Optimal Furosemide Therapy in Critically Ill Infants

قعود الكويتية

Optimal Furosemide Therapy in Critically Ill Infants

Optimale furosemide therapie bij ernstig zieke zuigelingen

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens het besluit van
het College voor Promoties.

De openbare verdediging zal plaats vinden
op donderdag 7 juni 2007 om 13.30 uur

door

Margaretha Maria Jacoba van der Vorst

geboren te Hilversum

ISBN 978-90-9021887-8

Product co-ordination	Regalis, Zeist
Design and lay-out	SQZI ConceptStudio, Arkel
Printing	HoekmanTotaal, Genemuiden

Promotiecommissie

Promotoren	Prof.dr. A.J. van der Heijden Prof.dr. D. Tibboel
Overige leden	Prof.dr. A.J. Bogers Prof.dr. A.F. Cohen Prof.dr. W.A. Helbing
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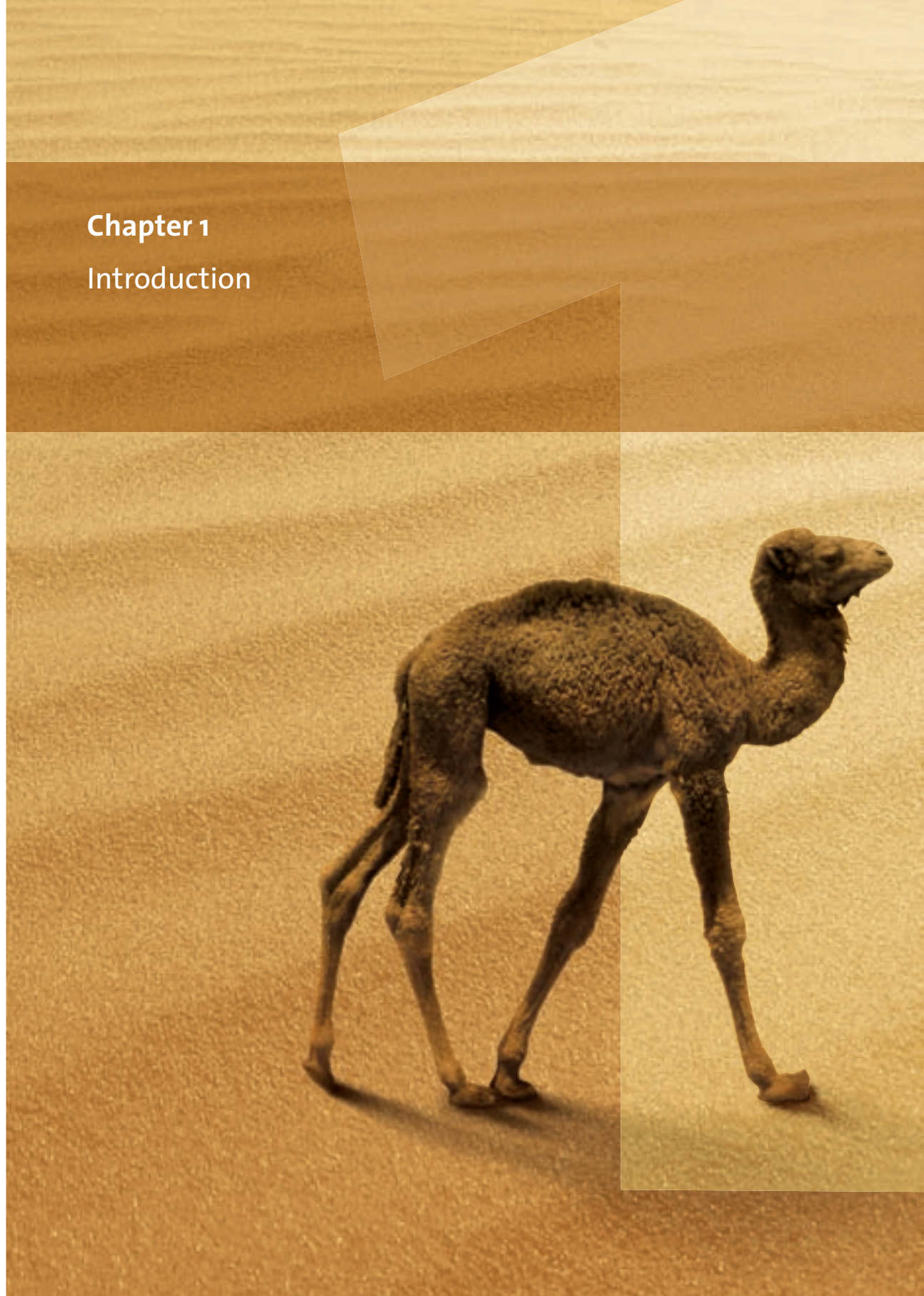
Chapter 1

Introduction



Furosemide

a. History

Roots, plants and minerals were known from ancient to renaissance times to increase the flow of urine, and it was thought that this was helpful in the treatment of cardiac oedema, or dropsy. [1]

However, there was no satisfactory treatment for cardiac failure until William Withering discovered the diuretic properties of digitalis in 1775. [2]

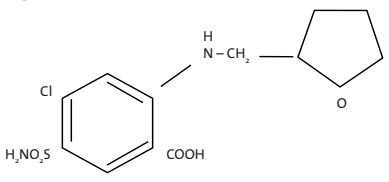
The era of modern diuretics started with the observation in 1937 that patients receiving the new antibacterial agent sulfanilamide, developed metabolic acidosis and showed an increase in urine Ph. [3,4] The connection between sulfanilamide and carbonic anhydrase was made in 1940, when the specific inhibition of carbonic anhydrase by sulfanilamide was observed. [5,6] The enzyme carbonic anhydrase was found in the kidney in 1941. [7] In 1954 the carbonic anhydrase inhibitor, acetozolamide came on the market. The thiazide diuretic, chlorothiazide was in 1958 released on the market.

The increased understanding of the renal handling of sodium in the late 1950's led to the quest for more potent diuretics that could act at a more proximal site of the nephron than thiazides, where larger quantities of sodium are reabsorbed.

The search to develop diuretics that are more potent started at two laboratories. One laboratory developed an agent based on the structure of chlorothiazide and eventually synthesized ethacrynic acid, a potent inhibitor of sodium reabsorption in the thick ascending limb of the loop of Henle. The other laboratory took the structure of sulfonamyl derivates as starting point and finally synthesized furosemide in 1959, which was released on the market in 1964. [1,8-11] Its principal site of action is also the thick ascending limb of the loop of Henle, with a minor additional inhibitory effect on sodium reabsorption in the proximal tubule attributable to its sulfonamide structure.

In 1965 the first reports on furosemide therapy, clinical effects and age-specific dosing regimens in infants and children were published. [12,13]

Fig 1.



4-chloro-N-(2-furylmethyl)-5-sulfamayl-anthranilic acid

b. Chemical Structure

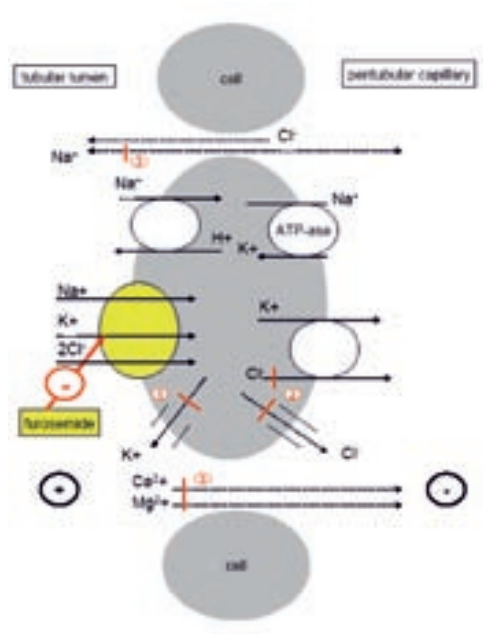
The chemical structure of furosemide is derived from a sulfonamide. The NH2 group of the sulfonamyl derivate, 4-chloro-5-sulfamayl-anthranilic acid is replaced by furfuryl. [1,9-11] (Figure 1) The sodium excretion of the new-formed chemical structure was two to three times greater than any known diuretics.

c. Mechanism and Site of Action

Furosemide reaches the proximal tubular lumen by glomerular filtration and/or proximal tubular secretion via the organic acid transporters (OAT), OAT1 and OAT3 in the basolateral membrane of the proximal tubular cell. Subsequently secretion into the proximal tubular lumen and transport to the thick ascending limb of Henle's loop takes place. [14,15]

Sodium and chloride are reabsorbed through the Na^+-K^+- $2Cl^-$ - cotransport system in the luminal membrane of the thick ascending limb of the loop of Henle. Furosemide blocks the site of chloride in the Na^+-K^+- $2Cl^-$ -membrane carrier and consequently reabsorption of sodium, chloride and potassium into the tubular cell is diminished. (Figure 2) Natriuresis will occur followed by diuresis due to the decreased interstitial hypertonicity [16].

Fig 2. Tubular cell of the thick ascending limb of the loop of Henle



transport of Sodium (Na^+), Potassium (K^+) and Chloride (Cl^-) into the tubular cell by the Na^+-K^+-$2Cl^-$-membrane carrier

secretion of K^+ via conducting channels in the luminal membrane and reabsorption Cl^- via conducting channels and potassium chloride cotransporters in the basolateral membrane ⟶ lumen-positive transepithelial potential difference, which leads to paracellular reabsorption of Na^+, Calcium (Ca^{2+}) and Magnesium (Mg^{2+})

furosemide blocks the Na^+-K^+-$2Cl^-$-membrane carrier by blocking one of the chloride binding sites ⟶ decreases Na^+, K^+ and Cl^- reabsorption via the Na^+-K^+-$2Cl^-$-membrane carrier and consequently decreases K^+ secretion (1) via conducting channels in the luminal membrane and Cl-reabsorption (2) via conductingchannels and potassium chloride cotransporters in the basolateral membrane which will decrease cell-polarization and subsequently paracellular reabsortion of Na^+, Ca^{2+} and Mg^{2+} (3)

solid lines represent active transport and dashed lines passive movement of ions

A lumen-positive transepithelial potential difference is created by potassium secretion through conducting channels in the luminal membrane, and chloride reabsorption via conducting channels and potassium chloride cotransporters in the basolateral membrane. The lumen-positive transepithelial potential difference will lead to paracellular reabsorption of sodium, calcium and magnesium. (Figure 2) As furosemide blocks the site of chloride in the Na^+-K^+- $2Cl^-$ -membrane carrier there will be decreased potassium secretion and chloride reabsorption for tubular cell polarization, and consequently abolish the voltage-dependent paracellular movement of sodium, calcium and magnesium. This explains why furosemide not only causes increased excretion of sodium, chloride and potassium but also losses of calcium and magnesium. [16-18]
Decreased sodium reabsorption leads to increased sodium delivery to the distal and collecting tubules. This results in compensatory increased sodium reabsorption and potassium secretion via the Na^+/K^+ countertransport system. As a result hydrogen excretion is stimulated by the K^+/H^+ countertransport system. [16-21]

Pharmacokinetics and Pharmacodynamics of Furosemide in Infants

a. General
Furosemide has to reach the tubular lumen to exert its action. Therefore pharmacokinetic (PK) factors that affect furosemide delivery to the thick ascending limb of the loop of Henle are major determinants of drug response. [17,22,23] These factors include volume of distribution, protein binding, renal clearance and non-renal clearance.
Total plasma clearance of furosemide in neonates is remarkably less than in older infants and adults and correlates with postnatal age. [17,24-27] The relative contributions of non-renal clearance and renal clearance to the overall clearance differ between neonates and older infants and adults. [17,27-29] Non-renal clearance is primarily the result of extra-hepatic glucuronidation, which probably occurs in the kidney tubule cells, and the formation of the acid metabolite CSA (4-chloro-5-sulfamoyl-anthranilic acid). [30-34] In general the contribution of non-renal clearance is less in neonates compared to older infants and adults. However, results of studies evaluating non-renal clearance in neonates have been conflicting and have not clearly established a correlation between age and the ability to metabolize the drug. [31,35,36]
Furosemide, as unchanged drug reaches the tubular lumen by glomerular filtration and/or proximal tubular secretion. Since only the unchanged drug interacts with the tubular receptor sites, renal clearance is most closely related with drug response. [37] The amount of furosemide excreted as unchanged drug in the urine exhibits a great inter-subject variability that is predominantly influenced by age, disease states and drug interaction. [32,38]
In premature neonates < 32 weeks gestational age, glomerular filtration is the main determinant to deliver furosemide into the urine whereas at term active secretion by the proximal tubule cell is the main component of renal clearance. [25,35,36] Plasma half-life is elevated in both preterm and term neonates compared to older infants and adults. [17,24-26,35,39] The prolonged plasma half-life has been attributed to the increased volume of distribution, slow renal clearance and to inability to compensate for decreased renal clearance with increased non-renal excretion. [17,24-26,35,40] Plasma half-life decreases with increasing postnatal age. [24,26]
The association between furosemide dose and diuretic response has been studied in adult and paediatric patients. [41,42] It was observed that urinary sodium excretion rate was more correlated with urinary furosemide excretion than with serum furosemide concentration, and that there was a significant relationship between urinary furosemide excretion rate and both sodium excretion and urine flow rate. The slope of these relationships defines the response to the drug. [22,40-42] In adults the relationship between urinary furosemide excretion rate and urinary sodium excretion rate is sigmoidal in nature with the existence of a maximally efficient delivery of furosemide in the urine (21.5 μg/min). [41,42] On the contrary, in infants the dose-response relationship appeared linear and no plateau in diuretic response occurred even at furosemide excretion rates ≥ 95 μg/min, which is the highest reported maximally efficient furosemide excretion rate for adults. [41,43,44] However, Sullivan observed in critically ill infants a linear increase in urine flow rate with increasing doses up to a bumetanide excretion rate of 7 μg/kg per hour and thereafter the urine flow rate reached a plateau or declined at a bumetanide excretion rate of 10 μg/kg per hour. [45]

b. Effect of Cardiopulmonary Bypass Surgery on the Pharmacokinetics/Pharmacodynamics of Furosemide
Cardiopulmonary bypass (CPB) circuit triggers an important inflammatory reaction. [46] This reaction is largely related to the ratio of the circuit area to body surface area and is therefore maximal in small children. Clinically this reaction is associated with a capillary leakage syndrome, resulting in intravascular hypovolaemia and renal hypoperfusion. [47] Therefore (transient) renal insufficiency is a frequent (17%) complication in children after CPB surgery and can lead to acute renal failure (2.3%), necessitating renal replacement therapy. [48-52] The management in post CPB

surgery patients is focused on a negative total body water balance and therefore loop diuretics, especially furosemide are commonly used to augment urinary output. Since furosemide is predominantly excreted by the kidneys and exerts its action only after excretion into the tubular lumen, the altered renal function in patients after CPB surgery will influence both the serum furosemide concentration and the urinary furosemide excretion. [14,15,17,22,23]

c. Effect of Extracorporeal Membrane Oxygenation on the Pharmacokinetics/Pharmacodynamics of Furosemide.

Extracorporeal membrane oxygenation (ECMO) is used to treat cardio-respiratory problems associated with conditions such as persistent pulmonary hypertension of the newborn, meconium aspiration, congenital diaphragmatic hernia, sepsis and cardiac anomalies. [53]
The ECMO circuit, like the CPB circuit, is clinically associated with a capillary leakage syndrome. [46] Therefore, the ECMO patient becomes increasingly oedematous in the first few days. Once the patient is stabilized, diuresis begins but is insufficient and needs to be enhanced with diuretics. Loop diuretics, especially furosemide are the most commonly used diuretics. [54]
The PK of drugs in the ECMO patient is characterized by a larger volume of distribution and prolonged elimination with a return to baseline after decannulation. The larger volume of distribution is probably a result of the addition of a large exogenous blood volume (± 300 – 400 ml) for priming of the circuit. The prolonged elimination is multifactorial with the reduction in renal function as primary determinant. [14,15,17,22,23,55,56] Consequently the altered PK in the ECMO patient will influence the pharmacodynamics (PD) of furosemide.
Contrary to the 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. [17,24-26,35,39,54,55,57] Wells studied the PK/PD of the loop diuretic, bumetanide in eleven term neonates treated with ECMO and reported that the steady state volume of distribution and the elimination half-life were all 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. Significant diuresis, natriuresis and kaliuresis were observed after an intravenous (IV) bolus of 0.1 mg/kg. However, the duration of the effects was less than expected given by the prolonged renal elimination. [54]

Adverse Effects of Furosemide

a. General

Furosemide may produce side effects like nausea, vomiting, gastro-intestinal tract irritation, weakness, fatigue, dizziness, cramps and paresthesia.

b. Serum electrolytes and acid-base balance

Blockade of the Na^+-K^+- $2Cl^-$ - membrane carrier will impede sodium, chloride and potassium reabsorption into the tubular cell and reduce paracellular reabsorption of sodium, calcium and magnesium because of decreased cell polarization. Consequently increased sodium delivery to the distal and collecting tubules will cause increased potassium and hydrogen secretion respectively via the Na^+/K^+ and K^+/H^+ countertransport systems. [16-21] In summary the use of furosemide will effect serum levels of sodium, chloride, potassium, calcium and magnesium, and may lead to metabolic alkalosis.[16-18,21]

c. Ototoxicity

Furosemide can cause both temporary and permanent hearing loss, especially with the co-administration of aminoglycosides. [17,58-67]
The marginal cells of the stria vascularis of the cochlear duct contain a Na^+-K^+- $2Cl^-$ cotransporter, which is similar to the one found in the thick ascending limb of the loop of Henle, and therefore furosemide can alter ion transport. [17,66-69]
Furosemide induces changes in receptor potentials, auditory-nerve responses and basilar-membrane vibration. [70-72] Furosemide is thought to exert these effects on these stimulus-related responses via interference with the stria vascularis function, through reduction of the positive endolymphatic potential.
The outer hair cell (OHC) from the organ of Corti of the cochlear duct plays a crucial role in hearing through its unique voltage-dependent mechanical responses. The sensitivity and frequency selectivity of basilar membrane responses are due to the mechanical activity of OHCs.
Santos-Sacchi reported the direct effect of furosemide on OHC motility. Although, the predominant effect of furosemide on hearing results via its effects on the endolymphatic potential, the direct effect of furosemide on OHC motility may, in part, contribute to sensory dysfunction. [70]
Risk factors for ototoxicity are reduced renal excretion, rapid infusion (≥ 25 mg/min) and synergistic interactions with aminoglycosides and other ototoxic drugs. [17,18,64,66,67,73-80] Reduced renal excretion due to renal insufficiency, not fully developed ability to excrete organic acids and decreased conjugation in (premature) infants can lead to potentially ototoxic plasma concentrations. [17,18,24,66,67,78, 81,82]

Although it is known that the risk of ototoxicity depends on high serum drug concentration (> 50 mcg/ml), therapeutic drug monitoring is not routinely performed for furosemide as it is done for aminoglycosides and other ototoxic drugs. [17,18,67,78,81,83] Consequently there are hardly any data on furosemide serum levels available in the literature.

d. Nefrotoxicity

Furosemide can cause interstitial nephritis in patients with and without known underlying renal disease. The onset after treatment varies from days to months. [84] The combination of mild proteinuria, microhaematuria, sterile pyuria with or without casts, and signs of tubular dysfunction: hyperkalemic-, hyperchloraemic- metabolic acidosis and nephrogenic diabetes insipidus, strongly suggest the diagnosis of interstitial nephritis.
Furosemide induced interstitial nephritis is most likely an allergic or hypersensitivity reaction and not a direct toxic effect due to the absence of acute tubular necrosis. [84,85,85] Although the exact pathophysiologic mechanism is not clear, two features related to the chemical structure of furosemide are important. First, furosemide is a sulfa drug, and sulfa drugs are among the most common agents causing hypersensitivity reactions. [1,8-10] Second, furosemide is an organic acid and reaches the proximal tubule by proximal tubular secretion. [14,15] Therefore, furosemide may become concentrated in the renal cortex where it may form a drug-hapten complex and, when it enters the interstitial space it is recognized by T-cells as foreign and incites an inflammatory response. [84,85]
In nearly all cases, furosemide interstitial nephritis is reversible after withdrawal of furosemide. The rate of recovery of renal function is variable and can take several months. Treatment with systemic corticosteroids has shown to be beneficial. [84,85] Of note furosemide can potentiate the toxicity of other nephrotoxic drugs like aminoglycosides. [86]

e. Renal calcifications

Furosemide may predispose (premature) infants to the development of renal calcifications, due to high urinary calcium excretion. [17,75,81,87-90] Hypercalciuria may also lead to bone demineralization. [91]

Drug Therapy in Critically ill Infants

Drug therapy in paediatric patients in general, and in critically ill infants in specific, is hold by a shortage in the availability of licensed drugs in an appropriate formulation. [92] This has lead to the use of unlicensed and/or off-label drugs in children, and consequently to adverse drug reactions. [93,94]
The use of unlicensed and/or off-label drugs in critically ill infants ranged from 50% - 90% respectively in paediatric and neonatal intensive care units. [92,95,96] The loop diuretic, furosemide is not only amongst the most frequently drugs prescribed, but also part of the most frequently used unlicensed and/or off-label drugs. [92,96]
This highlights the difficulties faced by those trying to ensure safe and effective drug prescribing for critically ill patients. Therefore the implementation of the Paediatric Regulation in the European Union on 26th of January 2007 is an important new piece of legislation (Regulation (EC) No 1901/2006). The Paediatric Regulation aims to improve health amongst children in Europe through measures designed to stimulate the development of new medicines for use in the paediatric population, to ensure that they are appropriately tested and authorised, and to improve the availability of information about the use of these medicines. With the new legislation a new committee of scientific experts, the Paediatric Committee is established within the European Medicines Agency (EMEA). The Paediatric Committee is responsible for the assessment and agreement of paediatric investigation plans, and to establish an inventory of the therapeutic needs of children, and to advise the EMEA on its development of a European network for clinical trials in children.

Furosemide Dosing Regimens in Critically ill Infants

a. Indication

Loop diuretics are potent diuretics with a rapid onset of action. Therefore loop diuretics, especially furosemide, are frequently used in critically ill infants with pathological fluid retention, to remove the excess salt and water, and consequently improve haemodynamics, facilitate weaning from mechanical ventilation and obtain adequate urine output. [45,97]

b. Furosemide regimen

In critically ill infants furosemide is administered as intermittent IV bolus or as continuous infusion.

Since the observation that continuous IV furosemide might be superior to intermittent administration, in infants and children after CPB surgery continuous furosemide infusions are increasingly used in patients after cardiac surgery. [98-101] Trials, assessing efficacy and safety of continuous versus intermittent IV furosemide in paediatric patients after CPB surgery revealed that the cumulative furosemide dose administered by continuous infusion was generally less than the dose given by intermittent administration. [99-101] No significant difference was observed in the main PD outcome parameter: urine production. Continuous IV administration of furosemide resulted in greater excretion of both sodium and water compared to equivalent doses of intermittent bolus infusions and significant less variance in urine output was observed. [99-101]
The observations of continuous IV furosemide in infants after CPB surgery lead to the use of continuous furosemide infusion in neonates treated with ECMO, since ECMO and CPB are 'comparable' procedures.
Although continuous IV furosemide is used in critically infants after CPB surgery and on ECMO, the dosing schedules are still largely empirical in this group of infants with varying renal function. Current practice is to start with a low continuous IV furosemide infusion (0.05 - 0.1 mg/kg per hour) and increase furosemide infusion until the desired urinary output is achieved. Thus it may take some time before the desired urine production is reached.

Tolerance to Furosemide

Tolerance to furosemide, a decreased natriuretic and diuretic response over time to the same amount of excreted furosemide in the urine, is an often encountered clinical problem after prolonged exposure. [17,18] Tolerance to furosemide has also been observed in healthy subjects after multiple intermittent doses. Why either repeated bolus or continuous administration of furosemide results in tolerance for the diuretic is unclear. It has been suggested that interference with the autonomic nervous system, the renin-angiotensin-aldosteron system or atrial natriuretic peptide may play a role. However, the role of all these hormones has been shown to be minimal if present at all. [19,102-105] Therefore it has been suggested that tolerance to furosemide can be induced through different but complementary homeostatic mechanisms in the kidney. It seems that the volume status plays a major role hereby. [19-21,106-109]

Conclusion

Furosemide is the most frequently used loop diuretic in infants after CPB surgery and in infants treated with ECMO to augment urinary output. Although, the PK and PD of furosemide in infants have been extensively reviewed, limited research has been performed on loop diuretics in infants treated with ECMO.
Serum furosemide levels (> 50 µg/ml) are associated with oto-toxicity. There are no data available on serum furosemide concentration in infants after CPB surgery nor in infants treated with ECMO and therefore we do not know if hearing loss observed in these infants is a sign of furosemide toxicity.
Since the observation that continuous IV furosemide might be superior to intermittent administration, in adult and paediatric patients after CPB surgery, continuous IV furosemide is increasingly used in infants after cardiac surgery. The observations of continuous IV furosemide in infants after CPB surgery lead to the use of continuous furosemide infusion in neonates treated with ECMO, since ECMO and CPB are 'comparable' procedures. The dosing schedules used are empirical and may not be optimal in this group of critically ill infants. Current practice is to start with a low continuous IV furosemide infusion (0.05 - 0.1 mg/kg per hour) and increase furosemide infusion until the desired urinary output is achieved. Tolerance to furosemide is often encountered after repeated bolus as well as after continuous infusion. The mechanism of development of tolerance to furosemide is not clear. However, it is clear that the volume status plays a major role. Therefore tolerance to furosemide may not develop in infants after CPB surgery and infants treated with ECMO since they are usually fluid overloaded when furosemide therapy is started.

Aim of the study

This thesis aimed to contribute to the development of safe and effective dosing regimen for continuous intravenous furosemide in critically ill infants after cardiopulmonary bypass surgery and infants treated with extracorporeal membrane oxygenation and therefore the following studies were carried out.

- To evaluate the PK and PD of continuous IV furosemide therapy in infants after CPB surgery with varying renal function.
- To investigate the relationships between clinically applicable measures that could be used to design a rational regimen for continuous IV furosemide in infants after CPB surgery.
- To evaluate serum furosemide concentration of continuous IV furosemide therapy in infants after CPB surgery with (transient) renal insufficiency.
- To develop a PK/PD model to investigate alternative furosemide infusion regimens with a predefined urine production as final outcome parameter
- To evaluate the efficacy and safety of the proposed furosemide regimen by the developed PK/PD model in infants after CPB surgery with varying renal function.
- To evaluate furosemide regimens used in neonates treated with ECMO
- To evaluate the efficacy and safety of the proposed furosemide regimen by the developed PK/PD model for infants after CPB surgery in neonates treated with ECMO.

Outline of the thesis

Chapter 1 gives an overview of the different aspects of furosemide therapy in critically ill infants. First the PK and PD of furosemide in children in general are described. Thereafter the effects of CPB and ECMO on the PK and PD of furosemide are discussed. The adverse effects of furosemide on serum electrolytes and acid base balance, nephro- and oto-toxicity and renal calcifications are summarized. The use of unlicensed and/or off-label drugs in critically ill infants is mentioned. Thereafter the currently used continuous IV furosemide regimens in infants after CPB and infants treated with ECMO are discussed. The chapter concludes with the aim of the study and the outline of the thesis.

Chapter 2 reviews current use of diuretics in children.
Diuretics in pediatrics: current knowledge and future prospects.
Maria MJ van der Vorst, Joana E Kist-van Holthe, Albert J van der Heijden, Jacobus Burggraaf.
Pediatric Drugs 2006; 8 (4): 245-64

Chapter 3 evaluates renal function in children after CPB surgery.
Acute renal insufficiency and renal replacement therapy after paediatric cardiopulmonary bypass surgery.
Joana E Kist-van Holthe, Charlotte A Goedvolk, Martha BME Doornaar, Maria MJ van der Vorst, Ronald Brand, Judith M Bosman-Vermeeren, Paul H Schoof, Mark G Hazekamp, Albert J van der Heijden.
Pediatric Cardiology 2001; 22: 321-32

Chapter 4 describes the results of an observational study that evaluated PK and PD of continuous IV furosemide in infants after CPB surgery.
Continuous intravenous furosemide in haemodynamically unstable children after cardiac surgery.
Maria MJ van der Vorst, Isabelle Ruys-Dudok van Heel, Joana E Kist-van Holthe, Jan den Hartigh, Rik C Schoemaker, Adam F Cohen, Jacobus Burggraaf.
Intensive Care Medicine 2001; 27 (4): 711-5

Chapter 5 discusses the development of a PK/PD model to simulate various furosemide regimens that adapt according to urine output.
Development of an optimal furosemide infusion strategy in infants with modeling and simulation.
Rik C Schoemaker, Maria MJ van der Vorst, Isabelle Ruys-Dudok van Heel, Adam F Cohen and Jacobus Burggraaf.
Clinical Pharmacology and Therapeutics 2002; 72:383-90

Chapter 6 evaluates the developed PK/PD model for continuous IV furosemide in infants after CPB surgery.
Absence of tolerance and toxicity to high-dose continuous intravenous furosemide in haemodynamically unstable infants after cardiac surgery.
Maria MJ van der Vorst, Joana E Kist-van Holthe, Jan den Hartigh, Albert J van der Heijden, Adam F Cohen, Jacobus Burggraaf.
British Journal of Clinical Pharmacology, in press

Chapter 7 describes furosemide regimens used in neonates treated with ECMO.
Evaluation of furosemide regimens in neonates treated with extracorporeal membrane oxygenation.
Maria MJ van der Vorst, Enno Wildschut, Robbert J Houmes, Saskia J Gischler, Joana E Kist-van Holthe, Jacobus Burggraaf, Albert J van der Heijden, Dick Tibboel.
Critical Care 2006, Dec 1; 10(6):R168

Chapter 8 evaluates the developed PK/PD model for continuous IV furosemide in infants after CPB surgery in neonates treated with ECMO.
An exploratory study with an adaptive continuous intravenous furosemide regimen in infants treated with extracorporeal membrane oxygenation.
Maria MJ van der Vorst, Jan den Hartigh, Enno Wildschut, Dick Tibboel, Jacobus Burggraaf.
Submitted for publication

Chapter 9 is the concluding chapter in which the results of the previous studies are discussed and suggestions are made for future research.

