retrospective observational study, performed in infants treated with continuous intravenous furosemide during ECMO. In thirty-one patients continuous furosemide therapy was started at a median rate of 0.08 (0.02 – 0.20) mg/kg/hr. after a median of 25 (4 - 149) (range) hours of ECMO, eight patients received a loading

dose prior to start of continuous infusion and eight patients received additional loop diuretics during the continuous infusion.
Urine production remained stable at a median 6.5 ml/kg/h irrespective of furosemide boluses. The forced diuresis was tolerated well, illustrated by stable hemodynamic parameters and a decrease in ECMO flow and vasopressor score over the observation period.
The used furosemide regimens varied widely, in both continuous and intermittent doses. However all regimens achieved adequate urine output. Furosemide dosing regimens should be developed for neonates treated with ECMO. In addition therapeutic drug monitoring studies are required to prevent furosemide toxicity.

In **chapter 6** furosemide and routine use of continuous venovenous hemofiltration (CVVH) treatment in 46 neonates on ECMO were compared in a retrospective 1:3 case-comparison study. Differences in time on ECMO, time till extubation after decannulation, mortality, and potential cost reduction were defined as primary outcome measurements. Differences in total and mean fluid balance, urine output in ml/kg/d, dosage of vasopressors, blood products and fluid bolus infusions, serum creatinine, urea and albumin levels were studied. Time on ECMO was significantly shorter in the CVVH-group: 98 (48-187) hours versus 126 (24-403) hours in the control group ($p = 0.02$). Time from decannulation till extubation was shorter as well: 2.5 (0-6.4) versus 4.8 (0-121.5) days ($p = 0.04$). There were no significant differences in mortality. Patients in the CVVH group needed fewer blood transfusions: 0.9 ml/kg/d (0.2-2.7) versus 1.8 ml/kg/d (0.8-2.9) in the control group ($p<0.001$). Consequently the number of blood units used was significantly lower in the CVVH group ($p<0.001$). The calculated cost reduction was €5000,- per ECMO run. Adding continuous hemofiltration to the ECMO circuit in newborns improves outcome by significantly reducing time on ECMO and on mechanical ventilation, due to better fluid management and a possible reduction of capillary leakage syndrome. Fewer blood transfusions are needed. All in all, overall costs per ECMO run will be lower.

Part IV covers the diagnosis and treatment of infectiuous diseases during ECMO treatment.
In Chapter 7 we set out to document our antibiotic treatment regimen, the rate of nosocomial infections, as well as outcome of patients on ECMO with suspected and proven nosocomial infections. We also tried to identify clinical and laboratory parameters that instigated a change in antibiotic management and evaluate CRP as a marker for nosocomial infections in a prospective observational study.
Seventy-eight patients (47 neonates and 31 children) were included. Twenty patients had a culture proven infection prior to ECMO cannulation. Overall nosocomial infection rate in our population was 17%, with a blood stream infection (BSI) rate of 14% or 23

BSI/1000 ECMO days. The BSI rate in the study population excluding all positive single skin contaminant cultures decreased to 9%, or 15 BSI/1000 ECMO days. Twenty-one different antibiotics were prescribed. Antibiotics were discontinued in only nine patients. In 18 patients (31%) antibiotic changes were made based on a clinical suspicion of infection. In 12 patients all cultures remained negative. Survival to discharge from the intensive care was 73% in the study population, but only 50% and 56% in patients with suspected or proven infection. CRP and leukocyte count at start of antibiotics did not differ between patients with a proven and suspected sepsis: (median (IQR)) 100 (34-144) mg/l vs. 57 (22-107) mg/l, p = 0.7 and 7.4 (4-9.4) x $10^{e}9$ vs. 6.7 (4.0-8.7) x$10^{e}9$, p = 0.7.
Infections are a significant problem in neonates and children on ECMO with 29 of 78 patients with a proven infection prior to or during ECMO support, and an additional 12 of 78 patients with suspected infection. A lack of reliable diagnostic tools to identify sepsis leads to high antibiotic use while pharmacokinetic data for most antibiotics is lacking. Our data suggest that surveillance cultures used to identify early sepsis results in a high number of possible false positive blood cultures leading to unnecessary antibiotic use and potential high costs. Cultures should therefore be done when there is a clinical suspicion of an infection.