Chapter 10 gives a summary of the thesis in English and Dutch.

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Chapter 2

Diuretics in pediatrics: current knowledge and future prospects

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Pediatric Drugs 2006; 8(4):245-264

Abstract

This review summarizes current knowledge on the pharmacology, pharmacokinetics, pharmacodynamics, and clinical application of the most commonly used diuretics in children.
Diuretics are frequently prescribed drugs in children. Their main indication is to reduce fluid overload in acute and chronic disease states such as congestive heart failure and renal failure. As with most drugs used in children, optimal dosing schedules are largely unknown and empirical. This is undesirable as it can potentially result in either under- or over-treatment with the possibility of unwanted effects.
The pharmacokinetics of diuretics vary in the different pediatric age groups as well as in different disease states. To exert their action, all diuretics, except spironolactone, have to reach the tubular lumen by glomerular filtration and/or proximal tubular secretion. Therefore, renal maturation and function influence drug delivery and consequently pharmacodynamics.
Currently advised doses for diuretics are largely based on adult pharmacokinetic and pharmacodynamic studies. Therefore, additional pharmacokinetic and pharmacodynamic studies for the different pediatric age groups are necessary to develop dosing regimens based on pharmacokinetic and pharmacodynamic models for all routes of administration.

Introduction

Diuretics are frequently used drugs in children. All diuretics, except spironolactone, have to reach the tubular lumen to exert their action. Therefore, renal development and function influence drug delivery to the end organ and consequently the pharmacodynamics of diuretics.
Prior to a discussion of the indications for diuretic therapy in (pre)term neonates, infants, and children for the most common diseases and treatment modalities, the site and mechanism of action, pharmacokinetics, pharmadynamics, and adverse effects of diuretics are described. Recommended doses for diuretics in the different pediatric age groups are largely based on adult pharmacokinetic/pharmacodynamic studies, which may lead to either under- or over-treatment, and adverse effects.
Suggestions for pharmacokinetic/pharmacodynamic studies of diuretics in the different pediatric age groups and development of dosing regimens, based on pharmacokinetic/pharmacodynamic models, are given.

Renal Function

Glomerular Function

Glomerular filtration depends on the number of nephrons, the mean arterial blood pressure, renal plasma flow, and intrarenal vascular resistance. An increase in glomerular filtration rate (GFR) before birth is mainly due to the increasing number of glomeruli, whereas the rapid increase after birth results from the rise in renal blood flow.
GFR is usually expressed in relation to body surface area for standardization and comparison between individuals of different sizes, and reaches its maximum around the age of 2 years.[1,2]
GFR cannot be measured directly but has to be determined by measuring the clearance of a filtration marker. Although traditional inulin clearance, by continuous intravenous infusion and timed collection of urine samples, is the gold standard for measurement of GFR, its application in clinical practice is cumbersome.[3]
Measurement of systemic clearance of inulin, which does not require urine collection, has been shown to be a valid and convenient substitute for measurements of renal clearance.[3]
Clinically, repeated serum creatinine levels and renal creatinine clearance are widely used measures of renal function.[4-7] Although creatinine clearance can be reliably determined by accurate urine collection, GFR is often estimated by formulae, such as Schwartz and Léger, or by repeated serum creatinine levels.[6,8-13] Serum creatinine levels measured with enzymatic assay or modified Jaffé method vary, which is important when formulae are used to calculate GFR.[8,12,13]
However, it should be realized that serum creatinine levels depend on muscle mass and that creatinine is eliminated from the circulation not only by glomerular filtration but by tubular secretion as well, which increases especially in advanced chronic renal failure (CRF).[7,14-17]
Cystatin C, a non-glycated 13 kDa basic protein, has been suggested as a useful indicator for GFR estimation in children. However, there is controversy about the use of cystatin C as an assessment of GFR especially in pre- and full-term neonates and infants.[2,14,15,18-20] In children and adolescents, cystatin C correlates more strongly with GFR than creatinine, although it can not replace the full clearance study in the detection of mildly impaired GFR.[16]

Tubular Function

The ultra-filtrate is modified through re-absorption and secretion processes in the different parts of the tubular system. Although most endocrine, secretory,

and absorptive tubular processes are relatively well developed at birth, postnatal maturational changes occur. Also, developmental changes take place regarding the activity of vasoactive substances, the dopamine system, and a variety of enzymes such as tubular cell Na^+/K^+-adenosine triphosphatase activity.[21]
Concerning salt and water handling in the tubular system, the fractional excretion of sodium (Fe_{Na}) is an efficient indirect index of tubular function.[22] The FeNa directly after birth can be as high as 5%. In full-term neonates, the high FeNa falls within hours.[23-25] In premature infants, the FeNa value correlated negatively to postnatal age and the velocity of the decrease was directly correlated to gestational age.[22]

Main Site of Action of Diuretics

Diuretics can be classified by type, site, and mechanism of action within the tubular system, and by chemical structure (table I).

Proximal Tubule

Carbonic Anhydrase Inhibitors
Carbonic anhydrase inhibitors are weak diuretics. They are secreted via the organic acid transporter, i.e. OAT1 and OAT3, in the basolateral membrane into the proximal tubular cell, and are subsequently secreted into the proximal tubular lumen.[26,27] The main site of action of carbonic anhydrase inhibitors is the proximal tubular lumen and cell. Blockade of carbonic anhydrase leads to decreased bicarbonate and sodium reabsorption via the Na^+/HCO_3^- co-transporter resulting in reduced water reabsorption (figure 1).[28]

Table I. Main site of action of diuretics

Type	Main site of action	Mechanism of action	Examples
Carbonic anhydrase inhibitors	Proximal tubule	Carbonic anhydrase inhibition	Acetazolamide
Osmotic diuretics	Proximal tubule	Osmotic effect	Mannitol
Loop diuretics	Loop of Henle	Block $Na^+/K^+/2Cl^-$ membrane carrier	Furosemide (frusemide) Bumetanide
Thiazide diuretics	Distal tubule	Block thiazide-sensitive Na^+/Cl^- co-transporter	Hydrochlorothiazide Chlorothiazide Metolazone
Potassium-sparing diuretics	Collecting tubule Collecting tubule	Block Na^+ channels Aldosterone antagonist	Amiloride Triamterene

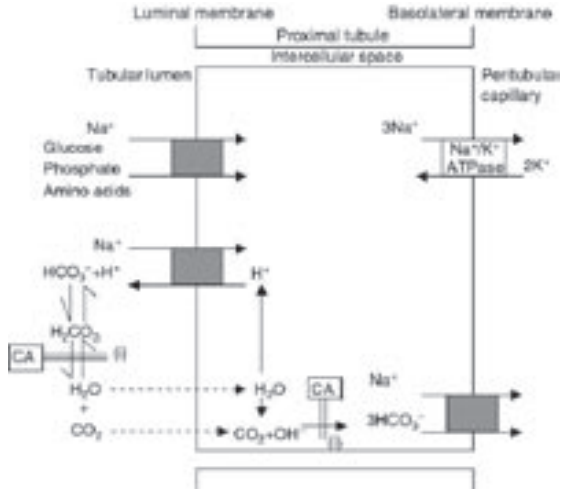

Fig. 1. Passive sodium transport via the Na^+/K^+-adenosine triphosphatase (ATPase) pump into, and active sodium transport out of, the proximal tubular cell. (i) Blockade of carbonic anhydrase (CA) leads to decreased bicarbonate and sodium reabsorption via the Na^+/HCO_3^- co-transporter.

Loop and Thiazide Diuretics
Loop and thiazide diuretics also block carbonic anhydrase and, therefore, have a weak action on the proximal tubule.[29,30]

Osmotic Diuretics
Osmotic diuretics are potent diuretics that mainly act at the proximal tubule. These compounds undergo glomerular filtration and are not reabsorbed along the tubular system. Therefore, they increase osmolality of the tubular fluid and subsequently water and sodium excretion.

Thick Ascending Limb

Loop Diuretics
Loop diuretics are among the more potent diuretics because they can block up to 25% of sodium reabsorption. They reach the proximal tubular lumen via OAT1 and OAT3 in the basolateral membrane of the proximal tubular cell. Then, secretion into the proximal tubular lumen and transport to the thick ascending limb takes place.[26,27] Loop diuretics block the site of chloride in the $Na^+/K^+/2Cl^-$ membrane carrier and thereby inhibit sodium, chloride, and potassium entering the tubular cell. Thus, reabsorption of sodium will be diminished. Blockade of the $Na^+/K^+/2Cl^-$ membrane carrier by loop diuretics also diminishes potassium secretion through specific channels in the luminal membrane and chloride reabsorption via chloride-conducting channels in the basolateral membrane (figure 2). This implies that no luminal-positive transepithelial potential difference will be created and, thus,

paracellular reabsorption of sodium, calcium, and magnesium will not take place. This explains why loop diuretics not only cause increased excretion of potassium and chloride but also losses of calcium and magnesium.[29,30] Decreased sodium reabsorption leads to increased sodium delivery and a compensatory increase in sodium reabsorption in the distal and collecting tubules. The compensatory increased sodium delivery causes increased potassium secretion.[29-33]

Although etacrynic acid has a different chemical structure to loop diuretics, its action on the thick ascending limb is similar.

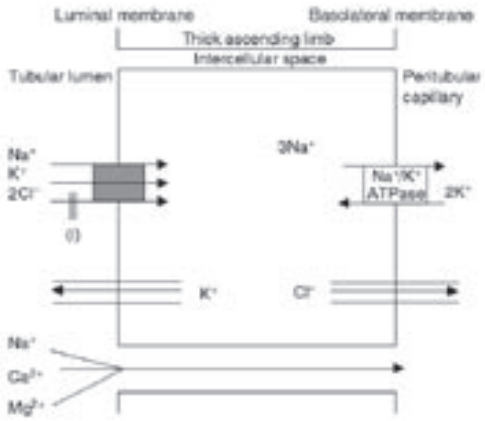

Fig. 2. Passive sodium transport with potassium and chloride, via the $Na^+/K^+/2Cl^-$ membrane carrier, into and active sodium transport, by the Na^+/K^+-adenosine triphosphatase (ATPase) pump, out of the tubular cell of the thick ascending limb of the loop of Henle, and paracellular reabsorption of the cations Na^+, Ca^{2+}, and Mg^{2+}. (i) Loop diuretics block the site of chloride in the $Na^+/K^+/2Cl^-$ membrane carrier, which leads to decreased sodium reabsorption.

Distal Tubule

Thiazide Diuretics

Thiazides are of moderate potency. These drugs reach the luminal side of the proximal tubules via OAT1 and OAT3 in the basolateral membrane in the cells lining the proximal tubular cell. Thereafter, these are transported to the distal tubule where they exert their effects.[26,27] Because thiazides block the thiazide-sensitive Na^+/Cl^- co-transporter, decreased reabsorption of sodium, potassium, and chloride occurs (figure 3). As potassium recycling does not result in a luminal-positive potential difference, thiazides are not associated with urinary magnesium or calcium loss.[30] In fact, by an as yet unknown mechanism, thiazides enhance distal tubule calcium reabsorption, which may even lead to hypercalcemia. It is now suggested that hypovolemia decreases the expression of Ca^{2+} transport proteins and is therefore a critical determinant for thiazide-induced hypocalciuria.[34]

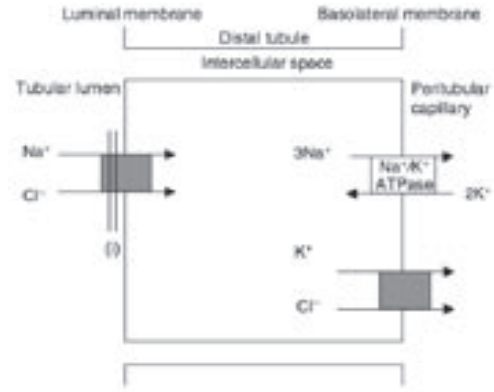

Fig. 3. Passive sodium transport, via the Na^+/Cl^- membrane carrier, into and active sodium transport, by the Na^+/K^+-adenosine triphosphatase (ATPase) pump, out of the tubular cell of the distal tubule. (i) Thiazides block the Na^+/Cl^- membrane carrier, which leads to decreased sodium reabsorption.

Metolazone, although a quinazoline, is classified as a thiazide diuretic, because its action on the distal tubule is similar to thiazides.

Collecting Tubule

Potassium-Sparing Diuretics

Potassium-sparing diuretics have a moderate potency. Both amiloride and triamterene reach the proximal tubular lumen via the organic cation transporter OCT2 in the proximal tubular cell, and are then transported to their sites of action.[26,27] These drugs directly block sodium entry through the epithelial sodium channels in the luminal membrane (figure 4). The lack of sodium movement across the luminal membrane will lead to decreased potassium secretion and chloride reabsorption.

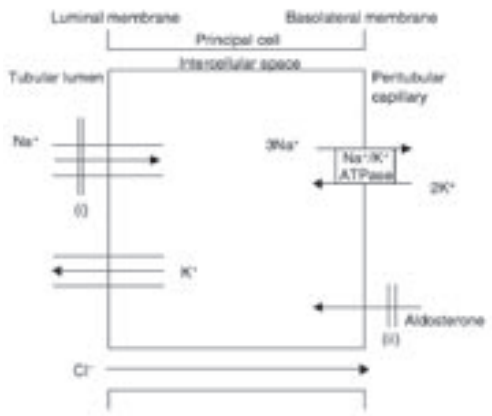

Fig. 4. (i) Passive sodium transport through sodium channels into and active sodium transport, by the Na^+/K^+-adenosine triphosphatase (ATPase) pump, out of the principal tubular cell. Amiloride and triamterene directly block sodium entry through the sodium channels, which leads to decreased sodium reabsorption. (ii) Paracellular chloride reabsorption and potassium secretion are promoted by aldosterone. Spironolactone, a competitive aldosterone antagonist, leads to decreased potassium secretion and decreased sodium and chloride reabsorption.

Spironolactone, a competitive aldosterone antagonist, is the only diuretic that does not have to reach the tubular lumen to exert its action (figure 4). Spironolactone competes with aldosterone for the mineralocorticoid receptor. The blockade of the mineralocorticoid receptor by spironolactone will lead to decreased potassium secretion (or even potassium reabsorption) and decreased sodium and chloride reabsorption in the principal cells.[30]

Pharmacokinetics and Pharmacodynamics of Diuretics in Children

General

It is a well known fact that the pharmacokinetics of drugs vary in different pediatric age groups. Absorption in preterm neonates and infants is influenced by gastric pH, delayed gastric emptying, and decreased intestinal transit time.[35] The volume of distribution depends on total body water, membrane permeability, and to some extent on plasma protein binding. Premature neonates have the highest percentage of total body water (83%) and extracellular water (53%). Total body water, predominantly from the extracellular compartment, decreases rapidly to 78% at term and 73% by the sixth postnatal day and will decline further during the first year of life.[30,36,37] Membrane permeability is increased in (pre)term neonates and infants, which may lead to penetration of drugs into the CNS.[35]
The liver is the most important organ for drug metabolism. Other organs in which drugs are metabolized are the kidneys and the intestinal epithelial cells.[35,38-40]
Drugs are metabolized by phase I reactions, oxidation, reduction, and hydrolysis, and phase II conjugation reactions. At birth, phase I reactions are better developed than phase II reactions. Glucuronidation, a phase II reaction will not reach adult values until 3–6 months of life.[40-42]
Drugs are eliminated by renal and/or biliary excretion. Renal excretion of drugs depends on glomerular filtration, tubular secretion, and tubular reabsorption. Transport proteins have an important role in regulating the absorption, distribution, and excretion of drugs. P-glycoprotein mediates transcellular drug transport. For instance, altered expression of P-glycoprotein decreases intestinal absorption and renal excretion and thus influences the pharmacokinetics of drugs.[35,43,44]
The pharmacokinetics of drugs may also vary due to disease states. This will predominantly affect drug delivery to the end organ.[36,37]
Diuretics, except spironolactone, need to reach the tubular lumen to exert their action. Osmotic diuretics reach the proximal tubular lumen via glomerular filtration whereas loop, thiazide, and potassium-sparing diuretics reach the proximal tubular lumen predominantly by proximal tubular secretion. In the case of tubular immaturity, the delivery of diuretics to their site of action is slow. This leads to a delayed onset of action and an increased elimination time of the drug and thus possibly to a prolonged effect. In addition, disease states may influence end-organ sensitivity, which may lead to changes in the pharmacodynamics of drugs.
Hence, the observed effect of diuretics is the result of a complex interplay between (gestational and postnatal) age, weight, body surface area, disease state, etc. This may partly explain why only limited pharmacokinetic and/or pharmacodynamic data are available for the different pediatric age groups. For this article, the pharmacokinetics and pharmacodynamics of diuretics in children will be described if available and relevant adult data will be mentioned where pediatric data are lacking. Pharmacokinetic and pharmacodynamic data of diuretics are summarized in table II. The pharmacokinetics and pharmacodynamics of loop diuretics are extensively studied both in different pediatric age groups and in various disease states and are therefore described more in detail.[29,45-49]

Loop Diuretics

Furosemide (Frusemide)
Pharmacokinetics
Furosemide (frusemide) is eliminated by hepatic and renal glucuronidation with approximately 90% of the dose appearing in the urine as unchanged drug.[29,47,58-61] The formed active metabolites are eliminated by renal and non-renal clearance.[45,46,59,60,62] In neonates, non-renal clearance is <1%, whereas in older children and adults this may account for ≈50%.[49,61-64]
In preterm neonates the inability to compensate for decreased renal clearance and the larger volume of distribution results in prolonged elimination half-lives. These long elimination half-lives decrease with increasing postnatal age.[29,45-49,61,63]
In neonates <32 weeks gestational age, glomerular filtration is the main determinant to deliver these diuretics into the urine, although loop diuretics are secreted predominately by the proximal tubule. When premature infants reach term, active secretion by the proximal tubule accounts for the majority of renal clearance.[48,61]
Because plasma clearance in pre- and full-term neonates is not uniform it is suggested that plasma clearance is not only influenced by gestational age but also by postnatal age.[29,45-49]
As furosemide is a potent bilirubin displacer of the albumin-binding sites, critically ill premature neonates may have increased risk for hyperbilirubinemia.

Table II. Pharmacokinetics (PK)/pharmacodynamics (PD) of diuretics in children; where pediatric data are not available, data from adults are included[29,50-57]

Drug class/drug	PK from	Elimination	t1/2 (h)		Excretion	PD from	Route	Onset of effect	Duration of effect (h)
Carbonic anhydrase inhibitors									
Acetazolamide	Adults	Renal	≈4		Renal	Adults	Oral	<1h	8–12
						Adults	IV	<5 min	4–5
Osmotic diuretics									
Mannitol	Adults	Renal	2–4		Renal	Children	IV	30–60 min	2–4
Loop diuretics									
Furosemide (frusemide)	Preterm	Hepatic/renal	≈12–24		Renal/biliary	Infants/children			
	Term	Hepatic/renal	≈4–8		Renal/biliary	Infants/children			
	Infants/children	Hepatic/renal	≈1–2		Renal/biliary		Oral	30–60 min	4–6
							IV	15–30 min	2–3
Bumetanide	Preterm	Hepatic/renal	≈6		Renal/biliary	Infants/children			
	Term	Hepatic/renal	≈2		Renal/biliary	Infants/children			
	Infants/children	Hepatic/renal	≈1–2		Renal		Oral	60 min	4–6
							IV	20–30 min	3–4
Thiazide diuretics									
Hydrochlorothiazide	Adults	Renal	6–15		Renal	Adults	Oral	1–4h	10–12
Chlorothiazide	Preterm	Renal	≈5		Renal	Adults	Oral	<1h	6–12
Metolazone	Adults	Renal/hepatic	5–6		Renal	Adults	Oral	<1h	12–24
Potassium-sparing diuretics									
Spironolactone	Adults	Hepatic	1.5		Renal/biliary	Adults	Oral	48–72h	72
Amiloride	Adults	Hepatic	2–9		Renal	Adults	Oral	2–6h	10–24
Triamterene	Adults	Hepatic	≈4		Renal	Adults	Oral	2–6h	7–9

IV = intravenous; t1/2 = elimination half-life.

However, a causal relationship between furosemide-induced bilirubin displacement and the development of kernicterus has not been shown.[30,64,65]

Pharmacodynamics

The relationship between furosemide dose and diuretic response has been studied in adult and pediatric patients.[66,67] A linear increase in urinary flow rate was observed with an increasing dose in all patients. However, in contrast with adults in whom a plateau in urinary flow rate occurs at a furosemide excretion rate of 95 µg/h, this plateau in urinary flow rate does not occur in children.[68]

Effect of Disease States

Studies evaluating pharmacokinetic parameters in different disease states such as

renal failure, nephrotic syndrome, congestive heart failure (CHF), and hepatic cirrhosis are mainly performed in adults.[69-80]
In children, furosemide pharmacokinetics and pharmacodynamics have been studied in patients with nephrotic syndrome compared with control patients with urinary tract infection and mild hypertension.[50,66,81-83] Initially the absorption of oral furosemide was increased in patients with nephrotic syndrome, but after a 2-week treatment with corticosteroids the absorption decreased.[50,66,82] Furosemide pharmacokinetics after oral or intravenous administration showed no significant differences in plasma clearance, elimination half-life, and volume of distribution between patients with nephrotic syndrome and control patients.
There was no difference in onset and duration of the diuretic effect after oral or intravenous furosemide in patients with nephrotic syndrome and control patients. However, urine production was significantly lower in patients with nephrotic syndrome compared with control patients after oral furosemide, and in patients with nephrotic syndrome compared with infants with miscellaneous diseases after intravenous furosemide.[50,68,81-83]

Bumetanide

Pharmacokinetics
Bumetanide, like furosemide, is eliminated by renal and non-renal clearance, with approximately 50% of the dose appearing in the urine as unchanged drug.[29,84,85] Inactive metabolites of bumetanide are formed by hepatic biotransformation and eliminated by conjugation and biliary excretion.[29,86] Both renal and non-renal clearance increases with postnatal ages. Renal clearance is tripled from birth to 6 months of age in full-term infants and non-renal clearance reaches adult values in infants >1 month of age.[29,51,52]
Sullivan et al.[52] conducted a pharmacokinetic study of bumetanide in critically ill infants with heart disease (n = 29), postoperative repair or palliation of congenital heart disease, and lung disease (n = 22). The pharmacokinetics of bumetanide were significantly influenced by age and disease. The difference between the patient groups was mainly due to differences in total clearance of the drug.
Bumetanide, as furosemide, is a potent bilirubin displacer of the albumin-binding sites.[64,65]

Pharmacodynamics
Sullivan et al.[53] evaluated in the same group of critically ill infants the relationship between bumetanide dose (0.005–0.1 mg/kg) and urinary output and observed a linear increase in urinary output with increasing dose. A plateau phase in urinary output was obtained at a bumetanide excretion rate of 7 μg/kg/h. Bumetanide

excretion rate of 7 μg/kg/h was reached after a single intravenous bolus of 0.035–0.04 mg/kg.[53] However, maximal bumetanide excretion rate was observed at a dose of 0.005–0.01 mg/kg and decreased at higher doses.[51] Pharmacodynamic response, as a measure of the bumetanide excretion rate, was not significantly different between infants with heart disease and infants with lung disease.[53] Lower doses of bumetanide had the greatest diuretic efficiency, suggesting that continuous infusion of low doses of bumetanide or intermittent low-dose boluses may produce optimal diuretic response in critically ill children.[51,87]

Adverse Effects of Diuretics

General Adverse Effects

All diuretics may produce adverse effects such as nausea, vomiting, gastrointestinal tract irritation, weakness, fatigue, dizziness, cramps, and paresthesia.

Specific Adverse Effects

All diuretics have an impact on serum electrolytes and the acid-base balance. Acid-base and electrolyte disturbances are summarized in table III. Specific adverse effects for the different types of diuretics are described in the following sections.

Carbonic Anhydrase Inhibitors

Acetazolamide may promote nephrocalcinosis and nephrolithiasis, i.e. calcium stones, when combined with loop diuretics as a result of increased calcium excretion. Hematopoietic effects and hirsutism have been mentioned occasionally in adults.[30,88,89]

Osmotic Diuretics

Mannitol results in a shift of extracellular fluid into the intravascular space especially in patients with low cardiac output and poor renal perfusion after cardiac surgery. It may thereby exacerbate CHF and induce pulmonary edema. Use of mannitol in patients with acute renal failure (ARF) and increased intracranial pressure (ICP) may lead to hypervolemia and hyperosmolality, which will increase the ICP further. Cerebral hemorrhage may be aggravated with mannitol, especially in preterm neonates.[90-92]

Table III. Acid-base and electrolyte disturbances (serum) caused by diuretics

Type of diuretic	pH <7.35	pH >7.45	↓ Na+	↓ K+	↓ Cl^-	↓ Mg^{2+}	↑ Ca^{2+}	↑ Na^+	↑ K^+	↑ Cl^-	↑ Ca^{2+}
Carbonic anhydrase inhibitors	++		+	+						++	
Osmotic diuretics			++[a]	++	+		+	++[b]			
Loop diuretics		+	++	+++	++	+	+				
Thiazide diuretics		±	+	++	+	+					±
Potassium-sparing diuretics									+		

a Acute intoxication.
b Chronic administration.
± indicates hardly ever or sporadic; + indicates seldom; ++ indicates sometimes; +++ indicates frequent; ↑ indicates increased; ↓ indicates decreased.

Loop Diuretics

The adverse effects of furosemide and bumetanide are uniform, but the adverse effects of furosemide are well documented in the literature compared with bumetanide.[30,54,93-95]
The use of loop diuretics in infants may lead to nephrocalcinosis and nephrolithiasis, due to a high urinary calcium excretion.[96] Hypercalciuria may also lead to bone demineralization. High serum drug concentrations are prone to cause nephro- and ototoxicity. It has been suggested that bumetanide may be less ototoxic than furosemide, but this may be because of under-reporting. As the risk of ototoxicity is dependent on high serum drug concentrations, continuous infusions instead of bolus doses may be used to reduce its incidence.[29,30,97] Premature neonates <32 weeks postconceptional age have an increased risk of developing high serum furosemide concentrations due to prolonged elimination half-lives and, therefore, dosing schedules should be adjusted for this age group. It is also important to avoid other ototoxic drugs (aminoglycosides) as combinations of drugs are known to potentiate ototoxicity.[29,30,97-101]
Other described adverse effects of loop diuretics include hyperuricemia, cholestatic jaundice and cholelithiasis (particularly in premature infants receiving total parenteral nutrition), drug fever, and skin reactions including Stevens-Johnson syndrome.

Thiazide Diuretics

Depending on the intake of calcium, phosphate, and vitamin D, thiazides may lead to hypercalcemia. Other described adverse effects include hyperuricaemia, drug fever, hypersensitivity reactions, cholestasis, dermatitis, and vasculitis. Long-term effects of thiazide therapy on lipid and carbohydrate metabolism as described for adults are unknown in children.[30]

Potassium-Sparing Diuretics

Nephrocalcinosis has been mentioned in preterm infants in the literature.[96] Other adverse effects of spironolactone, with the exception of hyperkalemia, are mainly described in adults.[30,102,103] Spironolactone, initially developed from progestational hormones, may induce gynecomastia, which is related to the dose and duration of the therapy and usually reversible with cessation of therapy.[30,104-106] An ovarian cyst in a premature infant treated with spironolactone has been reported.[107]

Drug Interactions

Diuretic drug delivery to the end organ can be influenced by the concurrent use of other drugs (e.g. probenecid) that decrease tubular secretion. Adverse effects of thiazide and loop diuretics (e.g. hypokalemia) can potentiate adverse effects of cardiac glycosides and vice versa other drugs. For instance, ACE inhibitors can potentiate adverse effects of diuretics (e.g. hyperkalemia) induced by the use of potassium-sparing diuretics.