A prospective observational study to collect pharmacokinetic and pharmacokinetic data from neonates and children on ECMO was conducted in the Intensive Care of the Erasmus MC-Sophia Children's Hospital, in collaboration with the Department of Pharmacy. By using blood samples taken during routine care and medication data from the patient data management system, drug concentrations of cefotaxime and its metabolite desacetylcefotaxime could be determined and a PK model created using LC-MS and nonlinear mixed-effects modeling) The results are discussed in **chapter 8.**
We included 37 neonates and infants on ECMO. Plasma samples were taken during routine care. A one-compartment pharmacokinetic model for cefotaxime and desacetylcefotaxime adequately described the data. Volume of distribution was twice as large, while clearance was comparable to non ECMO patients. Despite pharmacokinetic changes, overall cefotaxime concentrations were above a minimal inhibitory concentration (MIC) of 8 mg/L for the entire dose interval. Therefore the standard cefotaxime dose regimen provides sufficiently long periods of supra-MIC concentrations to achieve adequate treatment of infections in infants on ECMO. This is mostly due to the wide therapeutic range of cefotaxime enabling high doses in neonates in children without increased adverse events.

To evaluate the effect of extra corporeal membrane oxygenation support on pharmacokinetics of oral oseltamivir and oseltamivir carboxylate in children, plasma concentrations were analyzed in three patients aged 15, 6 and 14 years included in a larger prospective observational pharmacokinetic study. The results are presented in **chapter 9**. The age-specific oseltamivir dosage was doubled to counter expected decreased plasma drug concentrations due to increased volume of distribution on ECMO support. For two children the oseltamivir carboxylate plasma concentrations were higher than those found in children and adults not on ECMO. These increased plasma concentrations could be related to the increased oseltamivir dosage and decreased kidney function. In one patient suboptimal plasma concentrations of both oseltamivir and oseltamivir carboxylate were contributed to decreased gastric motility and hematemesis, resulting in inadequate intake or uptake of oseltamivir. Based on these findings oseltamivir pharmacokinetics do not seem to be significantly influenced by ECMO support, although data were insufficient to develop a PK model. Caution is required in case of nasogastric administration and decreased gastric motility

The general discussion in **chapter 10** provides recommendations for treatment protocols and suggestions for future research. The major findings and recommendations of this thesis are the following.

- High loss of lipophilic drugs occur in silicone membrane oxygenators and drug such as fentanyl and midazolam should be administered directly to the patient.
- A standardized sedation protocol using validated sedation and pain scores should be used to guide sedative and analgesic treatment.
- Increased sedative need should be expected in the first 48 hours
- Special attention most be given to decrease sedative and analgesic doses when possible
- Daily interruption of sedatives is feasible in neonates on ECMO resulting in overall low plasma concentrations of midazolam and morphine

- Continuous furosemide infusions lead to stable diuresis without hemodynamic complications if hemofiltration is not an option.
- Routine hemofiltration should be added to all ECMO circuits
- Infectious diseases are a major health care issue in ECMO patients.
- The use of surveillance cultures should be avoided since it leads to over diagnosing and unnecessary antibiotic use.
- cefotaxime and oseltamivir can be dosed according to normal age specific dosing regimens

Samenvatting

Extracorporele Membraan oxygenatie (ECMO) is een levensreddende techniek die wordt toegepast in patiënten met potentieel reversibel pulmonaal of cardiaal falen welke niet adequaat kunnen worden ondersteund met beademing of bloeddruk ondersteunende medicatie.

Overleving na ECMO varieert afhankelijk van de primaire diagnose en complicaties zoals ernstige intracraniële bloedingen, nierfalen en infecties. Reductie in mortaliteit en verbetering van morbiditeit hangt dus af van adequate therapie van het onderliggend lijden en de ontstane complicaties.

Geneesmiddelen spelen hierin een belangrijke rol. Desondanks zijn er maar weinig geneesmiddelenstudies verricht in neonaten en oudere kinderen aan ECMO en de interpretatie van deze studies wordt bemoeilijkt door de kleine studiepopulaties. De studies die er zijn laten een toegenomen verdelingsvolume en een verminderde klaring zien voor de meeste geneesmiddelen in kinderen aan ECMO.

In dit proefschrift worden meerdere klinische studies gepresenteerd die de farmacokinetiek en farmacodynamiek van verschillende geneesmiddelen in kinderen aan ECMO evalueren.

Hoofdstuk 1 beschrijft de techniek van ECMO en zijn effect op geneesmiddelen. Daarnaast worden enkele klinische problemen in de zorg voor ECMO patiënten geïdentificeerd; sedatie en analgesie, vochtbeleid en vochthuishouding en infecties tijdens ECMO, welke in dit proefschrift zijn onderzocht.

Deel I van dit proefschrift beslaat de relatie tussen het ECMO circuit en de dispositie van geneesmiddelen.

In hoofdstuk 2 beschrijven wij een *in vitro* experiment waarin verschillende determinanten van adsorptie van geneesmiddelen door het ECMO circuit worden getest. Adsorptie van geneesmiddelen is gecorreleerd met de lipofiliciteit (vet oplosbaarheid) van een geneesmiddel (uitgedrukt in log P). Dit effect is het sterkst in siliconen oxygenatie membranen. Een sigmoïdale curve beschrijft de correlatie tussen log P en adsorptie het best. Centrifugale pompen met polypropylene fiber oxygenatie membranen vertonen minder adsorptie ten opzichte van roller pompen met siliconen membranen. Dit wordt waarschijnlijk grotendeels veroorzaakt door het verschil in membranen. Adsorptie van geneesmiddelen aan ECMO circuits verklaart ten dele het toegenomen verdelingsvolume dat wordt gevonden in klinische PK studies. Doseringen voor niet ECMO patiënten van lipofiele geneesmiddelen zijn daarom waarschijnlijk niet afdoende in ECMO patienten. Indien mogelijk verdient het de voorkeur om lipofiele geneesmiddelen niet via het ECMO circuit toe te dienen. Morfine bindt minder aan het ECMO circuit en heeft de voorkeur als analgeticum boven fentanyl. De grootte van het ECMO circuit of de oxygenatie membraan lijkt weinig effect te hebben op adsorptie.

Deel II bevat twee farmacodynamische studies over sedatie en analgesie in neonaten en oudere kinderen aan ECMO.
Hoofdstuk 3 beschrijft het gebruik van een gestandaardiseerd sedatie- en pijnprotocol, gebaseerd op gevalideerde sedatie en pijn scores (COMFORT-B en NRS pijn) in 47 neonaten en 28 oudere kinderen aan ECMO. Het doel van de studie was om een geprotocolliseerd sedatie- en pijnprotocol in deze patiëntengroep te evalueren. Daarnaast werden potentiële risicofactoren voor inadequate sedatie geïdentificeerd. Sedatie- en pijnscores waren voornamelijk laag tijdens de studieperiode. De helft van alle patiënten had naast midazolam en morfine (standaard medicatie) additionele sedatie nodig gedurende ECMO. Deze sedatie werd met name in de eerste 48 gestart. Patiënten tussen de 1 en 23 maanden oud met langere intensive care opname en meer sedativa voor ECMO hadden additionele sedatie nodig. Patiënten met meer sedatie lagen langer aan ECMO. Na start van extra medicatie, vooral in de eerste dagen, vonden wij lage sedatie scores zonder dosis reductie. Dit zou bijgedragen kunnen hebben aan de gevonden langere ECMO duur. Nieuwe sedatie protocollen zoals dagelijkse sedatie interruptie of het gebruik van intermitterende sedatie protocollen dienen te worden geëvalueerd in deze patiëntengroep in gerandomiseerde studies.