Drug Resistance and Tolerance

Drug resistance, the inability to achieve normal diuretic response regardless of the urinary diuretic excretion rate achieved, has been described for patients receiving loop diuretics with various disease states such as nephrotic syndrome, CRF, and CHF. The mechanism of loop diuretic resistance is not well defined, but may involve enhanced proximal and distal sodium reabsorption. Increasing the dose, the administration frequency, or adding a thiazide diuretic may overcome loop diuretic resistance.[29,72,108-113]
Drug resistance may also be caused by genetic polymorphism in proteins involved in the pharmacokinetics and pharmacodynamics of diuretics, i.e. renal drug transporters and diuretic target sites.[114]

Drug tolerance, decrease in diuretic response over time, is observed after prolonged exposure to loop diuretics, regardless of the administration route.[29,33] Long-term administration of loop diuretics will lead to increased distal sodium delivery and subsequently increased sodium (and water) reabsorption. This enhanced sodium reabsorption in the distal tubule plays a key role in the attainment of a new steady state in patients receiving prolonged loop diuretic therapy.[29]

Diuretic Therapy in Premature and Full-Term Neonates

Respiratory Distress Syndrome

The rationale to use diuretics in preterm infants with respiratory distress syndrome (RDS) is that it may accelerate lung fluid reabsorption and therefore improve pulmonary mechanics.
A Cochrane systematic review evaluated the risk and benefits of diuretic therapy in preterm infants with RDS.[115] All six studies were performed before the era of prenatal corticosteroids and surfactant and fluid restriction therapies.[116-121] Although transient improvement in pulmonary function was seen, furosemide administration increased the risk for cardiovascular adverse effects and patent ductus arteriosus (PDA). The review concluded that there are no current data that support routine administration of diuretics in preterm infants with RDS.[115]

Chronic Lung Disease

Early stages of chronic lung disease (CLD) of prematurity are associated with alveolar and interstitial lung edema. Lung injury, CHF, and fluid overload are factors involved in lung edema.[122,123] Edema will not only decrease lung compliance but also increase airway resistance by narrowing terminal airways.[124] Diuretics, often used in these patients, may accelerate lung fluid reabsorption and therefore improve pulmonary mechanics. A Cochrane systematic review was performed to assess the risks and benefits of diuretic therapy in premature infants with or developing CLD.[125-127] The objectives of the review were to assess short- and long-term improvement and potential complications; however, most studies focused on pathophysiologic findings. Therefore, routine or sustained diuretic therapy in premature infants with or developing CLD cannot be recommended.[125-127]

Patent Ductus Arteriosus

In premature infants with symptomatic PDA, indometacin, a prostaglandin synthetase inhibitor, is often administered to promote ductus closure. Indometacin-related transient renal dysfunction is associated with inhibition of prostaglandin synthesis.[128] Furosemide increases prostaglandin synthesis and could therefore potentially prevent indometacin toxicity but also decrease ductal response to indometacin.
A Cochrane systematic review evaluated whether furosemide affects the incidence of failure of PDA closure and indometacin-related toxicity, and whether the effect of furosemide on renal function and water balance depends on prior extracellular volume.[129-132] The sample size was too small to show an increased or decreased risk of failure of ductus closure. Furosemide significantly increased urine output regardless of the initial extracellular volume, but the positive effects on renal function depended on initial extracellular volume.[129] Based on the available data furosemide administration in premature infants, treated with indometacin for symptomatic PDA, is not recommended.

Post-Hemorrhagic Ventricular Dilatation

Intraventricular hemorrhage is a serious problem in preterm infants and may lead to post-hemorrhagic hydrocephalus.[133] The only established treatment for persistent and progressive post-hemorrhagic hydrocephalus with raised intracranial pressure is surgical placement of a ventriculo-peritoneal shunt.[134] Ventriculo-peritoneal shunts are associated with frequent complications, for example, blockage and infection. In addition, the child is usually dependent on the shunt for the rest of his life. Therefore, non-surgical treatment, which avoids the need for ventriculo-peritoneal shunting, is very much needed.
Early lumbar or ventricular taps and intraventricular fibrinolytic therapy have been evaluated and found not to decrease the need for shunting.[135]
A Cochrane systematic review evaluated diuretic therapy in preterm infants developing hydrocephalus.[136] Acetazolamide and furosemide, known to decrease the production of cerebrospinal fluid, were compared with serial lumbar punctures.[137-143] Acetazolamide and furosemide did not reduce the risk for ventriculo-peritoneal shunts in infants with post-hemorrhagic hydrocephalus and, in addition, a borderline increased risk for motor developmental anomalies was observed at 1 year of age.[136,144]

Transient Tachypnea

Transient tachypnea of the newborn, particularly common after elective caesarean section is caused by delayed clearance of lung fluid. Transient tachypnea is difficult to distinguish from (congenital) pneumonia and therefore many infants receive antibacterials, in addition to respiratory support. Hastening the clearance of lung fluid should shorten the duration of symptoms and reduce complications. A Cochrane systematic review was performed to evaluate whether furosemide reduces the duration of respiratory symptoms, oxygen therapy, and hospital stay.[145]
Oral furosemide was compared with placebo. Patients treated with furosemide had a greater weight loss in the first 24 hours, but no difference was seen in the duration of respiratory symptoms or hospital stay. However, the question as to whether intravenous furosemide given to the newborn or to the mother before the caesarean section will shorten the duration of the illness still remains.[145,146]

Extracorporeal Membrane Oxygenation

The most common disorders in newborns treated with extracorporeal membrane oxygenation (ECMO) are persistent pulmonary hypertension of the newborn, meconium aspiration, congenital diaphragmatic hernia, sepsis, and cardiac anomalies.[147]
The ECMO circuit, like cardiopulmonary bypass (CPB), triggers an important inflammatory reaction and is clinically associated with a capillary leakage syndrome, resulting in intravascular hypovolemia and renal hypoperfusion.
Therefore, a patient receiving ECMO becomes increasingly edematous in the first few days. Once the patient is stabilized, natural diuresis begins but is low and needs to be enhanced with diuretics. However, there are no studies performed in patients receiving ECMO concerning the efficacy of diuretic therapy. Loop diuretics are the most commonly used diuretics in patients receiving ECMO.[148] Initial loop diuretics were administered as an intravenous bolus, but with the observation in infants after CPB surgery that continuous intravenous furosemide might be superior to intermittent administration, use of continuous intravenous furosemide is increasing in patients receiving ECMO.[87,149-151] Although continuous intravenous furosemide is now commonly used, the dosing schedule is largely empirical in this group of infants with varying renal function. Current practice is to start with a low continuous intravenous furosemide infusion and increase the furosemide infusion until the desired urinary output is achieved.

Nephrocalcinosis

Nephrocalcinosis is defined as a disposition of calcium, as calcium phosphate and calcium oxalate, in the kidney. Nephrocalcinosis is relatively common in premature infants due to an imbalance between stone inhibiting and promoting factors, use of diuretic therapy, i.e. furosemide, parenteral nutrition, and other drugs, such as corticosteroids.[152-154]
Drugs that promote nephrocalcinosis should be discontinued. Use of thiazides may be useful because they reduce urinary calcium excretion.

Diuretic Therapy in Infants and Children

Post-Cardiopulmonary Bypass Surgery

The CPB circuit triggers an important inflammatory reaction.[155] This reaction is largely related to the ratio of the circuit area to body surface area and is therefore maximal in small children. Clinically, this reaction is associated with a capillary leakage syndrome, resulting in intravascular hypovolemia and renal hypoperfusion. After CPB surgery children may develop ARF, which is related to the complexity of the operation as well as time on CPB.[156] The incidence of ARF in children after CPB surgery was described by Kist-van Holthe et al.[157] In a cohort of 1075 children (aged <17 years), 180 (17%) children developed ARF.
The management in post-CPB surgery patients is focused on a negative total body water balance and therefore loop diuretics are commonly used to augment urinary output. After an initial intravenous bolus of a loop diuretic, maintenance therapy is started as intermittent or continuous infusion and a potassium-sparing agent (e.g. spironolactone) is often added.[158]
Studies in pediatric patients after cardiac surgery have shown that continuous intravenous administration of furosemide results in greater excretion of both sodium and water and more controlled diuresis than the equivalent doses of intermittent bolus infusions.[87,149-151]
Therefore, continuous intravenous furosemide is now widely used after cardiac surgery but the dosing schedule is still largely empirical. In an attempt to rationalize the furosemide dosing regimen, the possible relationships between clinically applicable measures of renal function, urinary furosemide excretion, and urinary output were investigated.[159] The data from this study were used to develop a pharmacokinetic/pharmacodynamic model.[160] The model suggested starting with one or two loading boluses of 1–2 mg/kg and to proceed with continuous intravenous furosemide

infusion at 0.2 mg/kg/h for a desired urine production of 4 mL/kg/h. In contrast, current practice is to start with a low, continuous, intravenous furosemide infusion and increase furosemide infusion until the desired urinary output is achieved.
Lung mechanics are often compromised after cardiac surgery. Decreased lung compliance and increased airway resistance due to increased water content are considered to be responsible for difficulties in weaning from mechanical ventilation in these patients. It is reasonable to assume that selective reduction of lung water content could have a major impact on the weaning process. It has indeed been demonstrated that intra-tracheally applied furosemide in infants after cardiac surgery was absorbed from the lung and improved static lung compliance.[161] This can be an encouraging development as this therapy addresses two major issues and should be explored further.

Critically Ill Infants and Children

In critically ill infants and children pathologic fluid retention is often encountered and frequently associated with CHF, pulmonary disease, renal disease, or sepsis with capillary leakage syndrome.[52] Although the medical management should focus primarily on correcting the underlying disorder causing fluid retention, judicious administration of diuretic agents to remove excess salt and water is often required to improve hemodynamics, facilitate weaning from mechanical ventilation, and obtain or maintain adequate urinary output.[53]
Loop diuretics, furosemide, and bumetanide are commonly used to treat critically ill patients with fluid retention because they are potent diuretics with a rapid onset of action.[53] Yetman et al. studied acute hemodynamic effects of furosemide in 14 critically ill children with a median age of 42.9 months. A bolus of intravenous furosemide (1 mg/kg) resulted in an acute but transient deterioration in cardiac function before the maximal effect in diuresis. The decrease in cardiac output and increase in systemic vascular resistance index after an intravenous furosemide bolus may increase the potential risk of paradoxical pulmonary edema. With these observations, a continuous infusion should be considered in hemodynamically unstable, critically ill children.[162]

Acute Asthma

Several reports have suggested that inhaled furosemide has a protective effect against certain types of provocative challenges in asthmatic patients. However, the effect of furosemide in acute asthma exacerbations in adults is unproven and no studies have been performed in children to evaluate inhaled furosemide.[163]

The efficacy of combined furosemide and albuterol (salbutamol) has been evaluated in children with an acute asthma exacerbation. The increase in forced expiratory volume in 1 second (FEV1) was not significantly greater in the combined therapy compared with the single treatment with albuterol, suggesting that inhaled furosemide does not have a synergistic effect with albuterol in the treatment of asthma exacerbations in children.[164]

Exercise-Induced Asthma

Exercise-induced asthma (EIA) is characterized by a transient airflow obstruction associated with physical exertion. The severity of EIA can be classified by the decrease in peak expiratory flow rate (PEFR) and FEV1 after exercise. A reduction >15% in the PEFR after exercise is diagnostic for EIA. Only 9% of individuals with EIA have no history of asthma or allergy. Exercise, unlike exposure to allergens, does not produce a long-term increase in airway reactivity. Therefore, patients whose symptoms manifest only after strenuous activity may be treated prophylactically. Most asthma medications, even some unconventional ones such as heparin, furosemide, and calcium channel antagonists, given before exercise suppress EIA.[165] The beneficial effect of inhaled furosemide is caused by anti-inflammatory and immunomodulatory activities.[50] Different studies have been performed in children with EIA to evaluate the effect of inhaled furosemide on lung function changes. After furosemide inhalation, deterioration in lung function (FEV1 and PEFR) was significantly diminished compared with placebo.[166-169]
In adults, aerosolized furosemide and albuterol showed the same bronchodilator effect. However, furosemide was associated with some mild cardiovascular effects.[169] Studies in children comparing the effect of albuterol and furosemide have not been performed.
Furosemide, sodium cromoglycate, and nedocromil are effective in the prevention of EIA.[170-172] The combined administration of furosemide and nedocromil showed a significant increase in the protective effects.[170,171]
Novembre et al.[173] evaluated placebo and two doses (15 and 30mg) of inhaled furosemide on EIA in ten children. Both furosemide doses had a significantly greater protective effect than placebo, and no differences in the magnitude of the preventive effect were observed between the furosemide doses. However, the higher dose was associated with increased urine output and a longer duration of action.

Congestive Heart Failure

CHF can be defined as an inability of the heart to meet the metabolic demands of the

body. The syndrome of heart failure involves complex interactions of neurohumoral substances released in response to poor cardiac function. Developmental changes during infancy and childhood will affect both the activation of systemic neurohumoral responses and the pharmacokinetics and pharmacodynamics of diuretics.[174]
Despite diverse etiologies of heart failure (congenital heart defects, cardiomyopathies, inherited metabolic disorders, and infectious diseases) in the pediatric population, the presentation of heart failure represents a common constellation of signs and symptoms.[175] Diuretics are the mainstay of traditional therapy for CHF.[174] In addition to diuretics, digoxin, ACE inhibitors, and β-adrenoceptor antagonists (β-blockers) are used in the treatment of CHF. The most frequently used diuretics are chlorothiazide and furosemide.
The clear clinical benefit of diuretics in pediatric patients with CHF has been well established for more than 3 decades and needs no more review. Hobbins et al.[176] described in 1981 the efficacy of spironolactone, an aldosterone antagonist, in infants with CHF secondary to congenital heart disease, and concluded that the addition of spironolactone hastens and enhances the response to standard therapy with digoxin and chlorothiazide in infants with CHF. Recently, the diuretic spironolactone has attracted renewed attention because of RALES (Randomized Aldacton Evaluation Study), which showed reduced mortality and hospitalization in adults with severe CHF when treated with low doses (25mg) of this agent.[177] Although, the results of RALES are promising, an attempt to extrapolate these results to pediatric patients may be misleading, because of the different etiology of CHF in adults.

Hypertension

Antihypertensive medication is used extensively in children despite a paucity of randomized placebo-controlled trials. The US FDA Modernization Act has resulted in an increase in pediatric trials on antihypertensive medication and results should be available soon.[178] The goal of antihypertensive drug therapy is the reduction of blood pressure to a level below the 95th percentile.[179] The Working Group of the National High Blood Pressure Education Program provided guidelines for the use of antihypertensive drugs in acute and chronic hypertension in children.[179,180] Diuretics are often used in combination with antihypertensives, for example, α-/β-adrenoceptor antagonists or calcium channel antagonists, in hypertension in children and adolescents.[180] Pediatric experience with thiazides in the treatment of hypertension is extensive because these drugs are preferred as they provide a sustained and mild diuresis.[180] Loop diuretics are more powerful and may therefore be indicated only when relatively rapid diuresis is needed. Their use in long-term treatment is limited. Potassium-sparing diuretics are indicated in patients with elevated plasma aldosterone levels and in patients treated with loop and/or thiazide diuretics to minimize urinary potassium losses.

Renal Failure

ARF is defined as an abrupt decline in the renal regulation of water, electrolytes, and acid-base balance. It is important to differentiate between the pre-renal, renal, and postrenal origin of ARF in order to initiate proper treatment. Common causes of ARF in childhood are acute tubular necrosis, hemolytic uremic syndrome, glomerulonephritis, interstitial nephritis, and urinary tract obstruction.[181]
Treatment of ARF should focus on correcting the underlying cause. Loop diuretics are indicated in ARF if oliguria or anuria is manifest and pre- and post-renal causes are excluded.[181-183] Increased dosages of loop diuretics are necessary in patients with ARF to obtain diuretic response.[159,160,184-186] Continuous intravenous loop diuretics are often used in infants with ARF after CPB surgery.
Knowledge of drugs used for the prevention of ARF is scarce. Low-dose dopamine (0.5–2 μg/kg/min) is widely used to improve renal function. However, there is no sustainable evidence for a positive effect of diuretics combined with dopamine in both the prevention and treatment of ARF.[181,187,188] Mannitol increases plasma osmolality, leading to an increased extracelllular volume and thereby improving renal circulation. Therefore, mannitol is beneficial in reducing primary acute tubular necrosis in patients with renal transplant, if administered at the time of opening of the anastomosis.[181,189] Furosemide has been shown to have beneficial vascular and tubular effects in experimental ARF.[181,190,191] However, these renoprotective effects were not seen in adults, who received furosemide therapy during cardiac surgery.[181,192]
In CRF there is progressive loss of kidney function. Symptoms of kidney failure frequently emerge when residual renal function is <30%. Most patients maintain water balance until late in the course of CRF. Patients with CRF are less able to increase urine output to prevent acute water retention or to limit water excretion and prevent dehydration.[193] Diuretics, such as loop and thiazide agents, are indicated in those patients who cannot increase their urine output. Although it is commonly assumed that thiazides are ineffective in advanced renal failure (GFR <30 mL/min/1.73m2), co-administration of thiazides increases the efficacy of loop diuretics.[194] Blockade of sodium reabsorption in the distal tubule by thiazides will reduce the compensatory increase in sodium reabsorption seen after administration of loop diuretics and therefore potentiate the natriuretic efficacy of loop diuretics.[194,195]

Nephrotic Syndrome

Nephrotic syndrome is a clinical entity characterized by massive urinary protein losses, resulting in hypoalbuminemia and edema. Concepts of the pathogeneses of edema in nephrotic syndrome have been modified. It is now suggested that the basic abnormality is a primary disturbance in renal sodium excretion.[196,197] The management of nephrotic syndrome depends on the presence of hypervolemia or functional hypovolemia. Functional hypovolemia is present when distal Na+/K+ exchange ($[K^+]/[K^+] + [Na^+]$ in urine >0.6) is increased and the FeNa is <0.5%.[196-198] Standard treatment in children with nephrotic syndrome with normo- or hypervolemia and significant edema is a loop diuretic combined with an aldosterone antagonist.[196,197,199] A thiazide diuretic, for example, metolazone, combined with a loop diuretic will lead to increased losses of sodium and water in children with resistant edema and, therefore, may provide improved edema control especially in children with reduced GFR.[197,200]
Lewis and Awan[199] also described the benefits of the combination of furosemide and mannitol in children with diuretic-resistant edema. Albumin infusions combined with diuretics are only indicated in the child with edema and functional hypovolemia.[197,198]

Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus (NDI), congenital or acquired, is characterized by the inability of the kidney to concentrate urine in response to arginine vasopressin. Arginine-vasopressin receptor 2 gene (AVPR2) and aquaporin-2 gene (AQP2) are the two genes involved in NDI. In NDI the binding of arginine vasopressin to the AVPR2 or the translocation of AQP2 is affected resulting in decreased water reabsorption.[201,202]
The treatment of NDI focuses on the reduction of polyuria. Crawford and Kennedy[203] treated NDI with a low sodium diet and hydrochlorothiazide. In the 1980s NDI was treated with indometacin and hydrochlorothiazide.[204,205] Recent studies show that treatment with hydrochlorothiazide/amiloride is as effective as treatment with indometacin and hydrochlorothiazide and has less adverse effects.[206-208]

Nephrocalcinosis

Nephrocalcinosis is not a uniform entity, but rather a complication of various renal disorders, metabolic disturbance, or the administration of drugs. Hypercalciuria is the most common abnormality associated with nephrocalcinosis. Nephrocalcinosis may lead to renal dysfunction. Treatment of nephrocalcinosis consists of treatment of the underlining disorders. As previously noted; drugs that promote nephrocalcinosis should be discontinued. Use of thiazides may be useful because they reduce urinary calcium excretion.

Ascites

Ascites refers to a collection of fluid within the peritoneal cavity. Ascitic fluid may be non-inflammatory (hepatic venous outflow obstruction, cirrhosis, heart failure, nephrotic syndrome, and cancer), chylous (congenital lymphangectasia or surgical trauma to the vessels), or inflammatory. This section is limited to ascites caused by chronic liver disease.
In chronic liver disease, ascites reflects the expansion of extracellular water space due to the retention of water and sodium. Reduced intravascular volume in patients with cirrhosis will lead to increased sympathomimetic tone and circulating levels of arginine vasopressin and aldosterone. This will limit the excretion of salt and water and lead to ascites.[209]
The goal of treatment is to inhibit renal sodium retention and to produce gradual diuresis. This can be achieved by limiting sodium intake and enhancing urinary sodium excretion with diuretics, for example, thiazide diuretics and/or aldosterone antagonists.[210]
Therapy with the aldosterone antagonist spironolactone seems attractive as aldosterone levels are elevated in patients with cirrhosis. However, treatment with spironolactone alone may yield poor results. This has been ascribed to the fact that it takes time to reach maximum efficacy due to both continued accumulation of metabolites and delayed expressing of postreceptor effects.[30,211] Combination therapy with a thiazide or loop diuretic increases the initial diuretic response.[210] Prandota[212] reported that furosemide exerted a marked decrease in natriuretic effect in patients with liver cirrhosis compared with healthy individuals and, therefore, questioned the use of furosemide in these patients. Using high doses of spironolactone in the initial treatment phase seems attractive to investigate further.

Post-Traumatic Cerebral Edema

Cerebral edema after acute head injury is two to five times as common in children as in adults. Hyperemia has long been considered the cause of the diffuse cerebral swelling and elevated ICP.[213] Therefore, hyperventilation and avoidance of mannitol was the standard of care in children. However, Zwienenberg and Muizelaar[213]

studied the cerebral blood flow in healthy children and children with severe head injury and found no substantial differences in cerebral blood flow. It was concluded that hyperemia is not as common as previously thought and children should not be treated differently from adults.
The initial management is aimed at the prevention and treatment of secondary brain damage, which mainly results from systemic insults such as hypoxia, hypercarbia, and hypotension.[91]
The osmotic diuretic mannitol is now widely used and highly effective in the management of acutely raised ICP.[90,214] Mannitol increases serum osmolality and reduces cerebral swelling, provided that the blood-brain barrier is intact. Mannitol also reduces the production of cerebrospinal fluid, which further reduces ICP. However, in multi-trauma patients with head injury, mannitol should be used with care because it can aggravate hypovolemia and intracranial bleeding, causing secondary brain injury.[90-92]

Recommended Dosages of Diuretics in the Pediatric Age Group

Recommended doses for diuretics (intravenous and oral administration) are summarized in table IV.
Recommended doses of neither continuous intravenous administration nor inhaled administration of loop diuretics are available in the literature. Continuous furosemide infusion is usually started at a rate of 0.1 mg/kg/h and incrementally increased until the desired urine output is obtained or a maximum dosage of 0.4 mg/kg/h is reached.[159] However, infusion rates as high as 1 mg/kg/h have been reported in the literature, which were associated with arrhythmias (probably as a result of low serum potassium levels).[215] Furthermore, it is not unambiguously clear whether this high infusion rate (1 mg/kg/h) is associated with toxic serum concentrations. Serum concentrations >50 μg/mL are considered ototoxic.[97,100] No toxic serum furosemide concentrations were observed at a rate of 0.4 mg/kg/h.[159]
Inhaled furosemide is usually administered at a dosage of 1 mg/kg in premature infants. The duration of the effect of furosemide is usually 4–6 hours.[216,217]

Future Prospects

Pharmacokinetics/Pharmacodynamics of Diuretics

Thiazides and potassium-sparing agents are frequently used in all pediatric age groups, but only limited pharmacokinetic/pharmacodynamic data are available. Appropriate pharmacokinetic/pharmacodynamic studies should therefore be carried out for the separate pediatric age groups to further optimize dosing regimens and to decrease adverse effects. These experiments should take into account polymorphisms of renal drug transporters and of molecular targets of diuretics as they may affect the delivery of diuretics to the site of action and the diuretic effect.[26,114] Also, identification of relevant polymorphisms prior to therapy may eventually lead to individualized diuretic therapy, regarding drug choice and the dosing regimen.[43,114, 218,219]

Development of Dosing Regimens for Continuous Administration of Loop Diuretics

Dosing regimens, based on pharmacokinetic/pharmacodynamic models, for maximally efficient diuretic effect or predefined urinary output should be evaluated for loop diuretics used in various disease states in the pediatric population.
An example is the pharmacokinetic/pharmacodynamic model for continuous furosemide infusion reported in the literature that can be used to simulate dosing regimens on the basis of a predefined urine production.[159,160] The efficacy of this model was validated in a prospective study performed in hemodynamically unstable infants after cardiac surgery.[160] The usefulness of this model can also be evaluated for other pediatric patients who require continuous intravenous furosemide, for example, in pre- and full-term neonates and infants receiving ECMO and in children after CPB surgery.

Aerosolized Furosemide: Pharmacokinetics/Pharmacodynamics, Dosing Regimens, and Indications

Although pulmonary and systemic effects were observed after aerosolized furosemide, little is known about the effectively delivered amount of the drug with the various application devices.[161,216,217,220-225]
Research should focus first on the effectively delivered amount of drug, which may include characterization of the drug delivery devices, in order to study the pharmacokinetic/pharmacodynamic parameters of aerosolized furosemide.

Table IV. Recommended dosages for diuretics and dosage adjustment for renal failure in children

Type of diuretic	Age group data from	Pediatric dosage	Interval (h)		Route	Adjustment for renal failure[a]			
						parameter adjusted	GFR <50%	GFR 10–50%	GFR <10%
Carbonic anhydrase inhibitors									
Acetazolamide	Adults	5–12.5 mg/kg/24h[b]	24		Oral/IV	Dose	100%	50–100%	No
Osmotic diuretics									
Mannitol	Adults	0.25–1 g/kg/dose[b]	6		IV	Dose	100%	50–100%	No
Loop diuretics									
Furosemide (frusemide)	Neonates	1 mg/kg/dose	12–24		Oral/IV	None[c]			
	Infant/child	1–4 mg/kg/24h	6–12		Oral	None[c]			
		1–2 mg/kg/dose	6–12		IV	None[c]			
Bumetanide	Neonates	0.01–0.05 mg/kg/dose	24–48		Oral/IV	None[c]			
	Infant/child	0.015–0.1 mg/kg/dose	6–24		Oral/IV	None[c]			
Thiazide diuretics									
Hydrochlorothiazide	<6mo	2–3.3 mg/kg/24h	12		Oral	Dose	100%	50–100%	No
	>6mo	2 mg/kg/24h	12		Oral	Dose	100%	50–100%	No
Chlorothiazide	<6mo	20–40 mg/kg/24h	12		Oral	Dose	100%	50–100%	No
	>6mo	20 mg/kg/24h	12		Oral	Dose	100%	50–100%	No
Metolazone	Adults	0.2–0.4 mg/kg/24h[b]	12–24		Oral	None[c]			
Potassium-sparing diuretics									
Amiloride	Adults	0.625 mg/kg/24h[b]	12–24		Oral	Dose	100%	50%	No
Triamterene	Adults	1–4 mg/kg/24h[b]	12		Oral	Interval	12h	12h	No
Spironolactone	Preterm <32wk	1 mg/kg/24h	24		Oral	Interval	24h	48h	No
	Term	1–2 mg/kg/24h	12		Oral	Interval	12h	24h	No
	Infant/child	1–3 mg/kg/24h	6–12		Oral	Interval	6–12h	12–24h	No

a Percentage of dose that should be administered or recommended interval between drug dose administrations; 'No' indicates that the drug should not be used.
b Dosages for children are derived from adult pharmacokinetic/pharmacodynamic data.
c No dose or interval adjustment needed.
GFR = glomerular filtration rate; IV = intravenous.

Simultaneously, the effects on bronchial mucosa after (prolonged) use of aerosolized furosemide should be studied. This will provide recommendations for dosing regimens and define the indications for treatment with aerosolized furosemide. A first step could be to perform these experiments in mechanically ventilated pediatric patients who can be supposed to benefit.

Development of Novel Diuretics

With the discovery of AQPs new pharmacologic targets have become available. Agents that block water channels, i.e. reduce AQP2 levels, may in future be used as 'diuretics' in patients with volume overload, whereas agents that increase AQP2 levels may be effective in patients with renal concentration defects resulting from kidney resistance for vasopressin.[226]

Conclusions

Diuretic therapy is frequently prescribed in (pre)term neonates, infants, and children for a variety of diseases and treatment modalities. The clinician should realize that the currently recommended dosages for diuretics are largely based on adult pharmacokinetic/pharmacodynamic studies and that pharmacokinetic/pharmacodynamic studies of diuretics in children may differ from adults. Therefore, pharmacokinetic/pharmacodynamic studies in the various pediatric age groups are required to optimize dosing regimens for all routes of administration and to decrease adverse effects.

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Chapter 3

Acute renal insufficiency and renal replacement therapy after pediatric cardiopulmonary bypass surgery

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Pediatr Cardiol 22:321–326, 2001

Abstract

The aim of the study was to investigate renal function and renal replacement therapy after cardiopulmonary bypass surgery in children. Patient characteristics (sex, age, diagnosis), operation type, and death were listed. The study was performed retrospectively using serum creatinine level before, and peak values after, cardiopulmonary bypass surgery for assessment of renal function. Of the children on renal replacement therapy, indication, efficacy, and complications were recorded. In a 5-year period, 1075 children had cardiopulmonary bypass surgery at the Department of Cardiothoracic Surgery at Leiden University Medical Center and Academic Medical Center of Amsterdam. One-hundred eighty (17%) patients developed acute renal insufficiency. Twenty-five (2.3%) patients required renal replacement therapy. Peritoneal dialysis is a safe and effective treatment for children after cardiopulmonary bypass surgery. However, 15 (60%) of 25 children on renal replacement therapy died of nonrenal causes. In 9 out of 10 surviving children, renal function was normal at time of discharge from hospital. Acute renal insufficiency is a frequent complication after open-heart surgery, although renal replacement therapy was infrequently necessary. Peritoneal dialysis is a safe and effective therapeutic measure forchildren after cardiac bypass surgery.

Introduction

Acute renal insufficiency is a frequent complication of cardiopulmonary bypass surgery. This complication sometimes leads to acute renal failure, necessitating renal replacement therapy, which is associated with high mortality (20% to 75%) [1, 2, 4–6, 10–12]. We studied the incidence of acute renal insufficiency in children after cardiopulmonary bypass surgery, which has not been described before, in a 5-year period at our institution. Furthermore, we investigated the indication, efficacy, and complications of all children who received peritoneal dialysis after cardiopulmonary bypass surgery in the same period.

Methods

From January 1994 to January 1999, cardiopulmonary bypass surgery was performed on 1075 children (<17 years) at Leiden University Medical Center and Academic Medical Center of Amsterdam. Postoperative renal function and indication, efficacy, and complications of renal replacement therapy at the Pediatric Intensive Care are studied retrospectively from medical records.

Acute Renal Insufficiency

Age, sex, type of cardiac surgery performed, preoperative serum creatinine level, peak postoperative serum creatinine level, the day peak postoperative serum creatinine level occurred, and death within 30 postoperative days are recorded. Although serum creatinine may not be the most sensitive marker of renal function, since it cannot detect minor changes in glomerular filtration rate, it meets the requirements of this study. Acute renal insufficiency is defined as at least doubling of preoperative serum creatinine level in children older than 8 weeks. For children younger than 8 weeks, a postoperative serum creatinine level >75 µmol/L is considered acute renal insufficiency. Serum creatinine level is measured using a photometric method on an automatic analyzer (Hitachi 747-100; Roche, Almere, The Netherlands).

Renal Replacement Therapy

In a second part of the study, all children who received renal replacement therapy were analyzed retrospectively from medical records. Peritoneal dialysis (PD) was chosen as renal replacement therapy because of its relatively easy employment and infrequent complications. The indications for PD are anuria (>24 hours), hyperkalemia (>5.5 mmol/L), hyperphosphatemia (>4 mmol/L), or severe edema. In our study, patients who received renal replacement therapy had acute renal failure. The causes of acute renal failure were divided in low cardiac output and/or acute tubular necrosis. A patient was considered to have acute tubular necrosis if, after prolonged resuscitation, acute renal failure occurred with exclusion of persisting low cardiac output. A standard Dacron-cuffed pediatric silicone catheter (Tenckhoff, Sherwood Medical Company, St. Louis, MO 63103, USA) was surgically inserted through a paraumbilical tunneled approach. Standard PD solutions (initially glucose 2.27%, and later, if necessary, either glucose 3.86% or 1.36%) were used. Peritoneal dialysis was started with a dialysate volume of 10 ml/kg, a dwell time of 30 minutes, and a drainage time of 20 minutes. After 24 hours, dialysate volume was doubled and, if necessary, dwell time was adjusted. Age, sex, weight, diagnosis, type of cardiac surgery performed, cardiopulmonary bypass time, and aortic cross-clamp time of the patients were recorded. Postoperative artificial ventilation, continuous intravenous inotropic agents, cause of acute renal failure, indication for renal replacement therapy, prerenal replacement therapy values for central venous pressure, serum sodium, -potassium, -calcium, -phosphate, -bicarbonate, -urea, and -creatinine, were noted. Elapsed time after open heart surgery to institution of PD, duration of PD, dialysis efficacy measured by fluid removal rate (ml/kg/day) and time to correction of hyperkalemia, and complications were investigated. Nephrotoxic medication

(e.g., aminoglycosides) was avoided, or the dose was adapted to renal function, and, if possible, was checked by serum levels. Death and cause of death were noted. Of surviving children, serum urea and creatinine level before discharge from hospital were studied.

Statistics

Logistic regression analysis was used to estimate the probability of renal insufficiency using age and preoperative serum creatinine level as independent risk factors (covariates); likewise, the probability of death was estimated as a function of age and renal insufficiency. The risk factors were entered both as main effect and as their interaction. Interaction terms were retained if the p-value was below 0.10, and main effects were considered significant if the p-value was below 0.05.

Results

Acute Renal Insufficiency

Of 1075 children <17 years who had cardiopulmonary bypass surgery, 637 (59%) were boys. One hundred eighty (17%) patients had renal insufficiency. Seventy (6.5%) children died <30 days after cardiopulmonary bypass surgery. Table 1a denotes the type of cardiac surgery performed, age, preoperative- and peak postoperative serum creatinine level, and the day the peak serum creatinine level occurred. Table 1b depicts the type of cardiac surgery performed, the number of patients with postoperative acute renal insufficiency, patients requiring renal replacement therapy, and death of patients.

The age of the patients is inversely related to both renal insufficiency ($p < 0.001$) and death (p 4 0.001). Furthermore, children with renal insufficiency have a significantly higher chance of dying (odds ratio 5.4 95% CI 3.3–8.8) as compared with children without renal insufficiency. Likewise, the interaction between age and renal insufficiency was significantly related to death of patients. Preoperative serum creatinine level, corrected for the age of the patient, is significantly correlated to renal insufficiency ($p < 0.001$). The difference between the group with renal insufficiency (mean serum creatinine level 53 [sd 27] µmol/L) and group without renal insufficiency (mean serum creatinine level 44 [sd 15] µmol/L), however, is minor.

Table Ia. Age and serum creatinine of patients before and after cardiopulmonary bypass surgery

Cardiopulmonary bypass surgery	Age median (range)	Screat preop µmol/L	Screat postop µmol/L	Peak level on day X postop
Atrial septum defect closure	3 y 11 m (4 m–16 y 7 m)	40 (16)	45 (41)	1 (1–21)
Ventricular septum defect closure	1 y 1 m (1 m–15 y 3 m)	38 (11)	47 (23)	2 (1–9)
Atrioventricular septum defect correction	5 m (3 w–15 y)	43 (9)	70 (46)	2 (1–14)
Tetralogy of Fallot (re)operation	1 y 5 m (2 w–16 y 9 m)	42 (12)	60 (45)	2 (1–10)
Arterial switch	7 d (1 d–2 y 5 m)	67 (30)	91 (36)	3 (1–8)
Common arterial truncus correction	2 m 2 w (11 d–9 y 1 m)	42 (9)	105 (62)	3 (2–4)
Double outlet right ventricle correction	10 m (2 m–6 y 11 m)	41 (6)	53 (13)	2 (1–14)
Pulmonary valve surgery	2 y 1 m (1 d–16 y 11 m)	41 (18)	44 (19)	1 (1–4)
Conduit replacement	10 y 5 m (5 y 2 m–15 y)	57 (11)	57 (11)	2 (1–8)
Mitral valve surgery/replacement	7 y 11 m (5 w–16 y 8 m)	47 (14)	65 (73)	2 (1–9)
Aortic valve surgery/replacement	4 y 6 m (3 d–15 y 2 m)	59 (27)	97 (120)	2 (1–8)
Resection subvalvular aortic stenosis	5 y 10 m (1 m–16 y 7 m)	42 (15)	45 (23)	1 (1–3)
Ross operation	10 y 2 m (5 w–16 y 9 m)	57 (13)	64 (20)	2 (1–8)
TAPVD/Scimitar correction	2 m (7 d–10 y 4 m)	44 (15)	65 (28)	2 (1–7)
Fontan/Total Cavo-Pulmonary connection	4 y 11 m (1 y 9 m–13 y 5 m)	44 (10)	123 (116)	2 (1–13)
Glenn/Bidirectional Cavo-Pulmonary shunt	2 y 1 m (5 w–5 y 7 m)	42 (8)	63 (62)	1 (1–19)
Rastelli operation	3 y 7 m (1 y 11 m–12 y 9 m)	46 (9)	123 (84)	2 (1–6)
Miscellaneous	1 y 5 m (1 d–16 y 7 m)	49 (23)	97 (99)	2 (1–18)
Median	**1 y 11 m (1 d–16 y 11 m)**	**45 (18)**	**67 (61)**	**2 (1–21)**

Screat, Serum creatinine mean (SD) mmol/L preoperative and peak postoperative levels; Peak level on day x postop, peak serum creatinine level on day x postoperative given as median (range); Pulmonary valve surgery consists of commissurotomy/reconstruction pulmonary valve and correction supravalvular pulmonary artery stenosis. Aortic valve surgery/replacement includes neonatal critical aortic stenosis, endocarditis, and ascending aorta aneurysms. Arterial switch includes transposition with VSD and Taussig-Bing anomalies. TAPVD total anomalous pulmonary vein drainage (re)operation. Miscellaneous operations consist of 1-stage repairs (e.g., VSD and coarctatio aortae, VSD and interrupted arch); correction of pulmonary atresia, VSD, and Major Aorto-Pulmonary Collateral Arteries; aorto-pulmonary window; ascending aorta and aortic arch repairs or replacements; correction Ebstein's disease; correction Aberrant Left Coronary Artery from Pulmonary Artery; hemitruncus; operations for monoventricular heart other than Glenn or Fontan, Norwood stage 1, and others. y, year; m, month; w, week; d, day.

Table Ib. Type of cardiopulmonary bypass surgery, acute renal insufficiency, renal replacement therapy, and mortality <30 days after open-heart surgery

Cardiopulmonary bypass surgery	Number of patients n	Acute renal insufficiency n (%)	PD n	death <30 days n (%)
Atrial septum defect closure	139	1 (0.7)	—	—
Ventricular septum defect closure	165	8 (4.8)	1 (0.6)	6 (3.6)
Atrioventricular septum defect correction	100	24 (24)	2 (2.0)	7 (7.0)
Tetralogy of Fallot (re)operation	158	17 (11)	2 (1.3)	10 (6.3)
Arterial switch	71	42 (59)	2 (2.8)	5 (7.0)
Common arterial truncus correction	15	8 (53)	1 (6.7)	4 (27)
Double outlet right ventricle correction	10	—	—	2 (20)
Pulmonary valve surgery	19	1 (5.3)	—	1 (5.3)
Conduit replacement	18	—	—	—
Mitral valve surgery/replacement	48	4 (8.3)	2 (4.2)	2 (4.2)
Aortic valve surgery/replacement	20	6 (30)	—	4 (20)
Resection subvalvular aortic stenosis	36	1 (2.8)	—	—
Ross operation	40	1 (2.5)	—	2 (5.0)
TAPVD/Scimitar correction	27	6 (22)	—	4 (15)
Fontan/Total Cavo-Pulmonary connection	29	11 (38)	6 (21)	3 (10)
Glenn/Bidirectional Cavo-Pulmonary shunt	37	6 (16)	—	2 (5.3)
Rastelli operation	7	3 (43)	1 (14)	1 (14)
Miscellaneous	136	41 (30)	8 (5.9)	17 (12)
Total	**1075**	**180 (17)**	**25 (2.3)**	**70 (6.5)**

PD, Peritoneal dialysis. Pulmonary valve surgery consists of commissurotomy/reconstruction pulmonary valve and correction supravalvular pulmonary artery stenosis. Aortic valve surgery/replacement includes neonatal critical aortic stenosis, endocarditis, and ascending aorta aneurysms. Arterial switch includes transposition with VSD and Taussig–Bing anomalies. TAPVD total anomalous pulmonary vein drainage (re)operation. Age is given as median (range). Miscellaneous operations consist of 1-stage repairs (e.g., VSD and coarctatio aortae, VSD and interrupted arch); correction of pulmonary atresia, VSD, and Major Aorto-Pulmonary Collateral Arteries; aorto-pulmonary window; ascending aorta and aortic arch repairs or replacements; correction Ebstein's disease; correction Aberrant Left Coronary Artery from Pulmonary Artery; hemitruncus; operations for monoventricular heart other than Glenn or Fontan, and others.

Renal Replacement Therapy

Of all children after open heart surgery, 25 (2.3%) patients required renal replacement therapy. Patient characteristics are recorded in Table 2. In Table 3, diagnosis and type of cardiac surgery performed are listed. All but one child requiring renal replacement therapy were on artificial ventilation, and all received continuous intravenous inotropic agents at the initiation of renal replacement therapy. The predominant cause of acute renal failure, requiring renal replacement therapy, was low cardiac output (n = 15; 60%). Sometimes low cardiac output was combined with acute tubular necrosis after prolonged resuscitation (n = 4; 16%). For some patients, acute tubular necrosis after prolonged resuscitation (n = 6; 24%) was the single reason for acute renal failure requiring renal replacement therapy. The indications for, and time from, operation to institution of renal replacement therapy are given in Table 2.

Table II. Data of patients on peritoneal dialysis after cardiopulmonary bypass surgery

Patient characteristics		Indications for PD	n (%)
Age	1 y 10 m (6 days–8 y 9 m)	Anuria (>24 hours)	21 (84)
Weight	11.5 (2.5–25.8) kg	Hyperkalemia (>5.5 mmol/L)	11 (44)
Males	17 (68%)	Hyperphosphatemia (>4 mmol/L)	1 (4)
Cardiopulmonary bypass time	183 (SD 69) minutes	Severe edema	3 (12)
Aortic cross clamp time	88 (SD 43) minutes		
PD characteristics		**Complications of PD**	
Time to initiation of PD	54 hours (21 hours–86 days)	Hyperglycemia	16 (64)
Duration of PD	67 hours (9 hr–26 days)	Insulin therapy	2 (8)
Fluid withdrawal day 1	44 (–3–140) ml/kg/day	Leakage PD catheter	2 (8)
Fluid withdrawal day 2	46 (–3–101) ml/kg/day	Revision PD catheter	1 (4)
Fluid withdrawal day 3	48 (7–84) ml/kg/day	PD catheter replacement	2 (8)

PD, peritoneal dialysis; y, year; m, month. Data are given as median (range), mean (SD), or percentage (%)

Peritoneal dialysis was chosen as renal replacement treatment because of its relatively easy employment and infrequent complications. Mean central venous pressure before initiation of PD was 16 (SD 4) cmH_2O. Mean (SD) predialysis serum levels were: creatinine 204 (96) µmol/L, urea 20.1 (9.2) mmol/L, sodium 140 (8) mmol/L, potassium 5.0 (1.0) mmol/L, calcium 1.81 (0.3) mmol/L, phosphate 2.47 (0.86) mmol/L, and bicarbonate 18 (4) mmol/L.

Table III. Diagnosis, operation, and survival of 25 patients on renal replacement therapy after open-heart surgery

No.	Diagnosis	Open-heart surgery	Alive
1	TOF, hypoplastic LPA	Correction of TOF	No
2	TOF	Correction of TOF	No
3	TGA	Switch	Yes
4	CA VSD, coarctatio aortae	Correction CAVSD, coarctectomy	Yes
5	Tricuspid atresia	Fontan	No
6	TGA	Switch	Yes
7	MI after Fontan	MVR	No
8	Monoventricle	Fontan	No
9	VSD, PDA	Occl. Aortic arch after closure VSD and PDA	Yes
10	TOF, hypoplastic LPA	Fontan	No
11	Ebstein	Correction Ebstein	No
12	Multiple VSD	Closure multiple VSD, debanding PA	No
13	Endocarditis mitral valve prothesis	MVR	No
14	cTGA, PS, VSD, ag RPA, TI, bad RV funct	TVR	Yes
15	Heterotaxia	Biventricular correction (Rastelli)	No
16	CA VSD, TOF	Total correction	Yes
17	Monoventricle	Fontan	No
18	CA VSD	Correction CA VSD	Yes
19	PA, VSD, MAPCAs	Part. corr with homograft, fenestr VSD patch	No
20	PA, VSD, MAPCAs	Total correction	No
21	CA VSD, TOF	Total correction	No
22	DORV, TGA, PS	Fontan	Yes
23	Heterotaxia, monoventricle, coarctatio aortae	Banding AP, coarctectomy, closure PDA No	No
24	Monoventricle	Fontan	Yes
25	Common arterial truncus	Corr arterial truncus with aortic valve repl	Yes

TOF, tetralogy of Fallot; LPA, left pulmonal artery; TGA, transposition of great arteries; CAVSD, complete atrioventricular septum defect; MI, mitral insufficiency; MVR, mitral valve replacement; VSD, ventricular septum defect; PDA, patent ductus arteriosis, cTGA, corrected TGA; TGA, transposition of great arteries; PS, pulmonal valve stenosis; ag RPA, agenesia right pulmonal artery; TI, tricuspid insufficiency; bad RV funct, bad right ventricle function; TVR, tricuspid valve replacement; MAPCAs, major aortic-pulmonal collateral arteries; part corr, partial correction; fenestr VSD patch, fenestrated VSD patch; corr arterial truncus with aortic valve repl, correction arterial truncus with aortic valve replacement

Peritoneal dialysis was continued for a median time of 67 hours (range 9 hours–26 days) until recovery of renal function or death occurred. Effective fluid withdrawal could be achieved in nearly all patients (Table 2). Hyperkalemia (potassium >5.5 mmol/L) normalized after a median time of 7 (range 3–14) hours. Complications of PD were minor (Table 2). No patient developed peritonitis. However, 15 (60%) of 25 children on renal replacement therapy died. The predominant cause of death was cardiac failure (n = 11), 2 patients were brain dead after resuscitation, and 2 children died of miscellaneous causes. None of the patients died of renal causes. Of the children who died, two children experienced peritoneal dialysis catheter malfunction or leakage, whereas, among the surviving patients, only one had leakage. The peritoneal catheters were revised or replaced. In 9 out of 10 surviving children, renal function was normal at time of discharge from hospital. Mean (SD) serum urea and creatinine levels of the surviving patients were 5.7 (2.7) mmol/L and 45 (10) µmol/L, respectively.

Discussion

Acute Renal Insufficiency

The incidence of acute renal insufficiency (17%) complicating open-heart surgery in children remains high, and the incidence is often related to the complexity of the operation. On one hand, better and more sophisticated surgical and cardiopulmonary bypass techniques are available. On the other hand, however, children with more complicated cardiac lesions requiring longer cardiopulmonary bypass time are operated on [8]. As is expected after relatively short and simple operations such as atrial septum defect closure, few children develop acute renal insufficiency (0.7%). After more complicated operations with long cardiopulmonary bypass times, such as arterial switch operation and common arterial truncus correction, there is a high incidence of acute renal insufficiency (59% and 53%, respectively) (Tables 1a, b). Cardiopulmonary bypass is deleterious because it triggers an important inflammatory reaction, including the release of kinins, coagulation factor XII, and complement factors by endothelial cells and leucocytes [7]. This reaction is largely related to the ratio of the circuit area to the patient's body surface area and is therefore maximal in children. Clinically, this is associated with a capillary leak syndrome, resulting in hypovolemia and renal hypoperfusion.
Furthermore, we found a high incidence of acute renal insufficiency in children with postoperative low flow state, for example, after a Fontan procedure (38%). The low-flow state similarly can cause renal hypoperfusion and can lead to renal insufficiency.

Of the patients after Fontan procedure, a high percentage (21%) required renal replacement therapy.
Although preoperative serum creatinine level, corrected for the age of the patient, is significantly correlated to renal insufficiency, the difference between the renal insufficiency group and the group without renal insufficiency is minor. This difference cannot be used clinically to predict renal insufficiency postcardiopulmonary bypass surgery. For the patients without renal insufficiency, there was a sharp decrease in the risk of dying with age. However, for patients with renal insufficiency, the risk of dying was significantly higher and moreover was hardly decreasing with age.

Renal Replacement Therapy

2.3% of patients required renal replacement therapy; this is in concert with other studies (1.6% to 7.7%) on children after open-heart surgery [1, 2, 5, 6, 10–12]. Only Dittrich treated a much higher percentage (33%) of infants after cardiopulmonary bypass surgery, but PD was started profylactically at the end of the operation. Thus, Dittrich was treating relatively healthy children [3]. The patients in our study on renal replacement therapy had complex cardiac surgery (Table 3), and most children had low postoperative cardiac output resulting in renal hypoperfusion. Peritoneal dialysis was chosen as renal replacement therapy because of its relatively easy employment, efficacy, and infrequent complications. In our patient group, fluid withdrawal (median 46 [range –3– 140] ml/kg/day) was effective in most patients, and hyperkalemia was corrected within hours, (median 7 [range 3–14] hours after initiating PD). These results are comparable to those of Werner, who reported mean fluid removal of 48 (SD 28) ml/kg/day with PD in a similar patient group [13]. Sorof achieved a higher mean ultrafiltration of 93 (range 43–233) ml/kg/day in less critically ill patients with extracellular volume overload and relatively normal renal function after cardiopulmonary bypass surgery [12]. Nevertheless, there is an ongoing controversy on the choice of renal replacement therapy after open-heart surgery [4, 9, 14]. Fluid withdrawal may be more effective when using continuous veno-venous hemofiltration. Fleming found an average fluid deficit of 9.2 ml/hr (range 3.5–26 ml/hr) in children on PD after open-heart surgery, as compared with 23 ml/hr (range 3.9–34 ml/hr) in patients on continuous veno-venous hemofiltration [4]. On the other hand, continuous arterovenous and veno-venous hemofiltration require anticoagulation. Anticoagulation might be hazardous soon after cardiopulmonary surgery. Furthermore, vascular access for hemofiltration may pose a problem, especially in neonates.
Complications from PD in our study were minor. No patient developed peritonitis. However, in concert with previous studies (58% to 75%), mortality of patients

requiring renal replacement therapy remains high (60%) [1, 4–6, 10, 11]. Nonetheless, three studies documented lower mortality in children (20% to 30%) [2, 3, 12]. In two studies, PD was performed for a selection of "healthier" patients, which may account for the lower mortality [3, 12]. In one study, PD was often already started prophylactically at the end of the operation [3]. In another study, PD was undertaken after a mean period of 22 hours postoperatively, whereas mean urine output of the patients still was 2.2 ml/kg/hr. No patients were anuric [12]. Death in our patients was not related to renal failure, but was generally the result of cardiac failure. Renal function normalized in 9 of 10 (90%) surviving children. This is in agreement with other studies, where 93% to 100% of survivors of renal replacement therapy after cardiopulmonary bypass surgery had normal renal function at discharge from hospital [1, 2, 5, 7, 10, 11].

Conclusion

Acute renal insufficiency is a frequent (17%) complication after cardiopulmonary bypass surgery in children, although renal replacement therapy was infrequently (2.3%) necessary. Peritoneal dialysis is a safe and effective treatment for children after cardiopulmonary bypass surgery. However, 15 (60%) of 25 children on renal replacement therapy died of nonrenal causes. In 9 of 10 surviving children, renal function was normal at discharge from hospital.

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Chapter 4

Continuous intravenous furosemide in haemo-dynamically unstable children after cardiac surgery

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Intensive Care Medicine 2001; 27 (4): 711-5

Abstract

Objective: The commonly used continuous intravenous (IV) furosemide dosing schedule after cardiac surgery in children is largely empirical and may not be optimal. This may even be more marked in children after cardiac surgery who are haemodynamically unstable, and in whom transient renal insufficiency may occur. A study was performed to obtain an impression regarding which clinically applicable measures may be used to design a rational scheme for continuous IV furosemide therapy in children after cardiac surgery.
Subjects and methods: Twelve paediatric patients (5F/7M), age (0-33 weeks) post-cardiac surgery, who were to receive 3 days of continuous IV furosemide treatment, were included in an open study.
Blood and urine samples were taken for furosemide, creatinine and electrolyte levels, and fractionated urinary output was measured. Furosemide in blood and urine was measured using high performance liquid chromatography (HLPC).
Results: The mean starting dose of continuous IV furosemide was 0.093 (± 0.016) mg/kg per hour. The mean dose was increased to 0.175 (± 0.045) mg/kg per hour on day 2, and changed to 0.150 (± 0.052) mg/kg per hour on day 3. Infusion rates were increased from day 1 to day 2 in ten cases, and decreased from day 2 to day 3 in three cases. Serum furosemide levels never exceeded ototoxic levels. The urinary furosemide excretion rate was inversely related to serum creatinine levels.
Conclusions: This study extends the observation of the beneficial effects of continuous IV furosemide also to those children who are haemodynamically unstable after cardiac surgery. However, as the effects of furosemide are dependent on renal function, it can be hypothesised that the dosing schedule may be optimised. Contrary to the current used dosage schedule in which the dose of furosemide is gradually increased over time, it may be more rational to start with a higher dose and adapt this dose (downward) guided by the observed effect (urine output). Because the infusion rate was increased to 0.2 mg/kg per hour in nine out of 12 patients on day 2 and was never increased further, this suggests that a starting rate of 0.2 mg/kg per hour may be optimal.

Introduction

Furosemide is frequently used as a diuretic in paediatric patients after cardiac surgery to augment urinary output, and its pharmacokinetics in children have been extensively reviewed [1, 2]. As furosemide blocks active sodium transport out of the tubular lumen, natriuresis, hence diuresis is dependent on furosemide reaching the tubular lumen to act [3, 4]. Urinary furosemide concentration reflects the actual concentration near the renal tubular receptor sites [5]. As a consequence, urinary excretion of furosemide, rather than serum concentration, determines the diuretic effect of the drug [6]. Studies in both critically ill adults and paediatric patients after cardiac surgery have shown that continuous intravenous (IV) infusion of furosemide results in a greater excretion of both sodium and water than equivalent doses of intermittent bolus administrations [7]. However, for the haemodynamically stable patients it has been suggested that intermittent furosemide administration may be as effective as continuous infusion [8]. Nevertheless, continuous IV furosemide is an accepted way of treatment to reduce volume overload in paediatric patients after cardiac surgery and has advantages over intermittent therapy [9]. Apparently, the current practice is to start with a low furosemide infusion rate and increase this depending on diuresis [9, 10]. However, the dosage schedule in this group of patients with varying renal function is largely empirical. The objective of the present study was to evaluate the pharmacokinetics and effects of continuous IV furosemide in haemodynamically unstable paediatric patients after cardiac surgery in order to investigate possible relationships between clinically applicable measures of renal function, the excretion of furosemide in urine, and urinary output. These relationships may provide a guide for a rational furosemide regimen to maximise diuresis while avoiding toxic concentrations.

Materials and methods

The study was performed at the intensive care unit of the department of paediatrics of Leiden University Medical Centre (LUMC). Approval of study protocol was obtained from the LUMC Committee on Medical Ethics. The study was conducted according to the principles of the "Declaration of Helsinki" and in accordance with the Guideline for Good Clinical Practice. Parental written informed consent was obtained for all patients.

Patients and treatment

Post-cardiac surgery patient were eligible who, in clinical judgement, were likely to need a prolonged (with a minimum of 3 days) IV infusion of furosemide because of volume overload. Further inclusion criteria were that there was clinical requirement for inotropic support (defined as: requiring at least = 10 µg/kg per minute dopamine) and a bladder catheter. Pre-term patients were excluded. For each patient, diagnosis, type of operation, cardio-pulmonary bypass time, and cross-clamp time were recorded. Each subject was allowed to start with bolus doses of furosemide when

clinically indicated because of volume overload or a urine production = 1 ml/kg per hour (timing and dosage were recorded). During the post-operative course the maintenance fluid was kept at a rate of 60 ml/kg per 24 hours. Additional volume was administered if necessary to maintain/ achieve an adequate circulating volume. An IV furosemide infusion was started according to the routinely applied dosage regimen. Each infusion was to be started at 12.00 am. The starting dose for the furosemide infusion was to be chosen within the range of 0.1 to 0.4 mg/kg per hour, and a change in furosemide dose (steps of 0.1 mg/kg per hour) was allowed every 24 hours depending on the clinical situation. The aim was to establish a urine output of 4 ml/kg per hour, as the children had substantial volume overload. The rate of the infusion was adapted upward as the urine production was below 2 ml/kg per hour and decreased if the urine production exceeded 6 ml/kg per hour. Obviously, as patient care took preference over the study objectives, minor deviations from the schedule were allowed, which was at the discretion of the treating physician. During the entire study period serum potassium levels were closely monitored and a supplement was given in order to keep serum potassium levels between 3.8 - 4.3 mmol/l.

Study days

The study protocol followed routine clinical care for the patient as closely as possible. All common clinical parameters derived from the patient file and were recorded daily. Blood and urine samples (using bags providing protection from UV light) were collected every 6 hours and split into two aliquots. One aliquot (of blood and urine) was used for measurement of sodium and creatinine. These assays were performed immediately after collection using standard methodology at the Central Chemical Laboratories of LUMC.
The other aliquots (of blood and urine) were stored at – 20 °C until the furosemide assay. These assays were performed using a validated HPLC method routinely applied at the laboratory of Clinical Pharmacy and Toxicology of LUMC. For determination in serum, the coefficient of variation of the assay at 1µg/ml was 2%, and the reproducibility of the slope of the calibration line was 8.9%. For the analysis of the furosemide concentration in urine, the samples were first deglucuronidated. The coefficient of variation for accuracy of the assay at 10 µg/ml was 3.4%, and the reproducibility of the slope of the calibration was 7.2%.