Hoofdstuk 4 evalueert de haalbaarheid van sedatie interruptie in 20 neonaten aan ECMO. Continue midazolam en morfine infusies werden 30 minuten na cannulatie voor ECMO gestopt. Sedativa en pijnmedicatie werden herstart op basis van COMFORT-B en NRS pijn scores. Dalspiegels voor midazolam, morfine en hun metabolieten werden afgenomen voor herstart van medicatie. Midazolam werd in alle patiënten gestopt, terwijl morfine in 18 patiënten werd gestopt. De mediane (Interkwartiel) tijd zonder sedatie of pijnmedicatie was 10.3 (5.0-24.1) uur. Gedurende deze periode deden er zich geen complicaties voor.
De gevonden dalspiegels voor midazolam en morfine waren beduidend lager dan eerder gerapporteerde concentraties in adequaat gesedeerde kritisch zieke neonaten met en zonder ECMO ondersteuning.
De duur zonder sedativa in onze patiënten was 2 tot 3 maal langer dan bij volwassen intensive care patiënten zonder ECMO ondersteuning. Interruptie van sedativa in ECMO patiënten is haalbaar. Gerandomiseerde studies zijn nodig om een verbetering van korte en lange termijn uitkomsten aan te tonen.

Deel III van dit proefschrift beslaat de evaluatie van twee behandelstrategieën voor overvulling in ECMO patiënten.

Hoofdstuk 5 beschrijft de uitkomsten van een retrospectieve observationele studie naar continue furosemide infusies in 31 kinderen. De mediane tijd voor start van de continue furosemide infusies was 25 uur (4-149uur). De mediane start dosering was 0.08 (0.02-0.2) mg/kg/u. Acht patiënten kregen een oplaaddosis furosemide voor aanvang van de continue infusies, terwijl bij nog eens acht patiënten additionele diuretica werden voorgeschreven naast continue furosemide infusies. Urineproductie bleef stabiel rond de 6.5 ml/kg/u onafhankelijk van additionele diuretica giften. De geforceerde diurese werd goed verdragen, getuige de stabiele hemodynamische parameters en gereduceerde inotropie en ECMO behoefte. Er was geen eenduidig behandelregime met wisselende doseringen in de studiegroep. Ondanks deze variabiliteit werd een adequate urineproductie behaald. PK en PD studies zijn nodig voor de verdere ontwikkeling van een eenduidig en optimaal doseringsadvies met daarin aandacht voor bijwerkingen en toxiciteit.

In Hoofdstuk 6 wordt furosemide therapie vergeleken met het routine gebruik van venoveneuze continue hemofiltratie in 46 neonaten aan ECMO. Als primaire uitkomstmaten werd gekeken naar duur van ECMO, duur van beademing na ECMO, mortaliteit en reductie in kosten. Daarnaast werden een aantal andere parameters geëvalueerd zoals het verschil in netto vochtbalans, urine productie in ml/kg/d, hoeveelheid vasopressoren, het gebruik van bloedproducten en vochtbolussen, serum creatinine, ureum en albumine.

De totale ECMO duur evenals de beademingsduur na decannulatie waren significant korter bij patiënten behandeld met CVVH vs. de controle groep; 98 (48-187) uur vs. 126 (24-204) uur ($p = 0.02$) en 2.5 (0-6.4) dagen versus 4.8 (0-121.5) dagen ($p = 0.04$).

Tevens kregen patiënten met CVVH minder bloedtransfusies, 0.9 (0.2-2.7) ml/kg/d vs. 1.8 (0.8-2.9) ml/kg/d ($p = <0.001$). Er was geen significant verschil in mortaliteit. In totaal resulteerde het routine gebruik van CVVH in ECMO patiënten in een kostenreductie van €5000,- per ECMO behandeling.