Results

Patients

Nineteen patients likely to require a 3-day treatment of continuous IV furosemide infusion were included. However, only 12 patients completed the full 3-day course of furosemide infusion, and the data of this group was used for the analysis. There was no need to significantly deviate from the protocol.
The population consisted of five female and seven male patients. Their median age was 13 weeks (range 0 -33 weeks) and body weight was 4.2 (3.0 - 6.6) kg. The medical condition for which the patients underwent surgery is shown in Table 1. Important characteristics during surgery were a median cardio-pulmonary bypass time of 123 (range 0 - 218) min, with a cross-clamp time of 81 (range 0 - 135) min. Hypothermia was present during 122 (range 0 - 220) min, and the median associated body temperature was 26.5 (range 18.0 – 37.0) °C. In the IC unit, all patients were haemodynamically unstable and required substantial inotropic support (Table 1). In addition to dopamine/dobutamine, nor-epinephrine (patient 2: 0.04 µg/kg per minute; patient 6: 0.25 µg/kg per minute), epinephrine (patient 1: 0.06 µg/kg per minute), and NO (patient 1: 15 ppm; patient 7: 10 ppm) was needed. There was a clear volume overload as shown by the elevated central venous pressure (CVP) median: 8 cm H_2O; range 7 - 12 cm H_2O. The median CVP was also 8 H_2O after 24 and 48 hours. Apart from the maintenance fluid (60 ml/kg per 24 hours) additional volume was administered before the furosemide infusion period: the median (range) amount of volume was 65.3 (41 - 181) ml/kg. This was decreased to 5.3 (0-26.7) ml/kg on day 1. No additional volume was needed on the second and the last study day, except for patient 2 and 3 who received additional volume on day 2.
All patients recovered from cardiac surgery, were disconnected from artificial ventilation after 4 - 13 days, and were discharged from the paediatric IC unit 6 - 14 days post-operatively.

Treatment

Prior to the start of the furosemide infusion scheduled for the study, ten patients received one or more furosemide bolus (Table 1). On average (± SD) the patients were administered 1.4 (± 1.1) bolus doses, with a mean dose of 1.3 (± 0.4) mg/kg. The furosemide infusions were started at a median time of 30 (range 21 - 48) hours after cardiac surgery with a rate of 0.1 mg/kg per hour, except for two patients who started with 0.05 mg/kg per hour and 0.07 mg/kg per hour. The mean starting dose was 0.093 (± 0.016) mg/kg per hour. The mean dose increased to 0.175 (± 0.045) mg/kg

per hour at day 2, and changed to 0.150(± 0.052) mg/kg at day 3. Infusion rates were increased from day 1 to day 2 in ten children and decreased from day 2 to day 3 in three children.
The average (± SD) furosemide serum concentration, urinary furosemide excretion rate, urine output, and serum creatinine profiles are given in Fig.1.
The median (range) furosemide serum concentration prior to the infusion was 2.5 µg/ml (0.6 – 14.5 µg/ml). The median furosemide level at the end of day 1 was 3.8 µg/ml (0.3 – 8.9 µg/ml); at the end of day 2 it was 3.3 µg/ml (0.4 – 15.6 µg/ml); and at the end of day 3 it was 2.1 µg/ml (0.4 – 17.5 µg/ml).
The median urinary furosemide excretion rate at the end of day 1 was 0.45 mg/h (0.08 -0.98 mg/h); at the end of day 2 it was 0.70 mg/h (0.22 -2.01 mg/h); and at the end of day 3 it was 0.69 mg/h (0.29 -1.71 mg/h).

Table I. Patients demographics and characteristics before starting continuous IV furosemide therapy

Patient	Diagnosis	Age (wks)	Weight (kg)	CVP (cmH_2O)	urine volume (ml/kg per 6 h)	Inotropic support		Furosemide therapy	
						Dopamine (µg/kg per min)	Dobutamine (µg/kg per min)	# Bolus	Total dose (mg/kg)
1	AVSD	17	4.6	8	31	15	10	3	3.26
2	TGA+VSD	7	4.5	8	24	10	5	1	2.22
3	AVSD	18	5.2	7	28	15	10	3	2.88
4	TGA	1	3.2	8	32	15	15	3	5.00
5	AVSD	11	3.6	10	59	20	10	0	
6	TOF	33	6.5	12	48	20	5	1	1.15
7	AVSD	16	5.0	8	36	15	5	2	3.00
8	CPS	0	3.1	8	4	20	5	0	
9	TGA	1	3.0	7	13	15	5	1	1.00
10	CPS	28	6.6	8	28	10	5	1	1.06
11	VSD	14	2.8	12	23	20	15	1	1.05
12	TGA	0	3.0	8	43	15	10	1	1.33

AVSD: Atrioventricular septal defect; TGA: Transposition of the Great Arteries; VSD: Ventricular septal defect; TOF: Tetralogy of Fallot; CPS: Critical Pulmonary Stenosis; CVP: central venous pressure;

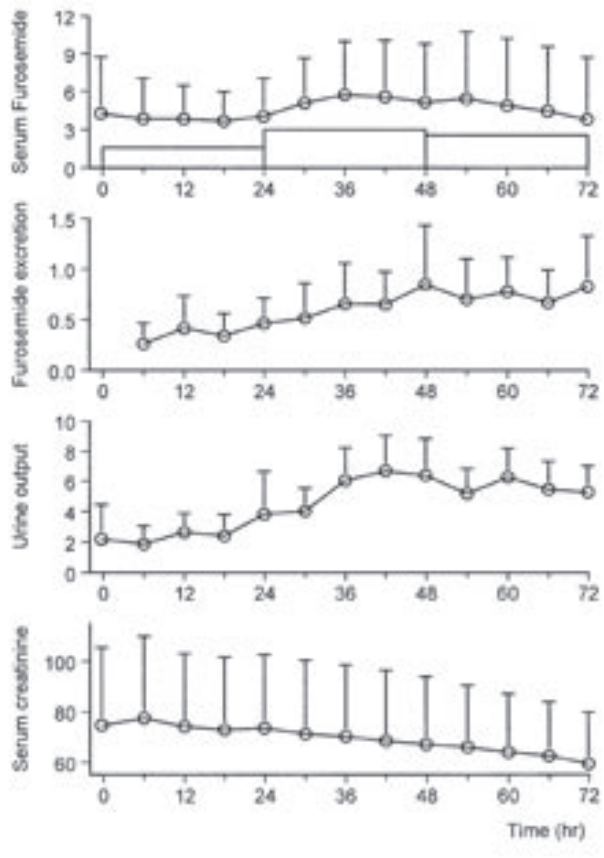

Fig. 1 Average (± SD) graphs of serum furosemide (µg/ml), furosemide excretion rate (mg/h), urine output (ml/kg per hour) and serum creatinine (µmol/l). Height of the boxes in the top graph is proportional to the average furosemide infusion rate.

Furosemide effects

The median (range) urinary sodium excretion was 2.1 (0.1 - 6.2), 9.4 (4.5 - 23.9), and 11.5 (2.7 - 18.4) mmol/kg per 24 hours over days 1, 2 and 3, respectively. The median urinary output was 2.4 (0.6 - 5.2), 5.8 (3.5 - 9.1), and 5.4 (3.6 - 7.4) ml/kg per hour over the respective treatment days.

Serum creatinine levels

The median serum creatinine level was 66 (37 - 130) µmol/l prior to the start of the continuous IV furosemide infusion. At the end of day 1 the creatinine level 65 (37 - 117) µmol/l and these levels changed to 56 (38 - 108) µmol/l and 55 (38 - 110) µmol/l at the end of the next 2 days. Figure 2 illustrates that the urinary furosemide excretion rate is inversely related to the serum creatinine levels.

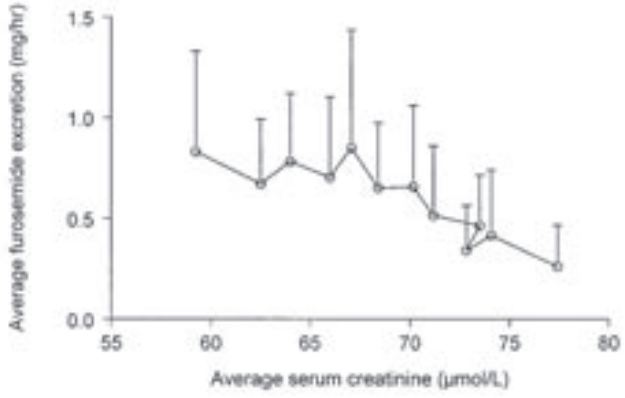

Fig. 2 The relationship between the averages (± SD) per time point of urinary furosemide excretion rates and serum creatinine levels

Discussion

Furosemide is the most frequently used diuretic for volume overload after cardiac surgery and in critically ill patients. Contrary to many other drugs, much research has been performed on furosemide in the paediatric population. There is a strong evidence that continuous IV furosemide is preferable compared to intermittent doses [7], although this may not necessarily be true for haemodynamically stable patients [8]. However, the dosing schedule for continuous furosemide infusion is largely empirical. This may even be more marked after cardiac surgery in children who are haemodynamically unstable and in whom transient renal insufficiency may occur. Therefore, a study was undertaken to investigate the response to continuous IV furosemide in this group of patients. The study was performed during routine clinical care with minor adjustment of measuring furosemide concentrations in serum and urine. This study was performed to obtain an impression regarding which clinically applicable measures could be used to design a rational scheme for furosemide infusion, following bolus administration, in haemodynamically unstable children after cardiac surgery. The rationale for the study was that the currently used infusion strategy may not be optimal. As furosemide acts only after reaching the tubular lumen [4], it can be expected that high plasma levels result in a higher concentration gradient which subsequently will provide a greater driving force to move the drug from the blood to its site of action.

This study confirms that the effect of furosemide on sodium excretion, and hence urine output, increases with decreasing serum creatinine levels. It can therefore be hypothesised that, contrary to the currently used schemes in which the dose of furosemide is gradually increased over time, it may be more rational to start with higher doses and adapt these (downward) guided by the observed effect (urine

output). Because the infusion rate was increased to 0.2 mg/kg per hour in nine out of 12 patients on day 2 and was never increased further, this suggests that a starting rate of 0.1 mg/kg per hour may be optimal. From a safety point of view this also seems justified, as in this study the observed maximal serum furosemide concentrations were approximately one-third of the commonly accepted safety level for ototoxicity (50 µg/ml) [11]. Even if starting rates were doubled, it can be expected that the levels will remain within the safety range. On the other hand, it appears that the infusion rate should not exceed 0.75 – 1.0 mg/kg per hour as occurrence of supraventricular tachycardia has been reported for these rates [12].

With the conventional analyses used in this study, it is not possible to test whether a starting rate of 0.2 mg/kg per hour is the optimal furosemide dosing regimen, and therefore a prospective study will be done to confirm this.

In conclusion, the results of this study extend previous observations on furosemide infusion to postoperative paediatric cardiac patients requiring substantial inotropic support. The results also suggest that the therapy may be more effective when the furosemide is given as a continuous IV infusion starting at relatively high infusion rates, preferable preceded by a loading dose. However, to test this hypothesis a control study has to be carried out.

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Chapter 5

Development of an optimal furosemide infusion strategy in infants with modeling and simulation

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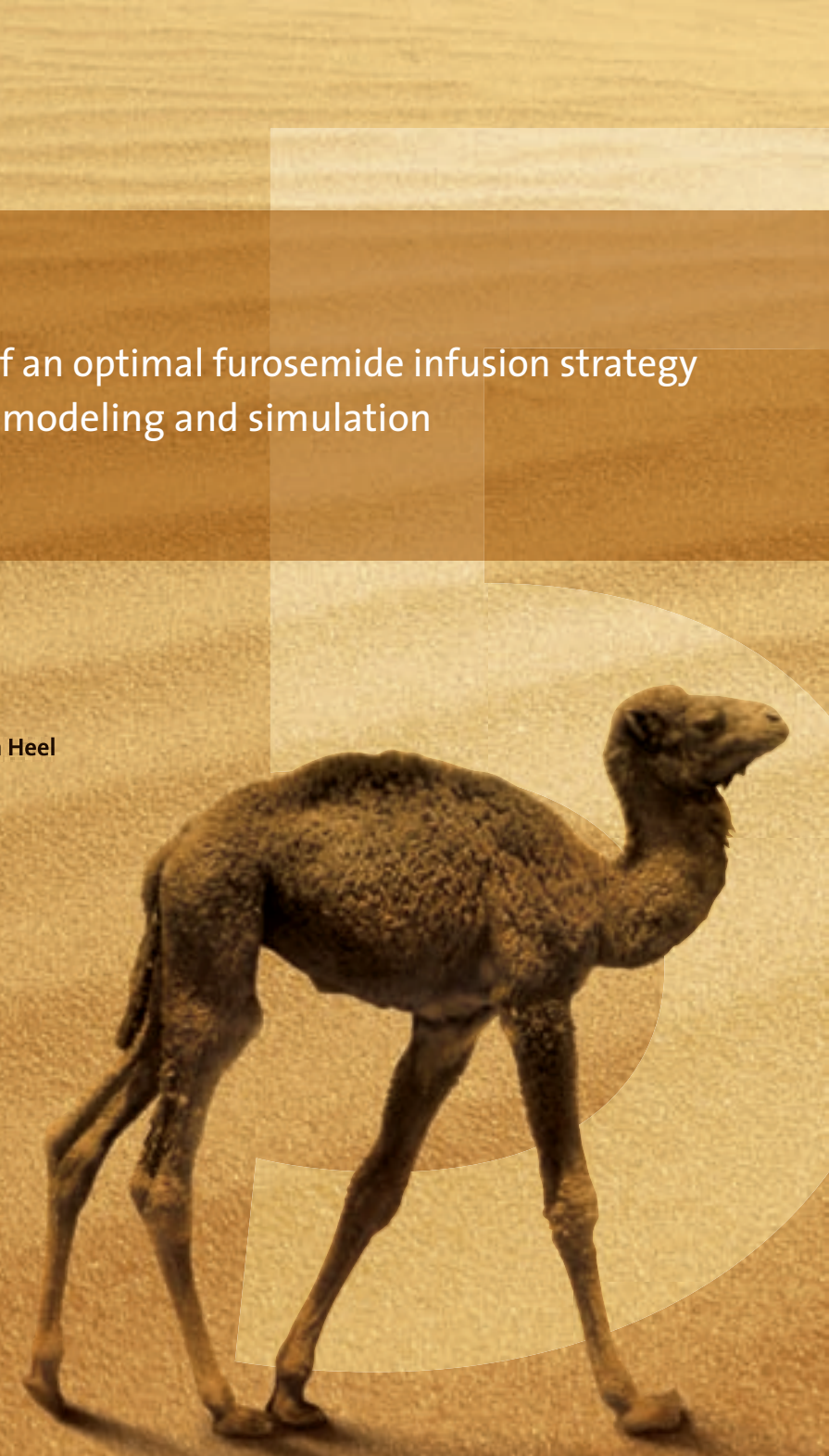

Clin Pharmacol Ther 2002;72:383-90

Abstract

Background: The optimal dosing strategy for continuous intravenous furosemide infusion is unknown in pediatric patients. Eighteen patients less than 1 year old were studied after cardiac surgery during routine clinical care. The current strategy starts with a continuous infusion of 0.1 mg/kg · h, which may be adapted.
Methods: A pharmacokinetic-pharmacodynamic model was developed that linked furosemide dose to furosemide serum concentrations, renal function (creatinine clearance), and urine output. Various regimens were simulated that adapt according to urine production. The modified dosing schedule was prospectively tested in a subsequent population of 18 pediatric patients after cardiac surgery.
Results: Data from the follow-up study suggest that urine production is more controlled for the proposed regimen.
Conclusions: Both the modeling and simulation results and the follow-up study indicated that a bolus dose of 1 mg/kg followed 6 hours later with a 1- or 2-mg/kg loading dose and a 0.2-mg/kg · h intravenous infusion provides a rational starting point for furosemide therapy after cardiac surgery in pediatric patients less than 1 year old. Adjustment of this regimen every 12 hours in steps of 0.1 mg/kg · h on the basis of clinical assessment should lead to adequate control over urinary output.

Introduction

Furosemide is the most commonly used diuretic in postoperative pediatric patients to increase urinary output1 and manage acute renal failure.[2,3] Continuous intravenous furosemide administration is an accepted treatment in the postoperative pediatric cardiac patient group treated in the Pediatric Intensive Care Unit of Leiden University Medical Center, Leiden, The Netherlands. Continuous intravenous furosemide has distinct advantages over repeated bolus administrations, such as comparable excretion of both sodium and water at much lower furosemide doses, with smaller fluctuations in urine output and less need for volume replacement therapy.[4] However, the optimal dosing regimen in this patient group with varying renal function has not yet been established. This study was designed to evaluate the current regimen and to obtain data that may allow a rational approach to investigating possible alternatives through mathematic modeling and simulation. On the basis of the simulation results, a second clinical study was performed to examine the performance of the proposed regimen.
Furosemide blocks the active resorption of chloride and sodium from the tubular lumen. This induces sodium excretion, with diuresis as a result.[2,5] Furosemide acts on receptor sites in the tubular lumen and can, therefore, induce its diuretic effect only when it has been excreted. For this reason, urinary excretion rates of furosemide are better predictors than serum concentrations with regard to the diuretic effect of the drug.[6] Furosemide is predominantly excreted by the kidneys, and because it only exerts its action after excretion, this means that both the serum concentration profile and the effect profile are influenced by renal function. After cardiac surgery, renal insufficiency may occur, leading to volume overload. When renal function is diminished, furosemide excretion is limited, and consequently, the diuretic effect is small at the time when it is most needed. The current treatment starts at relatively low infusion rates that may be increased if response is insufficient. In view of the anticipated initial low excretion rate of furosemide, it may be preferable to start high and titrate downward when renal function improves. Although high serum furosemide concentrations can be expected to induce at least some diuresis, serum concentrations should not become too high because of the danger of ototoxicity. An upper limit of 50 mg/L is generally accepted as safe.[7] Proper treatment may, therefore, require adjustment of furosemide dosage to the excretion capacity of the kidneys. In practice, this is done on the basis of observed urine production and clinical assessment of the infant and serum creatinine concentration. A proposal for a furosemide infusion regimen should, therefore, include both a starting dose and an algorithm for adjusting the dose.
To investigate alternative regimens, a quantitative model describing the relationship between furosemide input, serum concentrations, and urinary excretion leading to urine production must be developed. Simulations of different regimens may then be performed on the basis of this model, with the aim of discovering the most favorable regimen.

Methods

The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Guideline for Good Clinical Practice. The study protocol was approved by the Committee on Medical Ethics of the Leiden University Medical Center. Parental written informed consent was obtained for all patients. Because this article focuses on modeling of the obtained data, clinical results and assay methods are described elsewhere.[8]
Eighteen postoperative pediatric cardiac patients were studied during routine clinical care. Each subject was scheduled to receive at least 3 days of continuous intravenous furosemide infusion, which could be preceded by bolus doses of furosemide when clinically indicated. The starting dose for continuous intravenous furosemide infusion

was in the range of 0.05 to 0.1 mg/kg · h, according to current practice. Depending on the clinical situation, the furosemide infusion rate could be adjusted every 24 hours in steps of 0.1 mg/kg · h. Dose and time of furosemide administration were recorded. Urine was collected over 6-hour periods, and blood samples were drawn at the end of these periods. Urine volume was recorded, and serum and urine were analyzed for sodium, creatinine, and furosemide.

Data analysis

A quantitative model was developed in 3 stages, describing the relationship between furosemide input (dosage), furosemide serum concentrations, and urinary furosemide excretion leading to urine production. In stage I the relationship between furosemide input and serum concentrations was modeled. In stage II furosemide excretion was modeled as a function of serum furosemide and renal function. In stage III the relationship between furosemide excretion and urine production was described. For each stage, models were investigated on the basis of explicitly stated assumptions, and correspondence between predictions and measurements was assessed. Because transition between the different stages involved inclusion of extra variables or measurements, common model comparison strategies such as the Akaike information criterion or other goodness-of-fit measures could not be used. Finally, all 3 models were combined in an overall model, allowing description of the observed profiles and simulation of alternative regimens.

The different (sub)models were investigated by means of graphic techniques, linear regression, and nonlinear mixed-effect modeling. The latter method allows nonlinear parameter estimation for all subjects combined. The advantage is that all subjects are described by the same model, and competing models may be formally compared for the population sample as a whole. Because information is combined for all subjects, more stable parameter estimates may be obtained and all subjects can participate, even those who do not complete the entire 3-day treatment course. Nonlinear mixed-effect modeling does not result in individual parameter estimates but does result in estimates of population mean parameters and measures for interindividual variability. Individual empirical Bayes estimates can be constructed, however, on the basis of a weighted combination of the individual data and the population estimates. These estimates allow information to be shared between individuals.9 They may be used for obtaining individual model predictions and for simulating alternative regimens. Parameters were estimated by means of nonlinear mixed-effect modeling as implemented in NONMEM software, version V (GloboMax LLC, Hanover, Md), with first-order conditional estimation. Simulations were performed with the same NONMEM software, whereas linear regression and data handling were performed with SPSS for Windows, version 9.0.1 (SPSS Inc, Chicago, Ill).

Subject 5 (who only participated for 1.5 days) exhibited an unrealistic decrease in creatinine clearance estimates (from 4.5 to 0.7 mL/min), most likely caused by incomplete urine collection. Subject 5 was therefore removed from the final data analysis set, which ultimately included 17 subjects. All patients underwent major cardiac surgery and were receiving substantial inotropic support. Additional patient characteristics are shown in Table I.

Table I. Patient characteristics

	Initial study (n = 17, 9 male and 8 female)		Follow-up study (n = 12, 6 male and 6 female)	
	Mean and SD	Range	Mean and SD	Range
Weight (kg)	4.5 (1.6)	3.0-7.8	4.7 (1.1)	3.2-6.2
Age (wk)	14.6 (14.0)	0.5-48.4	16.0 (10.9)	0.5-35.0
Serum creatinine before infusion (μmol/L)	68.9 (28.7)	37-130	86.5 (44.8)	36-167
Urine output before infusion (mL/kg · h)	1.4 (1.0)	0.2-3.9	2.2 (2.2)	0.1-7.0

Stage I: Furosemide pharmacokinetics

To relate serum furosemide to administered dose, it is necessary to describe the pharmacokinetics of furosemide. The serum profile was initially described with use of a basic 1-compartment pharmacokinetic model incorporating the bolus dosing information before initiation of the infusion regimen. The expected and observed concentrations (Fig 1, left panel) clearly indicate that the predictions are too low in the initial part of the curve and too high in the terminal part. This can be attributed to increased furosemide clearance over time, associated with improved renal function. To model this process, an indicator for renal function over time must be obtained. In a situation in which renal function is changing, the standard formulas for translating serum creatinine into creatinine clearance are not appropriate because they generally require steady-state conditions. Renal creatinine clearance, however, may be used as a surrogate for renal function. Creatinine clearance was calculated by dividing the creatinine excretion rate into urine (amount excreted in 6 hours divided by the time span) by the corresponding serum creatinine concentration for each 6-hour period. Individual graphs (not shown) indicated that the resulting creatinine

clearance profile over time was rather erratic, probably because of various random measurement errors. To smooth this profile, a linear regression line for creatinine clearance versus time was determined for each subject.
Furosemide pharmacokinetics was subsequently described by a single-compartment model in which furosemide clearance is assumed to be proportional to the linearly increasing creatinine clearance over time. This requires a differential equation of the following form:

$$dC(t)/dt = [Input - CL(t) \times C(t)]/V] \quad \text{(Ia)}$$

in which dC(t)/dt describes the change in furosemide serum concentration in time, Input is the furosemide dosage regimen, CL(t) is the furosemide clearance as a function of time, C(t) is the serum furosemide concentration, and V is the volume of distribution. Furosemide clearance is described as follows:

$$CL(t) = R \times CLcr(t) \quad \text{(Ib)}$$

in which R is the ratio of furosemide to creatinine clearance and CLcr(t) is described as follows:

$$CLcr(t) \quad CLcri \quad CLcrs \quad Time \quad \text{(Ic)}$$

in which CLcri and CLcrs are the intercepts and slopes describing the time course of creatinine clearance [CLcr(t)]. Both furosemide pharmacokinetics and creatinine clearance were estimated simultaneously (meaning one can influence the other) with NONMEM, resulting in a marked improvement in the description of the furosemide serum concentration profile.

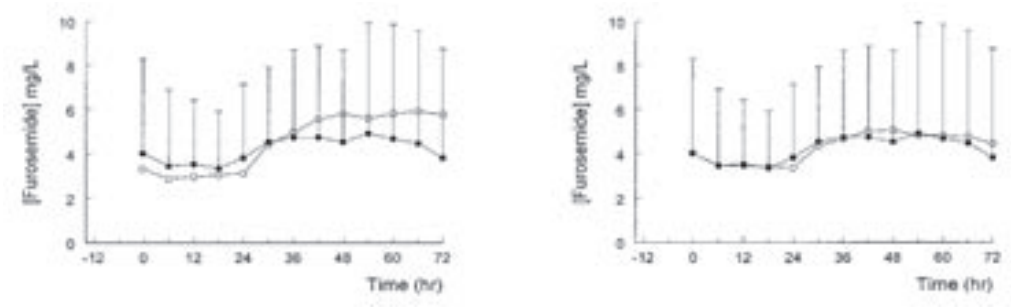

Fig 1. Predicted (open circles) and observed (closed circles) average furosemide serum concentration profiles assuming time-constant clearance (left panel) and clearance proportional to linearly changing creatinine clearance over time (right panel; stage I model). Error bars are standard deviations (SDs) of observed values.

Stage II: Urinary excretion of furosemide

To describe the relationship between urinary furosemide excretion, serum furosemide, and renal function, the second submodel must be constructed. The most basic model imaginable assumes that renal furosemide excretion is proportional to both serum furosemide and renal function. This means that a 20% increase in serum furosemide will lead to a 20% increase in furosemide excretion and that a 20% increase in renal function will also lead to a 20% increase in furosemide excretion. This model is given by the following:

$$\text{Furosemide excretion} = A \times \text{Serum furosemide} \times \text{Renal function} \quad \text{(IIa)}$$

Assuming that renal function is proportional to the linearly increasing creatinine clearance leads to the following model:

$$\text{Furosemide excretion} = B \times \text{Serum furosemide} \times (CLcr_i + CLcrs \times \text{Time}) \quad \text{(IIb)}$$

Furosemide excretion and creatinine clearance were estimated simultaneously as a function of serum furosemide (actual measurements) and time with NONMEM. Average and individual graphs (not shown) indicate that a reasonable description of urinary furosemide excretion is obtained, assuming proportionality to both serum furosemide and a linearly changing creatinine clearance over time.

Stage III: Relationship between furosemide excretion and urine production.

Individual graphs for urine production versus furosemide excretion indicated that the relationship between sodium excretion and urine production is linear, with an intercept near the origin. The most basic model is therefore as follows:

$$\text{Urine production} = C \times \text{Furosemide excretion} \quad \text{(IIIa)}$$

Clearly, this relationship can only hold for the situation in which furosemide is administered. When the patient has recovered, adequate urine production is achieved in the absence of furosemide, which is in contrast to this assumption. What is missing is a description of urine production under healthy normal conditions. The current data do not provide this information, so the final model may be used only for patients requiring furosemide administration.

The overall model: Stages I, II, and III combined

If the 3 submodels are combined, the following set of equations results:

$$dC(t)/dt = [Input - CL(t) \times C(t)]/V \quad (1)$$
$$CL(t) = R \times CLcr(t) \quad (2)$$
$$CLcr(t) = CLcr_i + CLcrs \times Time \quad (3)$$
$$Urine\ production(t) = UF \times C(t) \times CLcr(t) \quad (4)$$

in which UF is the proportionality factor between serum furosemide, creatinine clearance, and urine production. The independent variables are time and furosemide input, and the dependent variables are serum furosemide [C(t)], creatinine clearance [CLcr(t)], and urine production, eliminating the need for furosemide excretion data. This model was subjected to simultaneous estimation by NONMEM, and the average results are graphically presented in Fig 2. NONMEM parameters are presented in Table II. The graphs indicate that this final model provides an adequate description of serum furosemide, creatinine clearance, and urine production over time. Aside from describing the current data set, it may be used to simulate different dosing regimens in the search for an optimal strategy.

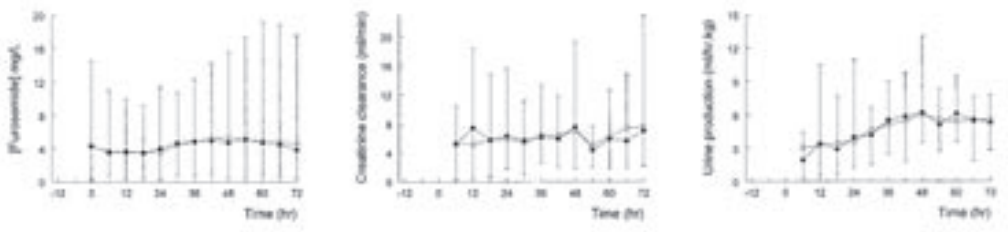

Fig 2. Predicted (open circles) and observed (closed circles) average serum furosemide (left panel), creatinine clearance (middle panel), and urine production (right panel) profiles for final model. Error bars indicate the minimum and maximum of observed values.

Table II. NONMEM estimates for final model*

Parameter	Mean	SEM	Interindividual CV
CLcri (mL/min)	2.89	1.15	147%
CLcrs (mL/min · d)	0.906	0.334	52%
R	0.525	0.0816	46%
V (L)	1.43	0.307	50%
UF	0.257	0.0430	44%

SEM, Approximate standard error of the population mean; CV, coefficient of variation describing variation between subjects; CLcri, creatinine clearance intercept at time zero; CLcrs, creatinine clearance slope; R, ratio of furosemide clearance to creatinine clearance; V, furosemide volume of distribution; UF, proportionality factor relating urine production (milliliters per 6 hours) to serum furosemide (milligrams per liter) and creatinine clearance (milliliters per minute).
*Residual error as follows: creatinine clearance versus time, 54%; serum furosemide versus time, 24%; urine production versus time, 46%.