Het routine gebruik van CVVH tijdens ECMO verbetert de klinische uitkomst in neonaten. Door een reductie in transfusies, beademingsdagen en ECMO dagen is er een daling in totale kosten per patiënt aan ECMO.

Deel IV van dit proefschrift beslaat de evaluatie van diagnostiek en behandeling van infecties gedurende ECMO behandeling.

Hoofdstuk 7 beschrijft de rol die infecties spelen in onze ECMO populatie. Infecties voor en tijdens ECMO evenals het antibioticagebruik en verdenking infectie worden geëvalueerd.

Achtenzeventig patiënten, waaronder 47 neonaten en 31 oudere kinderen, werden vervolgd. Twintig patiënten werden ondersteund middels ECMO in verband met een bewezen bacteriële infectie. In totaal ontwikkelde 17% een nosocomiale infectie waarvan 14% een sepsis. In totaal werden er 23 infecties per 1000 ECMO dagen gediagnosticeerd. Na exclusie van mogelijke contaminaties, vooral patiënten met een enkele positieve bloedkweek met een huidbacterie, had 9% van alle patiënten een sepsis, wat resulteerde in 15 infecties/1000 ECMO dagen.

In totaal werden er 21 verschillende antibiotica voorgeschreven. In negen patiënten werden antibiotica gestaakt tijdens ECMO. In 18 patiënten (31%) werden antibiotica gewisseld of gestart op basis van een klinische verdenking op een bacteriële infectie. In twee derde van de gevallen werd geen verwekker aangetoond.

Overleving tot ontslag van de intensive care in de totale studie populatie was 73%, terwijl bij patiënten met een bewezen of vermoedde bacteriële infectie de overleving 56% en 50% was.

C-Reactive Protein en leukocyten, tijdens start van antibiotica op basis van een verdenking infectie, waren niet verschillend in patiënten met een positieve kweek versus patiënten met een negatieve kweek; 100 (34-144) mg/l vs. 57 (22-107) mg/l en 7.4 (4-9.4) x 10^{e9} vs. 6.7 (4.0-8.7) 10^{e}9.

Infecties in patiënten tijdens ECMO komen veel voor; 37% van de patiënten hebben een bewezen infectie tijdens of voor ECMO terwijl nog eens 15% een verdenking op een bacteriële infectie heeft tijdens ECMO. Er zijn geen duidelijke diagnostische hulpmiddelen om een bacteriële infectie aan ECMO vroegtijdig te diagnosticeren. Dit resulteert in veelvuldig antibioticagebruik terwijl er nauwelijks farmacologische gegevens beschikbaar zijn voor deze patiëntengroep. In onze observationele studie leidde het gebruik van routine bloedkweken tot een aantal vals-positieve bloedkweken, met een toename in antibiotica gebruik. Wij pleiten er daarom voor om kweken alleen te verrichten bij een klinische verdenking op een infectie of ter controle van reeds positieve kweken.

In een samenwerkingsverband tussen de intensive care van het Sophia Kinderziekenhuis en de afdeling Farmacologie van het Erasmus MC werd een prospectieve observationele studie verricht met als doel; het verzamelen van farmacologische gegevens van veel gebruikte geneesmiddelen in neonaten en oudere kinderen aan ECMO. Door middel van gestandaardiseerde bloedafname en met behulp van een computerprogramma genaamd NONMEM zijn concentraties van verschillende geneesmiddelen in alle patiënten samengebundeld en is berekend hoe groot het verdelingsvolume en de klaring waren voor specifieke geneesmiddelen in de gemiddelde patiënt. Daarnaast is geschat hoe groot de variatie tussen de patiënten was; en zijn verschillende doseringen uitgeprobeerd op het computermodel om te voorspellen welke dosering de meest geschikte bloedconcentraties op zou leveren.