Simulations

Simulations were performed with the use of the empirical Bayes estimates from the final model along with the residual error estimates from the NONMEM analysis. To reduce the influence of starting values for the random errors, the data for each subject were replicated 60 times (without modifying the parameters). Simulated serum furosemide, creatinine clearance, and urine production profiles were generated with the use of different regimens. A starting bolus dose of 1 mg/kg was simulated in all cases, followed 6 hours later by loading doses of 0, 1, and 2 mg/kg with infusions of 0.1, 0.2, and 0.3 mg/kg · h in all 9 possible combinations. Because no information about urine production during the bolus doses was present in the original data set, predicted urine output is not presented until 6 hours after the loading dose.
Clinical practice adapts the infusion regimen according to dynamic response (typically urine production). It is, therefore, most informative to examine whether a strategy can be tested that will result in adequate urine production as quickly as possible. The aim is to keep urine production around 4 mL/kg · h for these infants. Residual error for urine estimates (deviation from prediction) for the final model is about 50%, so roughly two thirds of the measured urine production rates should be 50% of 4 mL/kg · h (between 2 and 6 mL/kg · h) for a perfect regimen. The rationale, therefore, is to adjust the furosemide infusion rate upward if urine production drops below 2 mL/kg · h and downward if the production exceeds 6 mL/kg · h.
For each subject and time point, the NONMEM simulation output provides both a

model prediction (based on the empirical Bayes estimates and the infusion regimen) and a simulated observation that equals the model prediction plus a simulated amount of error. The size of this error is obtained from the final NONMEM analysis (Table II). During the simulations, the simulated observations for urinary output (over the previous 6 hours) were examined every 12 hours, and if the simulated production was below 2 mL/kg · h, the infusion rate was increased by a step of 0.1 mg/kg · h. If the simulated production exceeded 6 mL/kg h, the infusion rate was decreased by a step of 0.1 mg/kg · h. If this would result in a rate of 0 mg/kg · h, the rate was set at 0.05 mg/kg · h. The model predictions for the urine production rates resulting from these 9 simulation regimens are presented in Fig 3.

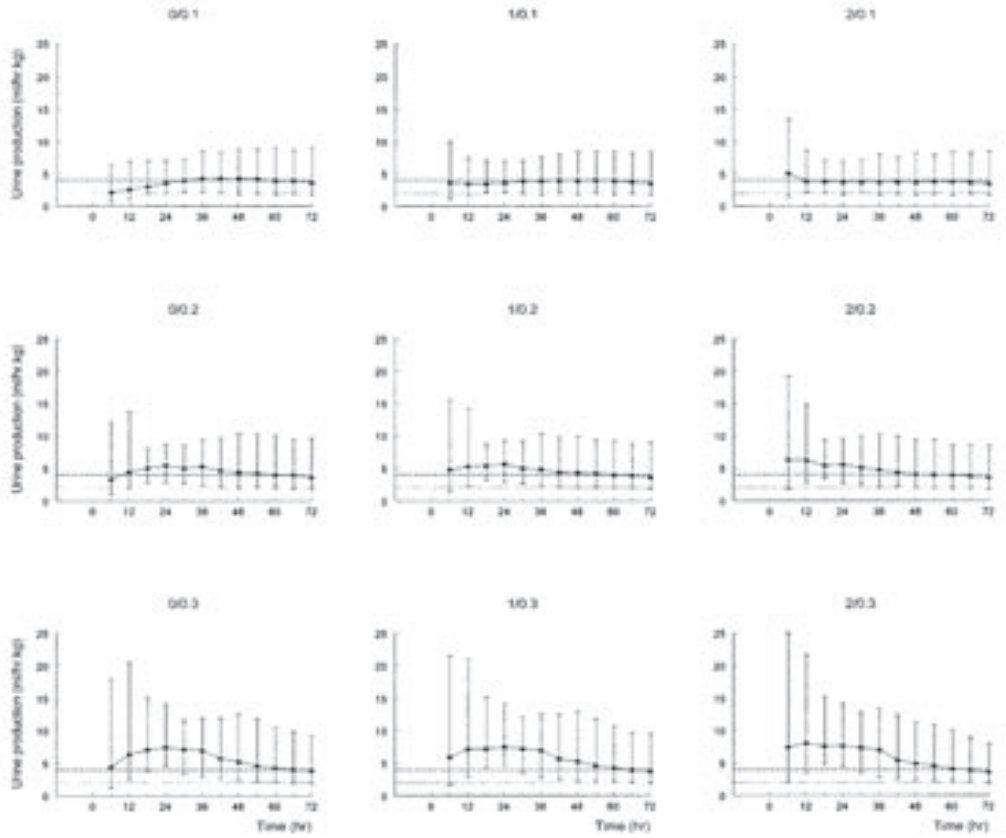

Fig 3. Simulated urinary output with possibility of adjustment every 12 hours. Graphs depict median output, and error bars encompass 95% of the model predictions. From left to right, infusions are preceded by a loading bolus dose of 0, 1, and 2 mg/kg. From top to bottom, infusions start at 0.1, 0.2, and 0.3 mg/kg · h. Urine production is aimed at 4 mL/kg · h (dotted horizontal line) and should preferably exceed 2 mL/kg · h (solid horizontal line).

The simulations suggest that the use of a 1-mg/kg loading dose, as compared with no loading dose, is beneficial for obtaining a swift onset of action. A 0.2- mg/kg · h continuous infusion, as compared with 0.1 mg/kg · h, leads to somewhat higher urine production for the least responsive subjects (the lower error bars). A 2-mg/kg loading dose may be too aggressive as a general starting dose, except for those infants in whom poor renal function may be anticipated. A 0.3-mg/kg · h intravenous infusion invariably leads to exaggerated urine output and the need for downward adjustment. These results suggest that the combination of a 1- or 2-mg/kg loading dose followed by an infusion rate of 0.2 mg/kg · h leads to swift and adequate urine production.

Follow-up study

To examine the proposed regimen, a follow-up study was performed. The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Guideline for Good Clinical Practice. The study protocol was approved by the Committee on Medical Ethics of the Leiden University Medical Center. Parental written informed consent was obtained for all patients. Because this article focuses on modeling of the obtained data, clinical results will be described elsewhere. Eighteen postoperative pediatric cardiac patients were studied for up to 3 days during routine clinical care. A standard bolus dose of 1 mg/kg was administered, followed 6 hours later by a loading bolus dose of 1 or 2 mg/kg, depending on the anticipated renal function of the patient. The 2-mg/kg loading bolus was administered if serum creatinine concentrations had doubled relative to the concentrations before surgery or, if the patient was less than 8 weeks old, if serum creatinine concentrations exceeded 75 µmol/L. A continuous infusion of 0.2 mg/kg · h was started at the same time as the loading bolus dose. This rate could be increased or decreased every 12 hours with steps of 0.1 mg/kg · h if urine production over the preceding 6 hours was lower than 2 mL/kg · h or higher than 6 mL/kg · h, respectively. All other methods were the same as for the previous study.

Results

Six subjects were excluded from the final analysis because of various protocol violations, leaving 12 evaluable subjects. All patients underwent major cardiac surgery and were receiving substantial inotropic support. Seven patients received a 2-mg/kg bolus loading dose. For 3 patients, the infusion rate was increased to 0.3 mg/kg · h and for 2 patients to 0.4 mg/kg · h. These latter 2 patients were severely ill and required reoperation (one because of severe aortic valve insuf- ficiency and

one because of severe tricuspid valve insufficiency and pulmonary regurgitation). Additional patient characteristics are shown in Table I.
Observed urine production (mean + SD) is presented in Fig 4 along with the corresponding results for the initial study, for the subjects who completed the entire 3-day treatment. These graphs suggest that the proposed regimen may lead to more controlled urine output, without the observed increase in urine production after 36 hours, as observed in the initial study.

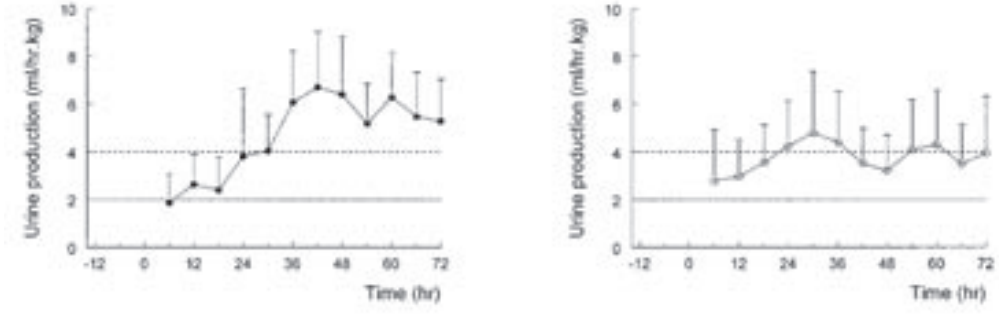

Fig 4. Observed average urine production profiles for initial study (left panel) and follow-up study (right panel) for subjects completing 3-day treatment. Error bars are SDs of observed values.

Discussion

After cardiac surgery, renal function tends to be poor whereas volume overload tends to be high. Because renal function is poor, furosemide excretion is limited, and consequently, the diuretic effect is small at the time when it is most needed. This can only be overcome by increasing serum furosemide concentration and thereby forcing furosemide excretion. As soon as renal function improves, furosemide excretion rates will increase and serum concentrations may then be lowered. This means that for furosemide to work properly the dosage should be high initially and may be titrated downward when renal function improves. This is in contrast with the current strategy that starts low and titrates upward if results are insufficient.
By modeling the relationship between furosemide dosing, furosemide serum concentrations, creatinine clearance, and urinary production, an adequate description could be obtained for the data collected in the initial study. These results were used to simulate alternative dosing strategies, suggesting that it may be possible to reach adequate urinary output hours sooner than by using the current strategy. Predicted concentrations for the proposed regimen remained well below the possibly ototoxic concentrations of 50 mg/L.[7]

However, a number of points should be noted. Given the richness of some of the modeling efforts described in the literature,10 the current model is rather crude. Observations were only made during the constant rate infusion periods, when concentrations are not expected to fluctuate much. These results and parameters, therefore, cannot be used to describe the effects of furosemide after isolated bolus dosages. The relationship between furosemide excretion and urine production is assumed to be linear, whereas the literature clearly indicates that this relationship is sigmoidal.[11] In the excretion range studied here, no clear indications could be found for a deviation from this straight line, and therefore the most parsimonious model was used. A perhaps more serious shortcoming of the model is the fact that urine production depends on the presence of furosemide, and the model predicts no urinary output in the absence of furosemide. This oversimplification disregards the natural course of renal recovery after surgery. The expectation is that the prescribed switch to low infusion rates (ie, < 0.05 mg/kg · h) will correspond to the cessation of furosemide infusion in real-life situations and adequate urinary output without medication. Finally, the reported occurrence of acute tolerance or "braking" has not been incorporated into the model. This phenomenon will be more pronounced with bolus administration than with continuous infusion and will be apparent primarily just after the furosemide intervention. Even if tolerance were to occur with continuous infusions, the effect would probably not be noticeable after 6 hours, and the model, therefore, does not need to take this into account.
Simulation could have been optimized if random samples had been drawn from a population described by population pharmacokinetic-pharmacodynamic parameters; instead, the empirical Bayes estimates obtained in this study were simply repeated. However, this would have required a set of population parameters that adequately described the relationship between body weight and the pharmacokinetic-pharmaco-dynamic parameters, along with an estimate of the full parameter covariance matrix to account for correlations of between-subject parameters.
The initial data set of 17 subjects was not large enough to support such a modeling exercise.
Given these restrictions, it nevertheless seemed reasonable to assume that a 1- or 2-mg/kg loading dose followed by a 0.2-mg/kg · h intravenous infusion could provide a rational starting point for furosemide therapy after cardiac surgery in pediatric patients. This strategy was subsequently investigated in similar group of patients.
The results from this follow-up study suggest that urine production is more stable and occurs without the increase in output observed for the initial regimen after 36 hours. This may be of particular importance for the hemodynamically unstable group of patients in this study.
In view of both the pharmacologic profile of furosemide and the results from the

simulations of the model, we had expected urine production to be higher in the first 24 hours than that actually observed in the follow-up study. As it turns out, the responsiveness to furosemide just after surgery in 2 of the 12 infants may be too low to allow an adequate response, even with increases in infusion rate of up to 0.4 mg/kg · h. Data from these severely ill patients distort the average results and make it difficult to prove that onset of adequate output is indeed superior compared with the initial regimen. The results do, however, clearly indicate that, by careful monitoring of the urine production and by changing the infusion accordingly, a more controlled urine production can be obtained. The final proof of superiority in terms of clinical outcome will need to be obtained from a new randomized study comparing the two regimens. For ethical reasons, this study will have to be carried out in a center where reasonable doubt exists regarding the superiority of either regimen.

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Chapter 6

Absence of tolerance and toxicity to high-dose continuous intravenous furosemide in haemo-dynamically unstable infants after cardiac surgery

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British Journal of Clinical Pharmacology, in press

Abstract

Aim: To evaluate a high-dose continuous furosemide regimen in infants after cardiac surgery.
Methods: Fifteen haemodynamically unstable infants with volume overload admitted to a paediatric intensive care unit were treated with an aggressive furosemide regimen consisting of a loading bolus (1-2 mg/kg) followed by a continuous infusion at 0.2 mg/kg per hour which was adjusted according to a target urine output of 4 ml/kg per hour. Frequent sampling for furosemide concentrations in blood and urine was done for 3 days with simultaneous assessment of sodium excretion and urine output.
Results: The mean furosemide dose was 0.22 (± 0.06), 0.25 (± 0.10), and 0.22 (± 0.11) mg/kg per hour on the first, second and third day respectively. Median urine production was 3.0 (0.6 - 5.3), 4.2 (1.7 - 6.6) and 3.9 (2.0 – 8.5) ml/kg per hour respectively on the first, second and third day of the study. The target urine production was reached at a median time of 24 (6-60) hours and this was maintained during the study period. The regimen did not result in toxic serum concentrations and was haemodynamically well tolerated.
Conclusion: High dose continuous furosemide infusion for 72 hours in haemodynamically unstable infants after cardiac surgery appears to be a safe and effective treatment for volume overload. Development of tolerance against the effects of furosemide and ototoxic furosemide concentrations were not observed.

Introduction

Intravenous (IV) furosemide therapy is an accepted way to reduce volume overload in paediatric patients after cardiac surgery [1]. There is evidence that continuous IV furosemide is superior to intermittent furosemide therapy, because continuous administration results in a more controlled diuresis [2-4]. However, the currently used continuous IV furosemide regimens are still largely empirical, especially in patients with varying renal function. Current practice is to start with a relatively low continuous IV furosemide dose of 0.1 mg/kg per hour followed by higher doses up to 0.4 mg/kg per hour as insufficient diuresis remains. As furosemide acts at the luminal site of the renal tubules and thus the driving force for furosemide to reach its site of action will be low in patients with a relatively low glomerular filtration rate. This may be the case in infants after cardiopulmonary bypass (CPB) surgery who are haemodynamically unstable and in whom transient renal insufficiency frequently occurs. Indeed, we have previously suggested that it may be more rational to start with a higher dose (0.2 mg/kg per hour) and adapt the dose guided by the urine output [5]. We also reported the preliminary results of a pharmacokinetic-pharmacodynamic model to support this suggestion [6]. However, it has been shown that after repeated bolus administrations of furosemide a diminished diuretic effect occurs [7;8]. In addition, it has also been suggested that tolerance to the diuretic effect occurs during continuous infusion [9]. This may have an impact on our suggestion that a continuous intravenous infusion with a relatively high dose may be superior to a relatively low dose regimen. Therefore we explored whether or not tolerance towards the diuretic effect of furosemide develops in haemodynamically unstable infants after cardiac surgery with CPB who are in need of diuretics.

Materials and Methods

The study was performed at the Paediatric Intensive Care Unit (PICU) of Leiden University Medical Center (LUMC). The study protocol was approved by the Committee on Medical Ethics of LUMC and conducted according to the principles of the Declaration of Helsinki. In addition, the trial was performed with the regulations on paediatric research set forward in Dutch law and in accordance with the recommendations for paediatric research of the Dutch Society of Paediatrics. Parental written informed consent was obtained for all patients.

Patients and methods

Consecutive patients less than one year of age who were admitted to the PICU of LUMC after CPB surgery were eligible if it was likely that they would need prolonged continuous IV furosemide because of volume overload and/or relatively low urine output (< 4 ml/kg per hour), despite initial treatment with a bolus IV furosemide.
All infants were haemodynamically unstable defined as at least 2/4 points for cardiovascular organ failure assessed with the modified Sequential Organ Failure Assessment Score [10]. The infants required inotropic support and this was quantified using the standard vasopressor score [11].
The infants were monitored with an arterial and a central venous line. During the post-operative course maintenance fluid was kept at 60 ml/kg per 24 hours. Volume expanders were administered when necessary to maintain or achieve adequate circulating volume and serum potassium levels were kept between 3.8-4.3 mmol/l, if necessary by supplementation. The observation period for this study was 3 days after the start of the continuous infusion.
The study protocol followed the routine clinical care for the patients as closely as possible and all drugs necessary for the treatment of the patients were allowed.

Furosemide regimen

When during the post-operative course the patients developed volume overload and/or insufficient urine output, first an IV furosemide bolus of 1 mg/kg was administered. When this was ineffective, a continuous furosemide infusion of 0.2 mg/kg per hour was started. This infusion was preceded by a loading dose of furosemide which dose depended on renal function. Patients with normal renal function received 1 mg/kg and patients with acute renal failure (ARF) received 2 mg/kg. ARF was defined as doubling of serum creatinine compared to pre-operative serum creatinine or a serum creatinine concentration ≥ 75 µmol/l in patients younger than 8 weeks [12]. The aim was to reach and maintain a urine output of 4 ml/kg per hour. It was therefore allowed to change the rate of the continuous infusion with steps of 0.1 mg/kg per hour. Adaptation of infusion rate was allowed at 12-hours intervals and was based upon the urine production over the preceding 6 hours.
If the urine production was less than 2 ml/kg per hour the rate of infusion was increased and if urine production was more than 6 ml/kg per hour the infusion rate was decreased.

Sampling and assays

For the blood sampling, it was taken into consideration that the total volume of blood taken for study purposes should not exceed 3% of the circulating volume. Blood and urine samples (using bags providing protection from UV light) were collected every 6 hours for measurements of sodium, creatinine and furosemide. Serum sodium and creatinine concentrations were measured using a photometric method on an automatic analyser (Hitachi 747-100, Roche diagnostics, Almere, The Netherlands). Furosemide concentrations were measured using a validated high performance liquid chromatography method routinely applied at the laboratory of Clinical Pharmacy and Toxicology of LUMC. For determination in serum the coefficient of variation of the assay at 1 µg/ml was 2%, and the reproducibility of the slope was 8.9%. For the analysis of furosemide concentration in urine, the samples were first deglucuronidated. The coefficient of variation of the assay in urine was 3.4% at 10 µg/ml, and the reproducibility of the slope was 7.2%.

Data analysis

Data showing a skewed distribution are given as median and range while the normally distributed haemodynamic parameters are presented as mean and standard deviation. The outcome evaluation included the median urine production

over each 24 hour time interval, the time at which the target urine production was reached, and the deviation from the target urine production. The time to attain the target urine production was defined as the time point at which urine production was at least 4 ml/kg per hour for 2 consecutive assessments. Deviation from the target urine production was defined as the absolute amount of urine either below or above target urine production.
The relationship for the time course of the serum furosemide concentrations, the urinary furosemide excretion, and the urine production were displayed graphically to explore the possible development of tolerance. Blood pressure values and heart rate were summarised over time. The values obtained before the start of the furosemide infusion were compared to the values obtained at the end of the experiment using paired Student's t-tests.

Results

General

Eighteen patients likely to require at least a 3-day treatment of continuous IV furosemide were included in the study. In three patients continuous IV furosemide was discontinued after 36, 30 and 60 hours, because it was not indicated anymore on clinical grounds. Thus, fifteen patients completed the full 3-day course of furosemide infusion and the data of these patients are reported (table 1).
The median (range) age of the infants was 12 (0.5 - 35) weeks and the weight was 4.0 (3.0 - 6.2) kg. All patients underwent major cardiac surgery with CPB. The median CPB time was 112 (33-272) min. Hypothermia was applied during surgery for a median period of 111 (20-188) min with a lowest body temperature of 27.7 (19.5-35.7) °C. At the start of the study, all patients were mechanically ventilated and haemodynamically unstable requiring substantial inotropic support as shown by a mean (SD) vasopressor score of 23 (15).
There was clear volume overload in the patients as shown by the mean elevated central venous pressure of 15 (range: 7-20) cm H_2O; table 2.
Disconnection from mechanical ventilation occurred after a median time of 131 (70-215) hours and discharge from the PICU was after a median time of 166 (86-257) hours after surgery.
To 10 patients aminoglycosides were administered. The routinely performed therapeutic drug monitoring showed the concentrations of these drugs to be in the therapeutic range. No other drugs with a potential for interaction with furosemide kinetics (e.g. NSAIDs) or other drugs with a nephrotoxic potential were given. At the

start of the study 9 patients were diagnosed with ARF (as defined before). At the end of the 3-day observation period ARF was still present in 4 infants, but in none of the infants renal function deteriorated, and all patients were discharged without evidence of renal insufficiency.
The mean (SD) total amount of blood taken for study purposes was 2.2% (0.5%) of the circulating volume.

Table I. Patient characteristics

Pat	Diagnosis	Gender	Age (wks)	Weight (kg)	T-CPB (min)	T-Clamp (min)	T-hypo (min)	T-low (°C)
1	IAA+VSD	F	1	3.3	122	60	107	19.5
2	PAIVSD	M	0.5	3.5	33	19	21	34.6
3	DORV	F	12	4	121	91	127	26
4	MAPCA	F	6	3.2	60	29	93	29.4
5	DORV	M	23	5.8	112	69	118	27.4
6	TOF	F	12	4.9	102	76	111	30.2
7	TOF	F	30	5.6	148	68	180	28
8	TGA	M	1	3.7	108	68	104	25
9	AVSD	M	26	6.1	33	0	20	35.7
10	VSD	M	10	3	130	101	121	27
11	VSD	F	4	3.5	166	112	156	27.7
12	VSD	M	22	5.5	97	54	64	30.2
13	DORV	F	35	6.2	125	68	125	24.7
14	VSD	F	12	4.5	62	39	52	30.6
15	TOF+PAPVC	F	10	3.8	272	107	188	24.2

Diagnosis: IAA: Interrupted Aortic Arch; VSD: Ventricular septal defect; PAIVS: Pulmonary Atresia with Intact Ventricular Septum; DORV: Double Outlet Right Ventricle; MAPCA: Major Aorto Pulmonary Collateral; TOF: Tetralogy of Fallot; TGA: Transposition of the Great Arteries; AVSD: Atrioventricular septal defect; PAPVC: Partial anomalous pulmonary venous connection; T-CPB: Time on cardiopulmonary bypass; T-Clamp: aortic cross clamp time; T-hypo: Hypothermia time defined as the period during which the body temperature of patient < 36°C; T-low: lowest temperature reached during cardiopulmonary bypass.

Table II. Haemodynamic status and inotropic therapy at the start of the study

Pat	CVP	SBP	DBP	HR	Vasopres. score	Dobu	Dopa	Adr	Nor-Adr	Enox	NO
	(cmH2O)	(mm Hg)		(bpm)		(µg/kg per min)					(ppm)
1	8	75	58	151	10	5	5	0	0	4	14
2	8	65	30	145	25	10	10	0	0.05	0	0
3	18	70	40	195	23	5	12	0	0.06	3	0
4	10	55	35	215	25	10	5	0.1	0	5	0
5	20	80	55	170	25	15	10	0	0	0	0
6	13	75	45	145	18	10	8	0	0	0	0
7	18	65	35	125	30	10	10	0	0.1	0	0
8	7	65	45	160	11	5	6	0	0	0	0
9	15	70	40	154	17	5	12	0	0	0	10
10	17	88	42	124	42	10	10	0.14	0.08	2	14
11	15	80	50	170	30	10	10	0	0.1	2	0
12	19	92	45	150	7	5	2	0	0	0	0
13	13	75	40	182	14	5	3	0	0.06	0	0
14	8	98	55	160	5	5	0	0	0	0	0
15	15	72	52	201	66	0	10	0	0.56	4	22

CVP: central venous pressure; S/DBP: systolic/diastolic blood pressure; HR: heart rate in beats per minute; Vasopres.: Vasopressor; Dobu: dobutamine; Dopa: dopamine; (Nor-)Adr: (nor-)adrenalin; Enox: Enoximone; NO: nitric oxide in parts per million.

Furosemide regimen

The mean (SD) total dose of furosemide boluses administered to the patients before the start of the continuous furosemide infusion was 2.94 (± 1.08) mg/kg. Continuous IV furosemide was started at a median time 25 (14-34) hours postoperatively. The mean continuous furosemide dose was 0.22 (± 0.06), 0.25 (± 0.10), and 0.22 (± 0.11) mg/kg per hour on the first, second and third day respectively. There was no need to change the dose over the entire observation period for 4 patients. Dose adaptation, all increases, was done in 4 infants on day 1. On both day 2 and day 3, an increase in dose was needed in 2 patients while the dose was decreased in 4 patients. Thus, there was a low need to adapt the doses within each day.

Furosemide kinetics

The mean furosemide concentrations over time are shown in figure 1. Before the start of continuous furosemide administration the median serum furosemide concentration was 1.6 (0.2-3.4) µg/ml and this increased to 5.2 (1-22.6), 3.9 (0.4-28.5) and 2.9 (0-23.2) µg/ml on the first, second and third day. Of note, the maximal furosemide concentration observed was 28.5 µg/ml. The urinary furosemide excretion (figure 1) which was relatively low at the first measurement at 6 hrs after initiation of the continuous infusion, increased rapidly and substantially in the next 18 hrs and remained stable thereafter. The median urinary furosemide excretion was 0.12 (0.04-0.22), 0.16 (0.1-0.27), 0.15 (0.03-0.40) mg/kg per hour for the three subsequent study days.

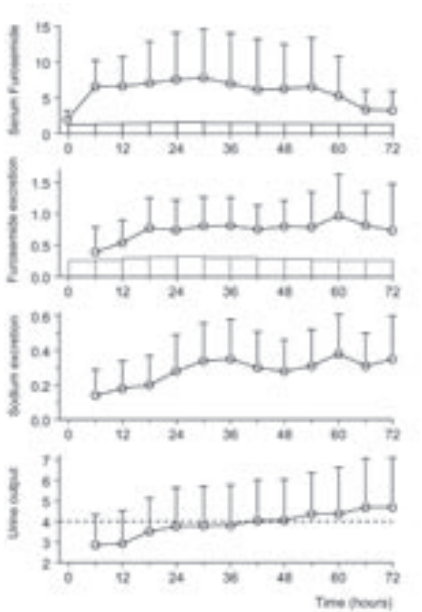

Fig 1. Average (± SD) graphs of serum furosemide (µg/ml), furosemide excretion rate (mg/kg per hour), sodium excretion (mmol/kg per hour) and urine output (ml/kg per hour). In the two top panels, the boxes indicated the average furosemide dose with the height of the boxes proportional to the dose with the first box indicating an infusion rate of 0.2 mg/kg per hour). In the bottom panel the target urine output (4 ml/kg per hour) is indicated by the dashed line.

Furosemide dynamics - urine output and sodium excretion

The mean urinary sodium excretion and the urine production in each 6 hours time interval over the entire observation period is given in figure 1. Median sodium excretion was 2.5 (0.3-11.0), 7.1 (1.1-15.2) and 6.3 (1.6 -17.5) mmol/kg per 24 hours over the first, second and third study day.
The median urine output before the start of the continuous infusion was 1.7 (0.2 – 7.6) ml/kg per hour. Median urine production over the consecutive study days was 3.0 (0.6 - 5.3), 4.2 (1.7 - 6.6) and 3.9 (2.0 – 8.5) ml/kg per hour on day 1, 2 and 3.

The target urine production was reached after a median time of 24 (6-60) hours. The median deviation form the target urine production was 1.0 (0.5 – 3.4), 0.9 (0.1 – 2.6) and 1.1 (0.0 – 4.5) ml/kg per hour for the three consecutive study days.
There was a strong linear relationship between sodium excretion and urine production with correlation coefficients ranging from 0.66 to 0.99 (range of p-values 0.02 - 0.0003). The relationship for the time course of the average group values of the serum furosemide concentrations, the urinary furosemide and sodium excretion and the resulting urine production (figure 2), indicates that there was no development of tolerance to the furosemide effect. With increasing urinary furosemide excretion higher values of sodium excretion and urine output were observed, without indication of tolerance. The data (illustrated in both graph 1 and 2) also indicates that, after some time, the urinary furosemide concentration remained stable despite decreasing serum concentrations, indicating that the renal function of the infants improved. This is also shown by the serum creatinine concentrations which decreased during the observation period from a median 95 (36-167) µmol/l prior to the start of the infusion to 82 (41-188), 64 (42-192) and 61 (42-154) µmol/l on respectively the first, second and third day.

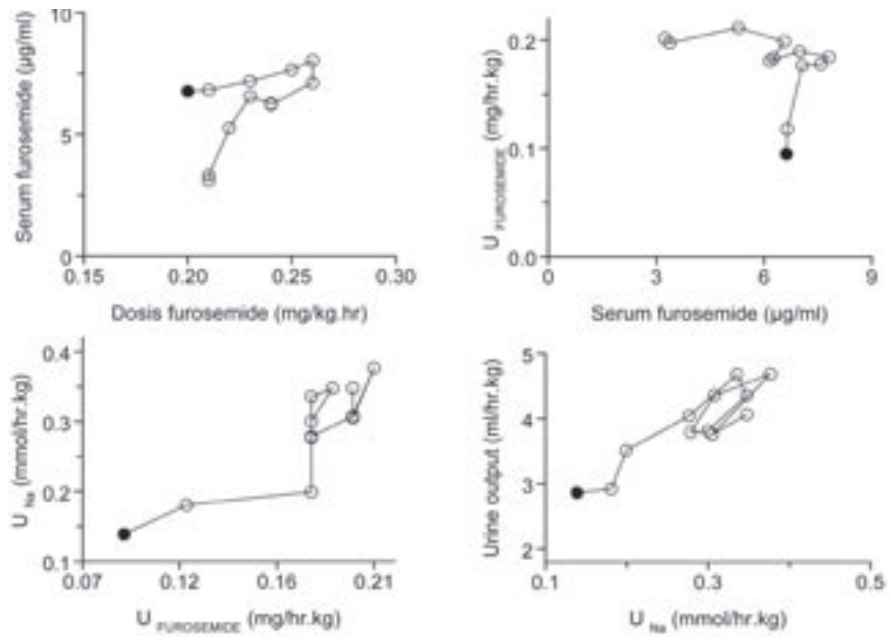

Fig 2. The relationship for the time course of the average group values of the serum furosemide concentrations, the urinary furosemide and the sodium excretion and the resulting urine production. The first observation is indicated with the closed symbols and the subsequent observations are connected with the lines.

Haemodynamic and metabolic effects

The fluid balance was negative for all 3 study days, albeit with substantial variability. The median values were -31 (-270/+305), -139 (-272/+128), -37(-790/+199) ml per 24 hours for day 1, 2 and 3 respectively. Apart from the maintenance fluid, 60 ml/kg per 24 hours, volume expanders were needed in 5, 4 and 2 patients at day 1, 2 and 3 respectively. The amount of volume expanders used varied between 10 and 80 ml per 24 hours. The patients tolerated the forced diuresis well; blood pressure increased slightly over the observation period (systolic BP +9.7 mm Hg; p=0.03 and diastolic BP +2.1 mm Hg; p= 0.34), while the CVP (-3.5 cm H2O; p= 0.007) and heart rate (-28.2 bpm; p= 0.007) decreased over time (figure 3).
Metabolic alkalosis, defined as pH > 7.45 and bicarbonate > 29 mmol/l, was not observed during the entire study period.

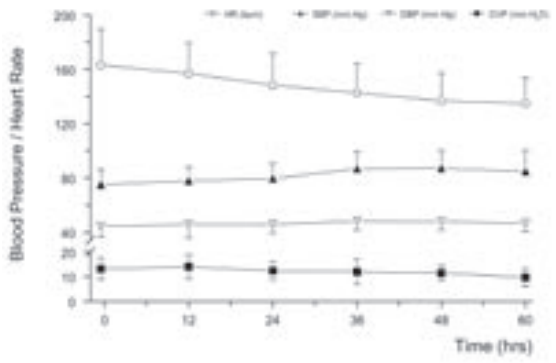

Fig 3. Average (± SD) graphs of systolic (SBP), diastolic (DBP) blood pressure, central venous pressure (CVP) and heart rate (HR).

Discussion

This study suggests that continuous high dose intravenous furosemide is a well-tolerated, safe and effective means to reduce volume overload in haemodynamically unstable infants after CPB surgery. We noticed that in our patients the urinary excretion of furosemide increased and serum creatinine concentrations gradually decreased over time. We infer that these changes are an indication of improving renal function. This seems also to be reflected in the need for lower doses of furosemide towards the end of the 3-days observation period, while the urinary output remained stable. Thus, our observations do not support the suggestion that tolerance against the furosemide effect may develop with prolonged diuretic exposure as suggested by Eades et al [9]. On the contrary, our data show that the diuretic effects expressed as

sodium excretion or as urine output increased shortly after initiation of the therapy until 24 hours and remained at least stable or even increased over the subsequent 48 hours. The reason why either repeated bolus or continuous administration of furosemide results in tolerance for the diuretic is unclear. It has been suggested that interference with the autonomic nervous system, the renin-angiotensin-aldosteron (RAA) system [13] or atrial natriuretic peptide [14;15] may play a role. However, the role of all these hormones has been shown to be minimal if present at all [13;15-17]. Therefore it has been suggested that the tolerance to furosemide can be induced through different but complementary homeostatic mechanisms in the kidney [16;18]. Whatever the mechanism underlies the development of tolerance, it is clear that dehydration plays a major role. This provides a possible explanation why tolerance was not observed in our patient population, because they were volume overloaded and certainly not dehydrated at any time during the continuous furosemide infusion. Our study supports observations that continuous IV furosemide results in a controlled diuresis [2-4]. We further observed that high dose continuous intravenous furosemide therapy for 3 days was effective to achieve a negative fluid balance, but it was not associated with cardiovascular instability. To the contrary, blood pressure increased while heart rate and CVP decreased over time. This is also supported by the remarkably low need for volume expanders.
Commonly occurring adverse events after high dose furosemide were not noted in our study population. The regimen was associated with improvement of the transient ARF that often occurs in infants after cardiac surgery with CPB. Thus it is unlikely that the high furosemide dose was associated with renal toxicity. In addition we found that the relatively high furosemide doses did not result in metabolic alkalosis in our patient population. However, it has to be noted that our patients were mechanically ventilated which may also have prevented the development of furosemide-induced metabolic alkalosis if it had occurred. Finally, despite the high furosemide doses, serum concentrations above 50 µg/ml, which are generally considered toxic [19], were not observed. In our study, therapeutic drug therapeutic drug monitoring for aminoglycosides was routinely performed and there was no indication that, at any time, toxic concentrations of these drugs were reached.
Although this may be an indication that screening for (oto) toxicity may be unnecessary in this population, caution is warranted when high dose furosemide is co-administered with other ototoxic drugs such as aminoglycosides.

In summary, there are no indications that tolerance develops towards the diuretic effect of furosemide in haemodynamically unstable infants with volume overload after cardiac surgery with CPB who are treated with a relatively aggressive diuretic regimen with furosemide. This strategy results in a negative fluid balance, while

cardiovascular stability is not compromised, presumably ototoxic concentrations are not observed and metabolic alkalosis does not occur.
The limitations of this study are that the study population was relatively small and that a study period of 72 hours was employed. However, in clinical practice an indication for continuous intravenous furosemide rarely exceeds 72 hours.
The current data suggest that the employed furosemide regimen can be used safely in haemodynamically unstable infants after cardiac surgery. However, in order to conclude that this approach with a high starting furosemide dose is superior to a regimen that employs a low starting furosemide dose has to be confirmed in a randomised controlled trial.

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Chapter 7

Evaluation of furosemide regimens in neonates treated with extracorporeal membrane oxygenation

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Critical Care 2006, 10:R168

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 on 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 hour. 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 = 0.2879). Although a positive effect of the 'loading' bolus was observed in urine output in the first 24 hours, there was no statistically significant difference in urine output (P = 0.0961) or in time (P = 0.1976) to reach a urine output of 6 ml/kg per hour between patients. After 24 hours, urine production remained a median of 6.2 ml/kg per hour irrespective of furosemide boluses. The forced diuresis was well tolerated as illustrated by stable haemodynamic parameters and a decrease in ECMO flow and vasopressor score over the observation period.
Conclusion: This is the first report on continuous intravenous furosemide therapy in newborns treated with ECMO. The 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 because 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, including 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 (CPB) circuit, triggers an important inflammatory reaction and is clinically associated with the so-called capillary leakage syndrome, resulting in intravascular hypovolaemia and renal hypoperfusion [2]. Hence, the ECMO patient usually becomes increasingly oedematous in the initial phase and diuretics are often used to enhance the diuresis to mobilise the fluid excess. Loop diuretics, generally given as an intravenous (IV) bolus, are the most frequently used diuretics in patients treated with ECMO [3]. Since the observation that continuous IV furosemide might be superior (especially in haemodynamically unstable patients) to intermittent administration in infants after cardiac surgery, the use of continuous furosemide infusion has been increasingly documented in patients after CPB surgery [4-8]. Although there are no data available evaluating the use of continuous IV furosemide in newborns during venoarterial (VA) ECMO, continuous furosemide infusion is used increasingly in our unit 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 a low furosemide infusion rate (0.05–0.1 mg/kg per hour) [3,9]. We retrospectively studied the use of continuous IV furosemide in neonates treated with VA ECMO over a two year period. In addition, neonates who did not receive continuous IV furosemide during VA ECMO were evaluated.

Materials and methods

The study was performed at the paediatric 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 two designated ECMO centres 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 furosemide, continuous and/or intermittent IV, 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 IV 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 (HR), mean

arterial blood pressure, and serum albumin, creatinine, and urea levels. Continuous IV furosemide was started at the time the patient was cardiovascularly stable. The patient was considered cardiovascularly 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 IV furosemide therapy, serum electrolyte levels (sodium, potassium, calcium, and magnesium) were closely monitored and supplements were given if necessary.

Statistical analysis

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

Results

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 IV furosemide during ECMO. Thirty-six patients were enrolled in the study. Five patients were excluded from analysis because they were treated with continuous veno-arterial haemofiltration (CAVH). Three patients were treated with CAVH 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 CAVH (trial). Thirty-one patients were analysed (Figure 1). The study population consisted of 12 female and 19 male patients.

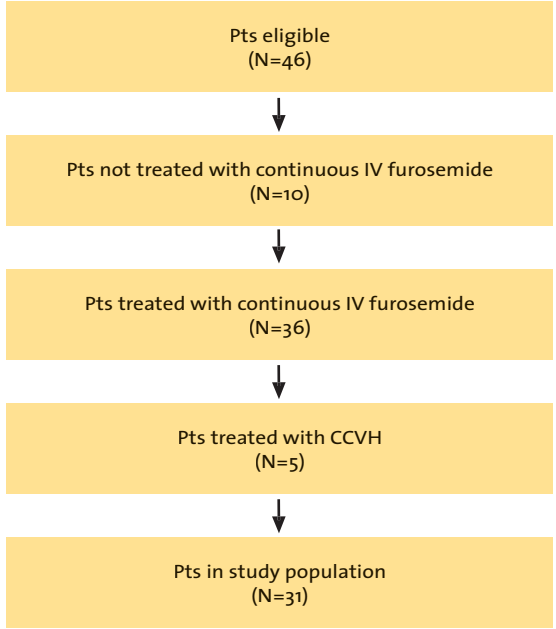

Fig 1. Flowchart of patient recruitment Flowchart of patient recruitment. CCVH, continuous venovenous haemofiltration; IV, intravenous; Pts, patients.

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 a median of 4 (0–46) hours after admission. All patients were weaned from ECMO after a median of 127 (44–339) hours. The median stay in the ICU was 11 (3–186) days. Due to recurrent and therapyresistant pulmonary hypertension, five patients with CDH died before discharge from the ICU.

Furosemide regimen

Prior to the start of continuous IV furosemide, seven patients received an IV furosemide bolus (dose 1 [0.4–2.4] mg/kg). Continuous IV furosemide therapy was started a median of 25 (9–149) hours after the start of ECMO at a median rate of 0.08 (0.02–0.17) mg/kg per hour. The continuous furosemide therapy in patients with CDH was started after a median of 33 (11–149) hours. The continuous furosemide dose in the patients who received a bolus prior to the infusion was 0.08 (0.04–0.13) mg/kg per hour; in the patients who did not receive a bolus, the dose was 0.08 (0.02–0.17) mg/kg per hour. The furosemide dose was not changed in the individual patient during the study period. The administered continuous IV furosemide dose over the span of 24 hours was a median of 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 administered continuous and intermittent IV furosemide doses on the first, second, and third days of the study were 1.92 (0.48–6.6), 1.92 (0.96–6.6), and 2.0 (0.5–6.6) mg/kg per 24 hours, respectively. The furosemide regimen is depicted in Table 1.
In 10 patients, continuous furosemide infusion was discontinued a median of 2 (0–144) hours before decannulation, 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 a median of 98 (21–294) hours, which is in accordance with a median of 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 per hour; in the patients (n = 24) who did not receive this furosemide bolus, it was 2.4 ml/kg per hour (P = 0.2879). Median urine production increased to 3.6, 5.7, and 6.4

ml/kg per hour, 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 per hour, respectively (P = 0.0961). The time that urine production of 6 ml/kg per hour was reached in the patients with and without a bolus prior to the continuous infusion was not significantly different (P = 0.1976). Median urine production remained 6.2 ml/kg per hour after 24 hours of continuous furosemide infusion in all patients irrespective of a bolus prior to the continuous furosemide infusion. Urine production is shown in Figure 2.
Fluid balances, calculated over eight hour intervals, were a median of +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 prior were +76.9, -21, 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, +28.2, and +12.0 ml, respectively.

Table I. Furosemide regimen

Furosemide	Before	0–24 hours	24–48 hours	48–72 hours
Furosemide bolus IV				
Patients (n)	7	4	2	1
Dose (mg/kg per 24 hours)	1.0 (0.4–2.4)	1.1 (1–3.6)	3.3 (1–3.6)	3.6
Bumetanide bolus IV				
Patients (n)			1	
Dose (mg/kg per 24 hours)			0.1	
Continuous IV furosemide				
Patients (n)		31	25	23
Dose (mg/kg per hour)		0.08 (0.02–0.17)	0.08 (0.02–0.17)	0.08 (0.02–0.17)
Total IV furosemide				
Patients (n)		31	25	23
Dose (mg/kg per 24 hours)		1.92 (0.96–6.6)	1.92 (0.48–6.6)	2.0 (0.5–6.6)

Data are presented as median (range). IV, intravenous.

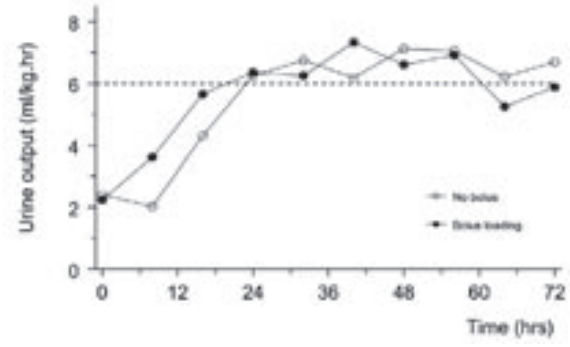

Fig 2. Median urine production over the observation period Median urine production over the observation period. The line with closed circles depicts the median urine production of the patients (n =7) who received a furosemide bolus prior to the continuous infusion. The line with open circles depicts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

ECMO regimen

The priming volume of the ECMO circuit was approximately 400 ml, the solution consisted of albumin and packed red blood cells, and the initial median ECMO flow was 130 (82– 185) ml/kg per minute, equalling 80% of the total cardiac output. Median ECMO flow values at the start of the continuous furosemide and after 8, 24, 48, and 72 hours of continuous furosemide were 87 (31–147), 86 (15–144), 76 (13–153), 50 (14–95), and 59 (14–90) ml/kg per minute, respectively. The ECMO flow in the CDH patients was not significantly different.

Cardiovascular effects

Median mean arterial pressure (MAP) and HR 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 MAP and HR after 8, 24, 48, and 72 hours of furosemide treatment were 52 (38–72) mm Hg 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 cardiovascularly stable during the administration of continuous IV furosemide and the inotropic support was gradually decreased during the observation period as illustrated by the vasopressor score. The number of patients requiring inotropic support during the study was decreased from 25/31 (81%) to 16/31 (52%). Median vasopressor scores at the start of ECMO and at the start of the continuous furosemide infusion were 11 (0–196) and 5 (0– 170), respectively. Median vasopressor

scores after 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 scores of the CDH patients at the start of ECMO, at the start of continuous furosemide infusion, and after 8, 24, 48, and 72 hours of continuous furosemide infusion were 33 (0–170), 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 the start of ECMO and at the start of continuous IV furosemide infusion were 55 (14–90) and 52 (14–90) µmol/l, respectively. Median serum creatinine levels after 24, 48, and 72 hours of continuous IV furosemide treatment were 50 (19–79), 49 (20–79), and 43 (22–66) µmol/l, respectively. Median serum urea levels at the start of ECMO and at the start of continuous IV furosemide were 3.1 (1–9.7) and 2.8 (1.3–6.5) mmol/l, respectively. After 24, 48, and 72 hours of furosemide infusion, median serum urea levels were 4.0 (1.5–23), 4.4 (1.5–8.6), and 5.4 (1.3–11.6) mmol/l, respectively. Median serum albumin levels at the start of ECMO and at the start of furosemide infusion were 16 (4–27) and 27 (16–36) g/l, respectively. During continuous IV furosemide treatment, median serum albumin levels were 27 (21– 36), 29 (16–41), and 30 (24–40) g/l after 24, 48, and 72 hours, respectively.

Patients who did not receive continuous IV furosemide during VA ECMO

General

Ten patients did not receive continuous IV furosemide during ECMO. Two patients were excluded from this evaluation because they were treated with CAVH. One patient was treated with CAVH 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 CAVH (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 a congenital cystic adenomatoid malformation of the lung. ECMO was started a median of 0 (0–198) hours after admission. Seven patients were weaned from ECMO after a median of 98 (8–275) hours. The median stay in the ICU was 6 (0–22) days. One patient with sepsis died on ECMO.

Furosemide regimen

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

Urine production and fluid balance

Median urine production values after 24, 48, and 72 hours on ECMO were 4.4, 5.4, and 5.6 ml/kg per hour, respectively. Median fluid balances after 24, 48, and 72 hours on ECMO were +173, +34, and +11.9 ml, respectively.

ECMO regimen

The priming volume of the ECMO circuit was approximately 400 ml, the solution consisted of albumin and packed red blood cells, and the initial median ECMO flow was 146 (111– 161) ml/kg per minute, equalling 80% of the total cardiac output. Median ECMO flow values after 24, 48, and 72 hours on ECMO were 135 (56–189), 116 (80–126), and 116 (80– 126) ml/kg minute, respectively.

Cardiovascular effects

Median MAP and HR 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, eight, five, four, and four patients, respectively, 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), 3 (0–40), 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. In contrast 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 steadystate 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 and that 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 IV furosemide might be superior (especially in haemodynamically 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 IV furosemide in paediatric 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 difference was observed in the main pharmacodynamic outcome parameter: urine production. However, significantly 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 also showed that there was no difference in urine production with continuous IV versus intermittent IV furosemide administration. However, the diuresis was more controlled with fewer haemodynamic 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 IV furosemide therapy was used in 78% of the neonates treated with ECMO. The dosing schedule of continuous IV furosemide in neonates treated with ECMO is largely empirical because of the variable renal function and altered PK [3,9]. This is supported by our observation that the continuous IV furosemide dose varied widely, from 0.02 to 0.17 mg/kg per hour, 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 IV furosemide therapy in infants treated with ECMO should be developed. Because 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 per hour in our institution. In all patients studied, the desirable urine output of approximately 6 ml/kg per hour was achieved within 24 hours of continuous IV furosemide infusion and remained at the desired level thereafter, but the furosemide regimens used in our study 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 IV furosemide at a median rate of 0.08 (0.02–0.17) mg/kg per hour, and 12 patients received additional loop diuretics prior to 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 after 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 urine output (Figure 2), but no statistically 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 per hour, which might be explained by the inter-individual variability and the difference in group size. In previous studies by our group on infants after CPB surgery, we suggested that continuous IV 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 [8,19].

The enhanced diuresis was well tolerated as illustrated by the stable haemodynamic 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 patients studied was within the normal range for age (that is, there were no signs of pre-renal failure before or during furosemide treatment). The observed increase in serum urea levels is most likely due the extremely 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 a median of 1.92 mg/kg per 24 hours in our study population. This dose is relatively low compared with the continuous IV furosemide dose used in infants and children

after CPB surgery [5-8]. In infants after CPB surgery, who received continuous IV 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 routine audiography data. Audiography is performed at the age of five years according to the nationwide standardised evaluation of ECMO patients in The Netherlands to evaluate hearing loss as a sign of furosemide toxicity (among other causes) [23].
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. Moreover, in the literature, no data are available on serum furosemide levels in newborns treated with ECMO [8]. Therefore, therapeutic drug-monitoring studies are now performed in our centre to prevent furosemide toxicity.
Unfortunately, we could not demonstrate the advantage of continuous IV furosemide over intermittent IV furosemide in our patients. Only eight patients who did not receive continuous IV furosemide were eligible for comparison. Urine production of these patients was a median of 4.4 ml/kg per hour after 24 hours on ECMO, approximately the median time that continuous IV furosemide was started in the study population. Because 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 IV furosemide in neonates treated with ECMO and it shows that continuous IV 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 statistically significant difference was observed after 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 furosemide regimens used in this study 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 IV furosemide is the preferred way of administration of furosemide in neonates treated with ECMO. Currently, a prospective study is being conducted in our unit to evaluate a continuous furosemide regimen, 0.2 mg/kg per hour, based on the PK/PD model developed for infants after CPB surgery for a predefined urine output of approximately 6 ml/kg per hour [19]. During the continuous furosemide infusion, serum furosemide levels are monitored at regular intervals to evaluate furosemide toxicity in newborns treated with ECMO.

Key messages

- Furosemide regimens in neonates treated with ECMO varied widely in continuous and intermittent doses.
- An advantage of continuous, over intermittent, IV furosemide could not be documented.

Table II. Furosemide trials

Furosemide	Singh [5] prospective RCT 24 hours (1992)	Luciano [6] prospective RCT 24 hours (1997)	Klinge [7] prospective RCT 72 hours (1997)				van der Vorst [8] prospective observational 72 hours (2001)		
Intermittent									
Patients (n)	12	15	23						
Continuous									
Patients (n)	8	11	23				12		
Intermittent									
Age	1.44 (± 1.4) years	3.7 (± 3.4) months	2.4 (± 2.1) years				13 (0–33) weeks[a]		
Continuous									
Age	2.3 (± 2.2) years	1.8 (± 2.5) months	3.4 (± 3.1) years						
Pvalue	NS	0.1	NS						
Study day			1		2	3	1	2	3
Intermittent dose mg/kg per 24 hours	6.23 (± 0.62)	6.8 (± 1.2)	1.6 (± 0.6)		0.9 (± 0.5)	1.0 (± 0.5)			
Continuous dose mg/kg per 24 hours							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 per hour)	3.53 (± 4.1)	3.3 (± 1.1)	3.1 (± 0.8)		2.9 (± 1.1)	2.9 (± 1.0)			
Continuous UO (ml/kg per hour)	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)[a]	5.8 (3.5–9.1)[a]	5.4 (3.6–7.4)[a]
P value	NS	0.05	NS		NS	NS			
Intermittent UO/variance	13.07 (±14.56) ml/kg per hour	3.8 (± 2.1)							
Intermittent UO/variance maximal			15.8 (± 3.7) ml/kg per hour						
Intermittent UO/variance minimal			0.3 (± 0.2) ml/kg per hour						
Continuous UO/variance	2.19 (± 1.92) ml/kg per hour	1.9 (± 1.6)							
Continuous UO/variance maximal			9.4 (± 4.1) ml/kg per hour						
Continuous UO/variance minimal			0.5 (± 0.3) ml/kg per hour						
P value	0.045	0.02	< 0.0001						

[a]Median (range). Data given as mean (standard deviation) unless indicated otherwise.
NS, not significant; RCT, randomised controlled trial; UO, urine output.

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Chapter 8

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

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Submitted for publication

Abstract

Objective: To explore a continuous intravenous furosemide regimen that adapts to urine output in infants treated with extracorporeal membrane oxygenation (ECMO).
Methods: Seven infants admitted to a paediatric surgical intensive care unit for ECMO therapy were treated with a furosemide regimen consisting of a loading bolus (1-2 mg/kg) followed by a continuous infusion at 0.2 mg/kg per hour which was adjusted according to the target urine production of 6 ml/kg per hour. Therapeutic drug monitoring for furosemide concentrations in blood was performed.
Results: Mean (± SD) furosemide dose was 0.17 (± 0.06), 0.08 (± 0.04) and 0.12 (± 0.07) mg/kg per hour respectively on the first, second and third day of the study. Median urine production over the consecutive study days was 6.8 (0.8 - 8.4), 6.0 (4.7 - 8.9) and 5.4 (3.4 – 10.1) ml/kg per hour. The target urine production was reached after a median time of 7 (3 - 37) hours. The regimen was haemodynamically well tolerated and furosemide serum concentration was median 3.1 (0.4 – 12.9) µg/ml, well below the toxic level.
Conclusion: The evaluated furosemide infusion appears to be an effective means to reduce volume overload in infants treated with ECMO. However, the data of this preliminary study suggest that the starting dose of furosemide was too high, because the urine output was excessive and required frequent adaptations. Therefore the results of this study indicate that a novel PK/PD model needs to be developed for infants treated with ECMO.

Introduction

Extracorporeal membrane oxygenation (ECMO) is used mainly in neonates to treat a variety of cardio-respiratory problems 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 hypovolaemia and renal hypoperfusion. [2] Consequently in the initial phase the ECMO patient becomes usually increasingly oedematous. Therefore diuretics, especially loop diuretics such as furosemide, are the mainstay in the enhancement of diuresis to mobilize fluid excess. Furosemide is often used as a continuous infusion in patients treated with ECMO, based upon the observations in infants after CPB surgery. [3-6]
Recently we made an inventory of furosemide regimens used in neonates treated with ECMO and concluded that continuous intravenous (IV) furosemide was frequently used, but the used regimens varied widely in continuous and additional intermittent doses. [7] Although with all regimens adequate urine output was achieved within 24 hours, the used furosemide regimens might not be the optimal regimen for infants treated with ECMO. In an accompanying editorial it was suggested that it would be preferable when more standardised and efficacious dosing regimens are developed. [8]
Since ECMO and CPB result in fluid overload, at least partially based on the same pathophysiology, it seems reasonable to assume that pharmacokinetic / pharmacodynamic (PK/PD) models developed for infants after cardiac surgery might also be applicable for infants treated with ECMO. [9]
Therefore we conducted a prospective exploratory study in infants treated with ECMO to evaluate a suggested furosemide regimen that was initially developed for infants after CPB surgery. The regimen consisted of a continuous furosemide infusion at a rate of 0.2 mg/kg per hour that was preceded by a loading bolus. The aim was to achieve a urine output of 6 ml/kg per hour. The main objectives of the study were to establish the efficacy of such a regimen and also to document serum furosemide concentrations to rule out oto-toxic levels.
Here we report upon the findings of the proposed furosemide regimen in infants treated with venoarterial (VA) ECMO in our unit.

Materials and methods

The study was performed at the paediatric surgical intensive care unit (ICU) of the Sophia Children's Hospital of Erasmus Medical Centre in Rotterdam, the Netherlands. The study protocol was approved by the Committee on Medical Ethics of the Erasmus Medical Centre and conducted according to the principles of the Declaration of Helsinki. Parental written informed consent was obtained for all patients.

Patients

Consecutive patients less than 1 year of age who were admitted to our unit for ECMO treatment were enrolled in the study. Continuous IV furosemide was started at the time the patient was in a cardiovascular stable condition. The patient was considered cardiovascular stable if there was no need for ongoing fluid resuscitation and/or increase in inotropic support. The amount of inotropic support was quantified by the vasopressor score. [10,11]
Demographic and clinical data were collected from the patient charts and from

the electronic patient data management system. This included: gestational and postpartum age, gender, weight, diagnosis, ECMO flow and duration of ECMO treatment, time continuous furosemide infusion was started, doses and duration of continuous IV 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 and mean arterial blood pressure. Serum albumin, creatinine and BUN levels, and arterial blood gas were determined at regular intervals during the observation period.
Blood samples for the determination of serum furosemide concentrations were taken at 10 minutes after the (loading) bolus dose, and additional samples were taken when possible. All patients had a urinary catheter as part of standard treatment according to the standard hospital ECMO protocol. The observation period for the study was 72 hours after the start of the continuous infusion. During continuous IV furosemide therapy serum electrolyte levels were closely monitored and supplements were given if necessary.

Furosemide regimen

The continuous furosemide infusion is started at a rate of 0.2 mg/kg per hour and is preceded by a loading bolus which dose depended on renal function. Patients with normal renal function received 1 mg/kg and patients with acute renal failure (ARF) received 2 mg/kg. ARF was defined on plasma creatinine levels and depended on gestational and post partum age. [12]
The aim was to reach and maintain a urine output of 6 ml/kg per hour. Adaptation of the infusion rate was allowed when at 2 consecutive hourly assessments the target urine was not reached. If the urine production was less than 4 ml/kg per hour the rate of infusion could be increased and if urine production was more than 8 ml/kg per hour the infusion rate could be decreased.