Er is een NONMEM-model gemaakt voor het antibioticum cefotaxim (CTX) en het werkzame afbraakproduct deacetylcefotaxim (DACT) in hoofdstuk 8.

Er werden 37 kinderen geïncludeerd. Een 1-compartiments model beschrijft de gegevens. Het distributievolume in patiënten aan ECMO is bijna twee maal groter dan in niet-ECMO patiënten, terwijl de klaring niet lijkt te zijn veranderd, ondanks het verschil in distributievolume. Doordat CTX een zeer veilig geneesmiddel is, wordt bij niet-ECMO patiënten aan de hoge kant gedoseerd. Zelfs met de verhoging van het verdelingsvolume (+100%) wordt hierdoor tijdens ECMO een voldoende hoge concentratie gehaald. Binnen ECMO patiënten lijkt de klaring tijdens ECMO hoger te zijn dan ervoor en erna; dit zou kunnen komen doordat er een betere doorbloeding is van de organen, of door het standaard gebruik van hemofiltratie in onze patiënten.

Tijdens onze prospectieve observationele patiënten werden drie patiënten van 15, 6 en 14 jaar behandeld met oseltamivir, een antiviraal middel tegen de H1N1 griep. Plasmaconcentraties van deze drie patiënten werden geanalyseerd om te evalueren of deze adequaat waren gedurende ECMO. In verband met een verwachtte toename van het verdelingsvolume aan ECMO werd de dosering van oseltamivir verdubbeld in alle patienten. In twee patiënten werden hogere spiegels gevonden van oseltamivir en de werkzame stof oseltamivir carbocylate in vergelijking tot niet ernstig zieke leeftijdsgenoten en volwassenen. De verhoogde plasmaconcentraties konden deels worden verklaard door de gebruikte doseringen en de verminderde nierfunctie. In één patiënt werden suboptimale concentraties gemeten van oseltamivir en de metaboliet. In deze patiënt was er sprake van een ernstig gestoorde maagontlediging met gallig en bloederig braken, resulterend in een inadequate opname van het geneesmiddel.
Gebaseerd op deze gegevens lijkt er geen groot effect te zijn van ECMO op de farmacokinetiek van oseltamivir en oseltamivir carboxylate. Voorzichtigheid is geboden bij patiënten met ernstige maagontledigings-stoornissen.

De discussie in hoofdstuk 10 geeft een overzicht van de aanbevelingen voor behandelprotocollen en nieuwe studies.
De primaire conclusies en aanbevelingen van de studies in dit proefschrift zijn:

- Er is een substantieel verlies van lipofiele geneesmiddelen, zoals midazolam en fentanyl, in siliconen membranen. Deze geneesmiddelen dienen dan ook direct aan de patiënt te worden gegeven.

- Een gestandaardiseerd sedatie- en pijnprotocol met gevalideerde scoringssystemen dient te worden gebruikt ter regulatie van sedativa en analgetica.
- Een toegenomen sedatie behoefte kan worden verwacht in de eerste 48 uur van ECMO.
- Er dient speciale aandacht te zijn voor het afbouwen van sedativa en analgetica.

- Interruptie van continue sedativa en analgetica is haalbaar en veilig in neonaten aan ECMO en leidt tot beduidend lagere plasmaconcentraties.

- Continue infusies van furosemide in kinderen aan ECMO leidt tot stabiele diurese zonder hemodynamische complicaties als hemofiltratie geen optie is.
- Continue venoveneuze hemofiltratie zou een standaard behandeling moeten zijn tijdens ECMO.
- Bacteriële infecties zijn een groot gezondheidprobleem in ECMO patiënten.
- Het gebruik van dagelijkse bloedkweken leidt tot over diagnostiek en onnodig antibioticagebruik en dient te worden vermeden.
- Cefotaxim en oseltamivir kunnen normaal worden gedoseerd in patiënten aan ECMO.

List of Abbreviations

AaDO2	Alveolar-arterial oxygen tension gradient
ARDS	Acute Respiratory Distress Syndrome
CVVH	Continuous venovenous hemofiltration
CDH	Congenital Diaphragmatic Hernia
CFZ	Cefazolin
Cmax	Maximum concentration
Cmin	Minimum concentration
COMFORT-B	COMFORT-Behavior SCALE
CPB	Cardiopulmonary Bypass
ECMO	Extracorporeal Membrane Oxygenation
ELSO	Extracorporeal Life Support Organization (ELSO)
FEN	Fentanyl
HPLC	High-performance liquid chromatography
IQR	Inter Quartile Range
LQD	The limits of quantification
M3G	Morphine-3-glucuronide
M6G	Morphine-3-glucuronide
MAS	Meconium Aspiration Syndrome
MDZ	Midazolam
MEM	Meropenem
MOR	Morphine
NRS	Numeric Rating Scale
OC	Oseltamivir Carboxylate
OI	Oxygenation Index
PAR	Paracetamol
PD	Pharmacodynamics
PDMS	Patient Data Management System
PELOD	Pediatric logistic organ dysfunction
(P)ICU	(Pediatric) Intensive Care Unit
PIM2	Pediatric Index of Mortality
PK	Pharmacokinetics
PPHN	Persistent pulmonary hypertension of the newborn
PRISM2	Pediatric Risk of Mortality version 2
SIRS	Systemic inflammatory response syndrome
VA	Venoarterial
VV	Venovenous
VAN	Vancomycin

Dankwoord

Lieve mensen, terwijl ik dit schrijf kan nog steeds niet helemaal geloven dat het volbracht is. Zoals velen van jullie weten was het niet altijd even makkelijk om een fellowship in een intensief klinisch vak te combineren met een promotie traject. De laatste maanden zijn fantastisch geweest; fantastisch hectisch, intens en motiverend.

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Curriculum vitae

Enno Diederik Wildschut was born in Leiderdorp, the Netherlands, on January 4th, 1973. He started his secondary education at the Adriaan Roland Holst Vrije School in Bergen (NH). In 1992 he passed his secondary exam (VWO) at the Montessori Lyceum, Amsterdam. From 1992 till 1999 he followed his medical training at the VU University (Vrije Universiteit), Amsterdam. After obtaining his medical decree he started as a resident in General Pediatrics at the Sint Franciscus Hospital Rotterdam. In 2001 he enrolled in the residency program in Pediatrics at the Sophia Children's Hospital Erasmus MC Rotterdam, the Netherlands (head Prof.dr. A.J.van der Heijden). Following his registration as a Pediatrician in 2005 he started his Fellowship Pediatric Intensive Care at the Sophia Children's Hospital. During his fellowship, under the guidance of Prof.dr. D. Tibboel, he started his research into pharmacotherapy in neonates and children during ECMO resulting in this thesis.

He finished his fellowship in 2008 and is currently working as a staff member in the Pediatric Intensive Care with a special interest in ECMO and Pharmacology. He is married to Barbara Kuijper and together they have two children; Mariza (2004) and Joram (2007).

List of Publications

Evaluation of furosemide regimens in neonates treated with extracorporeal membrane oxygenation.
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Microanalysis of beta-lactam antibiotics and vancomycin in plasma for pharmacokinetic studies in neonates.
Ahsman MJ, Wildschut ED, Tibboel D, Mathot RA.
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Population Pharmacokinetics of Midazolam and Metabolites during Venoarterial Extracorporeal Membrane Oxygenation in Neonates
Ahsman, M. J., Hanekamp, M., Wildschut, E. D., Tibboel, D., Mathot, R. A. A.
Clinical Pharmacokinetics, 2010 accepted for publication

Feasibility of sedation and analgesia interruption following cannulation in neonates on extracorporeal membrane oxygenation (ECMO)
E. D. Wildschut, M. N. Hanekamp, N. J. Vet, R.J. Houmes, M..J Ahsman, R.A. Mathot, S. N. de Wildt, D. Tibboel
Intensive Care Medicine, 2010, accepted for publication

Determinants of drug absorption in different ECMO circuits
E.D. Wildschut, M.J. Ahsman, K. Allegaert, R.A.A. Mathot, D. Tibboel
Provisionally accepted

Sedation and analgesia in children on extracorporeal membrane oxygenation (ECMO): are we performing well?
E. D. Wildschut, M.J Ahsman, M. van Dijk, R.J. Houmes, R.A. Mathot, D. Tibboel, S. N. de Wildt
Submitted

Plasma levels of oseltamivir and oseltamivir carboxylate in critically ill children on extracorporeal membrane oxygenation support
E.D. Wildschut, M. de Hoog, M.J. Ahsman, D. Tibboel, A.D.M.E. Osterhaus, P.L.A. Fraaij
PloS One, 2010, in press

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: E.D. Wildschut	PhD period: March 2006-July 2010
Erasmus MC Department: Pediatrics	Promotor(s):Prof.dr. Tibboel
Research School: Erasmus MC	Supervisor: Dr. S.N. de Wildt, Dr. R.A.A. Mathôt

1. PhD training

	Year	Workload (Hours/ECTS)
Specific courses (e.g. Research school, Medical Training)		
• Farmacokinetiek: achtergronden, gegevensinterpretatie en registratievereisten	2007	30
• Pediatric Cardiac Intensive Care Post Graduate Course	2007	12
• Grenzen aan de toekomst (SICK)	2006	3
• Onderwijsdag fellow intensive care	2005-2008	20
Seminars and workshops		
• Pharmacological Research Meetings, Pediatric Intensive Care Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands	2008-2010	50
• Pain in Children, Erasmus MC Pain Knowledge Centre, Rotterdam, the Netherlands	2009	3
• gemeenschappelijke Research Bespreking Moeder en Kind Centrum	2007-2009	20
Presentations		
• 11th Biannual European Society of Developmental, Perinatal and Pediatric Pharmacology, Rotterdam, the Netherlands		
• Poster: Feasibility of sedation and analgesia interruption in neonates on ECMO	2008	30
• Poster: Furosemide versus hemofiltration for fluid management in newborns undergoing extracorporeal membrane oxygenation; a case comparison study	2008	40
• 2nd Congress of the European Academy of Paediatrics	2008	40
• Poster: Cost effectiveness of CVVH during ECMO		
• Poster: Is preoperative ECMO in treatment of pulmonary hypertension (PHT) in patients with transposition of the great arteries (TGA) an option?		
• Oral presentation: The 26th CNMC Symposium:ECMO & the Advanced Therapies for Respiratory Failure.	2010	60
• Presentation:		
• Evidence based antibiotic use in patients on ECMO		
• Research meeting vergadering SICK, Wilhelmina kinderziekenhuis, Utrecht.	2008	30
• Reasearch meeting Moeder en Kind Centrum Erasmus MC Sophia kinderziekenhuis	2007	30
• Research meeting Moeder en Kind Centrum Erasmus MC Sophia kinderziekenhuis	2009	30

(Inter)national conferences		
• 5th World Congress on Pediatric Critical Care	2007	24
• 27th International Symposium on Intensive Care and Emergency Medicine	2007	24
• PCICS Europe 2008 European Symposium of the Pediatric Cardiac Intensive Care Society	2008	18
• 11th Biannual European Society of Developmental, Perinatal and Pediatric Pharmacology, Rotterdam, the Netherlands	2008	18
• 29th International Symposium on Intensive Care and Emergency Medicine	2009	24
• 2nd Congress of the European Academy of Paediatrics	2008	24
• The 26th CNMC Symposium:ECMO & the Advanced Therapies for Respiratory Failure.	2010	24
2. Teaching		
Introduction training Internship pediatrics	2006-2010	150
APLS raining residents	2008	6
PICU/NICU nurses education	2009	15
Medical training Pediatric residents	2005-2010	40
Total		805 hours