Sampling and assays

Routine blood samples were analyzed at the Clinical Chemistry Laboratory of the Erasmus MC. Furosemide concentrations were measured using a validated high performance liquid chromatography method routinely applied at the laboratory of Clinical Pharmacy and Toxicology of LUMC. [6] For determination in serum the coefficient of variation of the assay at 1µg/ml was 2%, and the reproducibility of the slope was 8.9%.

Data analysis

Data showing a skewed distribution are given as median and range while the normally distributed are presented as mean and standard deviation. The outcome evaluation included the median urine production over each 24 hour time interval and the time at which the target urine production was reached. The time to attain the target urine production was defined as the time point at which urine production was at least 6 ml/kg per hour for 2 consecutive hourly assessments.

Results

General

Continuous IV furosemide was evaluated in seven patients in whom VA ECMO was performed. The study population consisted of 6 female and 1 male patient. Median gestational age was 40 (26 - 41) weeks. On admission median postpartum age was 3 (0 - 136) days and median weight was 3.8 (3.0 - 5.0) kg. ECMO was performed for MAS in 3 patients, for respiratory insufficiency in 3 patients and for PPHN in 1 patient. ECMO was started median 2 (0 - 65) hours after admission. All patients were weaned from ECMO after median 109 (47 - 272) hours and discharged from the ICU after median 7 (4 - 33) days.

ECMO regimen

The priming volume of the ECMO circuit was approximately 400 ml and the solution consisted of albumin and packed red blood cells. The initial median ECMO flow was 101 (59-132) ml/kg per minute, equalling 80% of the total cardiac output. Median ECMO flow at the start of the continuous furosemide therapy, and after 8, 16, 24, 48 and 72 hours of continuous furosemide infusion were respectively 109 (59-139) ml/kg per minute, 102 (76-139) ml/kg per minute, 97 (67-167) ml/kg per minute, 125 (76-167) ml/kg per minute, 116 (52-153) ml/kg per minute and 82 (40-139) ml/kg per minute.

Furosemide regimen

Continuous furosemide infusion was started median 3 (0 - 22) hours after the start of ECMO at a rate of 0.2 mg/kg per hour and was preceded by a loading bolus of mean 1 (± 0.04) mg/kg. Mean (± SD) furosemide dose was 0.17 (± 0.06), 0.08 (± 0.04) and 0.12 (± 0.07) mg/kg per hour respectively over the first, second and third day of the study.

The dose needed to be decreased from the first to the second day in 5/7 patients, indicating that the starting dose was too high. No additional furosemide boluses were administered during the continuous furosemide infusion. The total administered furosemide dose was median 4.97 (2.70 – 7.02) mg/kg per 24 hours, 1.63 (0.75 – 4.31) mg/kg per 24 hours and 1.50 (0.09 – 6.3) mg/kg per 24 hours on the three consecutive study days. The total administered furosemide dose over 72 hours was median 7.0 (4.97 -14.21) mg/kg. The furosemide regimen is depicted in table 1.
The duration of the continuous furosemide infusion during ECMO was median 70 (19 - 276) hours, which is in accordance with median 75 (37 - 100) % of the ECMO time.
In six patients continuous furosemide infusion was discontinued median 23 (4 - 120) hours before and in one patient 4 hours after decannulation.

Table I. Furosemide regimen

Furosemide therapy time (hrs)	before	0-24 hrs	24-48 hrs	48-72 hrs	0-72 hrs
bolus IV furosemide patients (N)	7				
mean dose mg/kg	1 (± 0.04)				
continuous IV furosemide patients (N)		7	6	5	
mean dose (mg/kg.hr)		0.17 (± 0.06)	0.08 (± 0.04)	0.14 (± 0.09)	
total IV furosemide patients (N)		7	6	5	
median dose (mg/kg.24hrs)		4.97 (2.70-7.02)	1.24 (0-4.31)	1.60 (0.09-6.4)	
median dose (mg/kg.72hrs)					7.00 (4.97-14.3)

Data are presented as median (range) and as mean (SD); IV: intravenous

Furosemide serum concentrations

The furosemide concentration ten minutes after the loading bolus was median 1.95 (0.4 – 4.7) µg/ml and in the samples taken during the entire observation period median 3.1 (0.4 to 12.9) µg/ml.

Urine output and fluid balance

The overview of the median furosemide dose and urine production shows that the urine production first exceeds the target and is subsequently within the limits (figure 1). Urine production from the start of ECMO until the start of furosemide therapy was median 2.2 (0.7 – 9.6) ml/kg per hour and increased to 7.9 (0.3 -12.0) ml/kg per hour and 6.1 (0.2 – 9.2) ml/kg per hour after respectively 8 and 16 hours of continuous furosemide infusion. Median urine production over the consecutive study days was 6.8 (0.8 - 8.4), 6.0 (4.7 - 8.9) and 5.4 (3.4 – 10.1) ml/kg per hour. An overview of the median furosemide dose and urine production is depicted in table 2.
Over the entire study period median urine production was 6.7 (4.1-8.8) ml/kg per hour resulting in median cumulative urine production of 369 (168 – 524) ml/kg.
The target urine production was reached after a median time of 7 (3 - 37) hours. Thereafter the median urine production remained at the target level of 6.0 ml/kg per hour.
Median fluid balances in the first 24 hours, calculated over 8 hour intervals were respectively -50.9 ml, +63.1 ml and +82 ml. The median 24 hour balance over the three study days were respectively +3 (-267.9 - 624.1) ml, -4.6 (-202.0 - 397.3) ml and +45 (-430.0 - 283.0) ml.

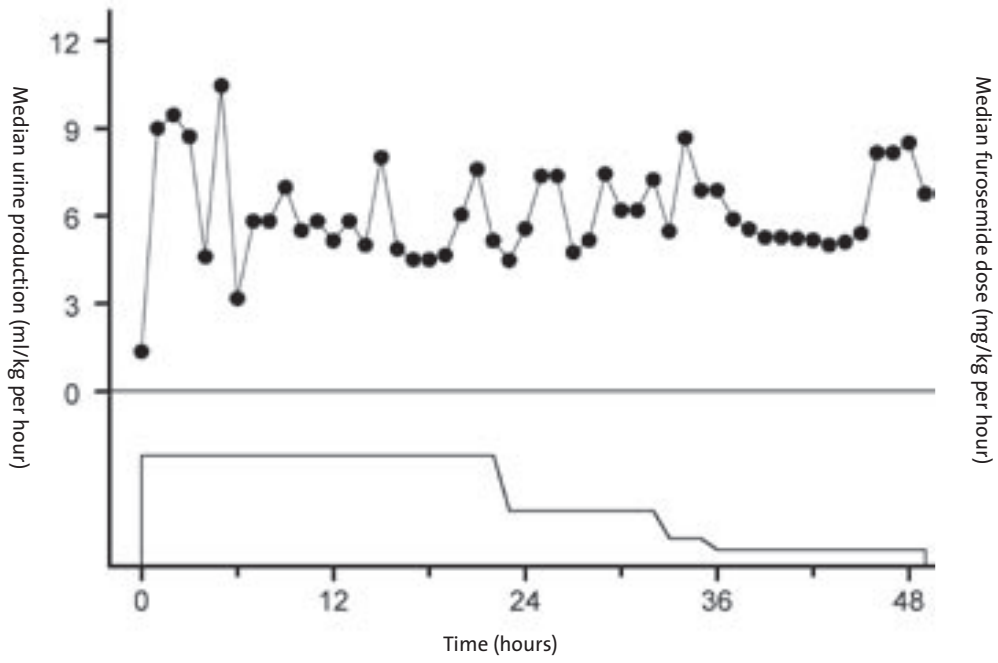

Fig 1. Median furosemide dose and urine production

Table II. Median furosemide dose and urine production

Furosemide therapy time (hrs)	Patients (n)	Median (range) furosemide dose (mg/kg per hour)	Median (range) urine production (ml/kg per hour)
0	7	0.20	2.2 (0.7 - 9.6)
8	7	0.20 (0.12-0.24)	7.9 (0.3 -12.0)
16	7	0.20 (0.05-0.30)	6.1 (0.2 - 9.2)
24	7	0.19 (0.04-0.21)	4.7 (2.0 - 9.4)
32	6	0.10 (0.00-0.16)	6.6 (0.6 - 9.2)
40	6	0.07 (0.02-0.10)	6.4 (2.4 - 8.7)
48	6	0.08 (0.03-0.19)	5.8 (4.3 - 8.0)
56	5	0.10 (0.03-0.30)	6.5 (3.4 -10.3)
64	4	0.08 (0.05-0.30)	3.9 (2.3 -10.9)
72	4	0.10 (0.05-0.23)	4.8 (3.3 - 7.9)

Cardiovascular effects

Median mean arterial pressure (MAP) and heart rate (HR) at the start of ECMO was 48 (37 - 64) mmHG and 156 (112-170) beats/minute and at the start of the furosemide treatment 51 (37 - 73) mmHG and 146 (131 - 170) beats/minute. Median MAP and HR were 49 (40 -107) mmHG and 161 (136 - 173) beats/minute, 52 (39 - 93) mmHG and 155 (135 - 175) beats/minute, 52 (46 - 68) mmHG and 162 (145 - 181) beats/minute, 51 (50 - 65) mmHG and 153 (134 - 185) beats/minute, and 47 (46 - 48) mmHG and 152 (117 - 155) beats/minute respectively after 8, 16, 24, 48 and 72 hours of furosemide treatment. All cardiovascular parameters were within the normal range for age. [13,14] All patients remained cardiovascular stable during the administration of continuous IV furosemide and the inotropic support was gradually decreased during the observation period. The number of patients requiring inotropic support was decreased during the study from 7/7 (100%) to 2/7 (29%). Median vasopressor score at start ECMO was 20 (5-130) and at the start of the continuous furosemide infusion 15 (0 - 110). Median vasopressor score was respectively 15 (0 - 90), 10 (0 - 90), 20 (0 - 55), 20 (0 - 42) and 5 (0 - 10) respectively after 8, 16, 24, 48 and 72 hours of continuous furosemide.

Renal function

Median serum creatinine levels at start ECMO and at start continuous IV furosemide infusion were respectively 35 (19-106) µmol/l and 30 (19 -106) µmol/l. Median serum creatinine levels after 24, 48 and 72 hours of continuous IV furosemide treatment were 41 (16 - 131) µmol/l, 44 (22 - 112) µmol/l and 23 (20 - 41) µmol/l respectively. Median serum BUN levels were 2.1 (1.1 - 3.8) mmol/l at start ECMO, and 2.2 (1.1 – 3.8) mmol/l at start continuous IV furosemide. After respectively 24, 48 and 72 hours of furosemide infusion median serum BUN levels were 3.7 (0.9 – 8.0) mmol/l, 6.0 (0.9 – 7.1) mmol/l and 2.1 (1.5 – 6.0) mmol/l. Median serum albumin levels at start ECMO and at start furosemide infusion were 24 (19 - 27) g/l and 26 (23 - 35) g/l. During continuous IV furosemide treatment median serum albumin levels were 28 (25 - 34) g/l, 28 (25 - 31) g/l and 29 (27 - 29) g/l after respectively 24, 48 and 72 hours.

Metabolic effects

Median pH at start ECMO and at start furosemide therapy were respectively 7.30 (6.97-7.47) and 7.40 (7.24 -7.47). Median pH after 24, 48 and 72 hours of continuous IV furosemide treatment were 7.42 (7.38 – 7.48), 7.47 (7.35 – 7.60) and 7.45 (7.36 – 7.67) respectively. Median (actual) serum bicarbonate levels at start ECMO and at start continuous IV furosemide infusion were respectively 22.2 (17.4 – 33.5) mmol/l and 24.2 (19 – 33.5) mmol/l. Median (actual) serum bicarbonate levels after 24, 48 and 72 hours of continuous IV furosemide treatment were 28.8 (23.4 – 35.2) mmol/l, 31.8 (23.8 – 35.1) mmol/l and 33 (26.3 – 36.5) mmol/l respectively. Metabolic alkalosis, defined as pH > 7.45 and (actual) serum bicarbonate > 29 mmol/l, was observed in two patients after 48 hours of continuous furosemide infusion.

Discussion

Since the observation that continuous IV furosemide might be superior to intermittent administrations in infants after CPB surgery, the use of continuous furosemide infusion has increasingly be documented in patients after CPB surgery. [3-6,15] Based upon the observations in infants after CPB surgery, the use of continuous IV furosemide in infants treated with ECMO is increasing.
Recently we evaluated furosemide regimens used in neonates treated with ECMO in our unit and concluded that continuous IV furosemide was frequently used in neonates (78%) treated with ECMO. [7] The used furosemide regimens varied widely, in continuous and in additional intermittent doses. Although, all used regimens

achieved adequate urine output within 24 hours, the use of additional furosemide bolus injections suggests that the used regimens might not be the optimal for infants treated with ECMO and therefore dosing regimens should be developed. [7] Since ECMO and CPB are 'comparable' procedures, the developed PK/PD model for infants after CPB surgery might also be applicable for infants treated with ECMO. [9] However, there are obvious differences between ECMO and CPB, in time of exposure to the procedure and hereby the presence of the 'circuit' with an ongoing inflammatory reaction, underlying illness and age of the patients. Therefore we conducted a prospective exploratory study in infants treated with ECMO to evaluate a suggested furosemide regimen developed for infants after CPB surgery.

The results suggest that the used regimen was effective and well tolerated in infants treated with ECMO.

The continuous IV furosemide was started in all patients at a rate of 0.2 mg/kg per hour and was preceded by a loading bolus of 1 mg/kg. The furosemide dose was adapted according to urine output. The dose was decreased from the first to the second day of the study, from 0.17 (± 0.06) mg/kg per hour to 0.08 (± 0.04) mg/kg per hour. The furosemide doses used in infants treated with ECMO, mean 0.17 (± 0.06), 0.08 (± 0.04) and 0.12 (± 0.07) mg/kg per hour were lower than the doses used in infants after CPB surgery, mean 0.22 (± 0.06), 0.25 (± 0.10) and 0.22 (± 0.11) mg/kg per hour respectively over the first, second and third day of furosemide therapy. [16]

The PK/PD model for diuretic therapy with furosemide in infants after CPB suggested that doses between 0.2 and 0.3 mg/kg per hour would result in a urine production of 6 ml/kg per hour. [9] Based upon our observational study which indicated that relatively low doses of continuous furosemide were used, we decided to use the lowest dose suggested by the model. The data of this study suggest that the starting dose was rather high, as indicated by the urine output exceeding the target urine output in the first 24 hours. Although a full understanding of this phenomenon is hard to reach, it seems logical to assume that contributing factors might be the ECMO circuit, the renal function and age of the patients. [17-23] The patients treated with ECMO were younger (median 3 days) than the patients after CPB surgery (median 12 weeks), and therefore by definition a less mature renal function which leads to a decreased renal clearance of furosemide.

The renal function (median creatinine 30 µmol/l) was normal for age in the ECMO patients whereas (transient) renal failure (median creatinine 95 µmol/l) was observed in the majority of the patients after CPB surgery. [12,16] Therefore it can be hypothesised that the acute renal failure observed in the patients after CPB surgery had a major impact on renal clearance which is most closely related with drug response, since furosemide is excreted renally and only acts after reaching the tubular lumen. [24-27] This might explain why higher doses were needed in the

patients after CPB surgery. In addition phase II reactions are better developed in infants and as a result the percentage of furosemide glucuronide will be higher. [23] Therefore it can be assumed that in the infants included in the cardiac surgery study less unchanged furosemide was available to interact with the furosemide receptor and consequently higher doses are needed to reach the same furosemide excretion rate. [25,26] This might clarify why higher doses were required in the patients after CPB surgery.

On the other hand the lower continuous furosemide doses after the loading bolus used in the ECMO patients might be explained by the effects of the ECMO circuit on furosemide PK. [17,18]

Specifically, the furosemide loading bolus seems to compensate for the increased volume of distribution, due to the addition of a large exogenous blood volume for priming of the circuit and the possible absorption of furosemide onto the ECMO circuit components. [18,28] Since the effects of furosemide are dependent on renal function, the apparent need for lower continuous furosemide dose might be explained, by the absence of impaired renal function and consequently increased renal clearance in the patients studied on ECMO compared to the patients post CPB surgery. [24]

Previously we noticed that in approximately 40% of the patients on ECMO therapy additional loop diuretics were needed during the continuous furosemide infusion. [7] In the present study no additional loop diuretics were needed, demonstrating that furosemide monotherapy is highly effective, which is a considerable advantage.

The total administered furosemide dose in the current study was substantial higher on the first day, median 4.97 mg/kg per 24 hours than the dose used in our retrospective study 1.92 mg/kg per 24 hours. On the second and third day the dose was slightly lower, 1.63 mg/kg per 24 hours and 1.50 mg/kg per 24 hours compared to 1.92 mg/kg per 24 hours and 2.0 mg/kg per 24 hours. [7] Importantly serum furosemide levels remained far below the commonly accepted safety level for ototoxicity (50 µg/ml). [29]

To obtain an acceptable fluid balance with a maintenance fluid of 120-140 ml/kg per 24 hours, the target urine production is set at 6 ml/kg per hour in our unit. In all patients studied, the target urine production of 6 ml/kg per hour was obtained in median 7 hours after the start of the continuous infusion. This is considerable faster than in our retrospective study in which the target urine production was reached in median 24 hours. The rapid attainment of the target urine may be explained by the initial higher infusion rate and loading bolus.

The observed variability in urine output was small (4.1 – 8.8 ml/kg per hour) throughout the entire observation period. Although it was striking that in one patient, despite administration of high dose of furosemide, urine output remained

low, if not negligible, for a period of approximately 33 hours. We could not identify an obvious cause for this. In our retrospective study in which the patients received additional intermittent furosemide bolus injections the variability in urine output was 0.7 – 16.1 ml/kg per hour during the study period. This is in accordance with studies in infants after CPB surgery were less variance in urine output was observed with continuous compared to intermittent furosemide administration. [3-5] This suggests that strict protocols for diuretic therapies reduce variability in patients' response. It is likely that a tailored PK/PD model for furosemide therapy in infants treated with ECMO may further optimise diuretic therapy for these critically ill infants.
The obtained fluid balances were approximately zero for all three study days, although with substantial variability. The forced diuresis was well tolerated as shown by the stable haemodynamic parameters and the reduction of the vasopressor score. A tendency to metabolic alkalosis was observed in two patients after approximately 48 hours of furosemide therapy. As contraction alkalosis was excluded based on the fluid balances, and also no signs of pre-renal failure or increased use of inotropic drugs was present in these two patients, we have no explanation for the observation. In the ongoing development and testing of a PK/PD model including more patients this aspect should be recognised.

In summary the evaluated furosemide regimen of 0.2 mg/kg per hour preceded by a loading of 1 mg/kg is an effective means to obtain rapid and sufficient diuresis without cardiovascular instability in infants treated with ECMO with a relatively low inter-patient variability in urine production. However, this exploratory study suggests that for infants on ECMO the proposed furosemide regimen as used in infants after CPB is using furosemide doses for the continuous infusion that are too high. Therefore a PK/PD model should be developed for infants on ECMO, identifying the factors, such as circuit age, renal function and albumin that influence drug disposition, during ECMO.

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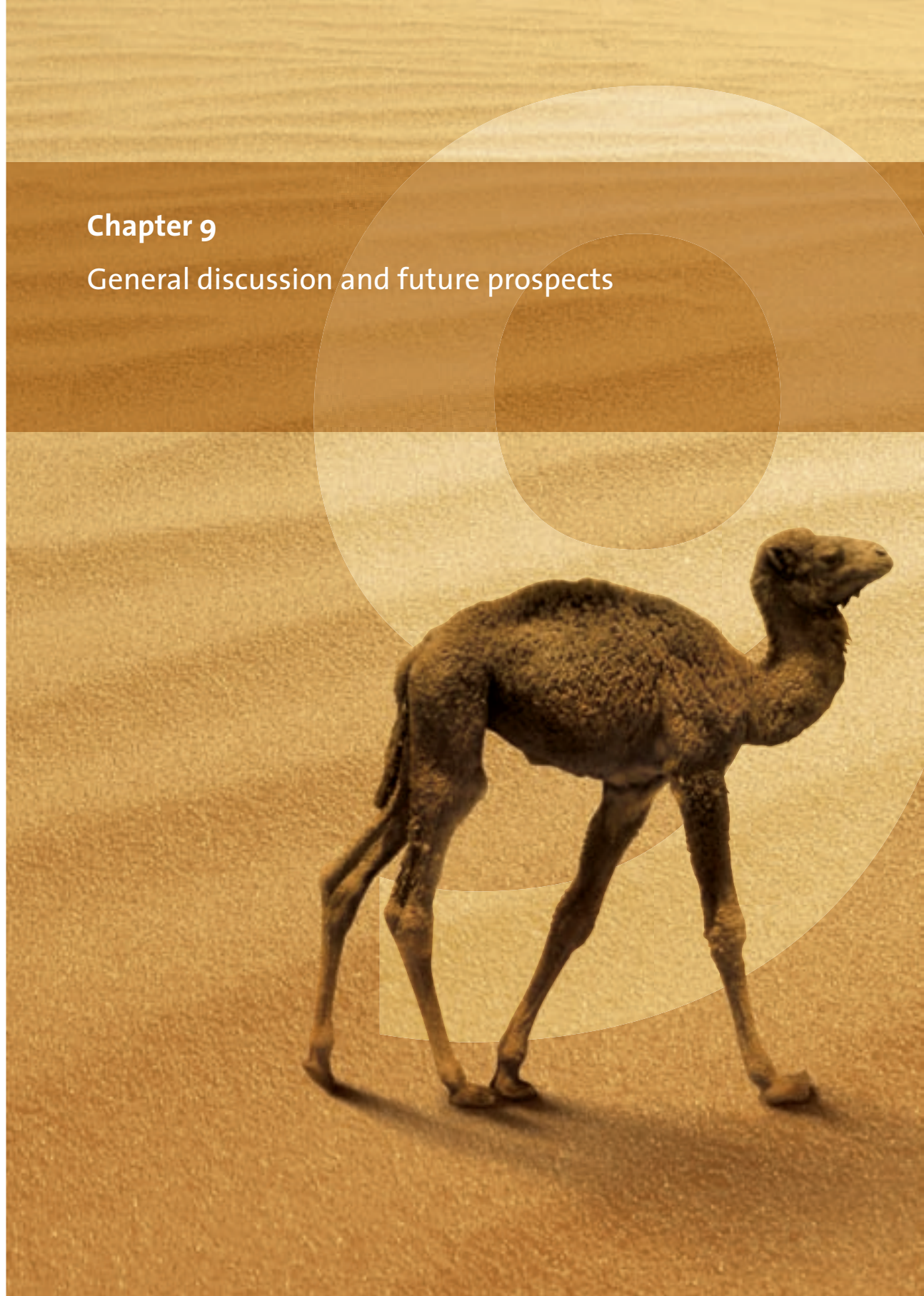
Chapter 9

General discussion and future prospects



General Discussion

Furosemide is the most frequently used diuretic in critically ill infants to augment urine output. With the observation that continuous intravenous (IV) furosemide might be superior to intermittent administration in infants after cardiopulmonary bypass (CPB) surgery, continuous furosemide infusions are increasingly used in patients after CPB surgery. [1-5] As extracorporeal membrane oxygenation (ECMO) and CPB are 'comparable' procedures the use of continuous IV furosemide in infants treated with ECMO is increasing. [6]
The currently used dosing schedules are largely empirical in infants after CPB surgery and during ECMO and might not be optimal.
Therefore the studies described in this thesis aimed to contribute to the development of safe and effective dosing regimen for continuous intravenous furosemide in critically ill infants after CPB surgery and infants treated with ECMO.
The studies performed in this thesis will be discussed.

The study to evaluate the pharmacokinetics (PK) and pharmacodynamic (PD) of continuous intravenous (IV) furosemide therapy in infants after cardiopulmonary bypass (CPB) surgery. (chapter 4)

Continuous IV furosemide therapy is an accepted way to reduce volume overload in infants after CPB surgery and has advantage over intermittent therapy. [7-10] However, current regimens which start with low dose and increase the dose depending on diuresis, may not be optimal in this group of patients with varying renal function.
Our study confirmed that the effects of furosemide on sodium excretion, and urine output increase with decreasing serum creatinine levels. Hence, the effects of furosemide are dependent on renal function. Since furosemide has to reach the tubular lumen to interact with the tubular receptor sites, renal clearance is most closely related to drug response. [11] Therefore it can be hypothesized that furosemide therapy may be more effective when continuous IV furosemide is started at a higher dose and titrated downward according to the observed urine production. Because the furosemide dose was increased to a maximum of 0.2 mg/kg per hour during the observational study, a starting dose of 0.2 mg/kg per hour seems to be optimal. From a safety point of view this dose also seems justified, as the observed serum furosemide levels in this study were approximately one-third of the commonly accepted safety level (50 µg/ml) for ototoxicity. [12]
The study identified the following clinically applicable measures: furosemide dose, furosemide serum concentration, renal function (creatinine clearance) and urine output that could be used to design a rational regimen for continuous IV furosemide in infants after CPB surgery.

Development of a PK/PD model to investigate alternative furosemide infusion regimens with a predefined urine production as the final outcome parameter (chapter 5)

By modeling the relationship between furosemide dose, furosemide serum concentrations, creatinine clearance, and urinary production, an adequate description could be obtained for the data collected in the observational study. We have to realize that in this model creatinine clearance has been used as surrogate for renal function. A linearly increasing creatinine clearance over time was assumed, although the creatinine clearance was calculated over 6 hour's interval. Various dosing regimens were simulated with the developed model for a predefined urine production of 4 ml/kg per hour. The simulated results suggested that adequate urine output could be obtained more rapidly with the currently used regimens. The predicted serum furosemide concentration for the proposed regimen by the model remained well below accepted safety level (50 µg/ml) for ototoxicity. [12]
The proposed furosemide regimen by the PK/PD model for a target urine production of 4 ml/kg per hour consisted of a loading bolus of 1-2 mg/kg followed by a continuous infusion at a rate 0.2 mg/kg per hour. Based on the observed urine production, adaptation of the dose in steps of 0.1 mg/kg per hour was allowed to a maximum of 0.4 mg/kg per hour.

The study to evaluate the efficacy and safety of the proposed furosemide regimen by the developed PK/PD model in infants after CPB surgery. (Chapter 6)

We may conclude that a furosemide regimen, starting at a rate of 0.2 mg/kg per hour is rational since adaptation of the furosemide doses was hardly needed. In addition the obtained urine production was satisfactory concerning volume, time to target urine production and deviation from the target urine.
The forced diuresis was well tolerated and produced negative fluid balances, albeit with substantial variability. The variability in the fluid balances can not fully be explained by the administration of additional volume and/or urine production. Therefore differences in drug delivery and effects might be responsible for the observed variability in the studied patients.
Disturbances in serum electrolytes and acid-base balance were not observed with this high dose furosemide regimen however, all the patients were mechanically ventilated which may have prevented the development of furosemide-induced

metabolic alkalosis.
As predicted by the PK/PD model serum furosemide concentration remained well below accepted safety level (50 µg/ml) for ototoxicity. [12]
Development of tolerance to furosemide, decreased natriuretic and diuretic response over time to the same amount of excreted furosemide in the urine, is frequently observed after prolonged furosemide administration. However tolerance was not observed in our study in infants after CPB surgery. Our data show that the diuretic effects expressed as sodium excretion or as urine output increased shortly after initiation of the furosemide therapy until 24 hours and remained at least stable or even increased over the subsequent 48 hours. The reason why either repeated intermittent bolus or continuous furosemide administration results in tolerance for the diuretic effect is not clear, although it is thought that the volume status plays an important role. [13-17]
The role of the volume status in the development of tolerance provides a possible explanation why tolerance was not observed in our patients after CPB surgery, because they had clear volume overload at start of the furosemide therapy and were certainly not 'dehydrated' at any time during the continuous furosemide infusion.
In summary, the current data support the efficacy and safety of the evaluated furosemide regimen for use in haemodynamically unstable infants after CPB surgery. Superiority of the high dose furosemide regimen could not be confirmed by historical comparison with the observational study for all parameters. However, important parameters indicative of a faster onset and more controlled urine production favoured the furosemide regimen starting at the higher rate (0.2 mg/kg per hour) in haemodynamically unstable infants after CPB surgery. To confirm the superiority of the furosemide regimen starting at a rate of 0.2 mg/kg per hour to the regimen starting at a rate of 0.1 mg/kg per hour, randomized controlled trials need to be performed.

The evaluation of furosemide regimens used in neonates treated with ECMO (Chapter 7)

Data that continuous furosemide therapy is more effective than intermittent furosemide therapy in patients treated with ECMO, like in patients after CPB surgery, are not available. [7-10]
Therefore we would have liked to compare continuous and intermittent furosemide therapy in neonates treated with ECMO. Unfortunately, the advantage of continuous IV furosemide therapy over intermittent furosemide therapy could not be demonstrated in our study, since only limited number of patients was available for comparison.

Our study showed that furosemide therapy was administered as continuous infusion in the vast majority of the neonates treated with ECMO. The dose of continuous IV furosemide therapy varied widely and in addition up to 40% of the patients received additional loop diuretics. With all regimens target urine production was reached within 24 hours and remained at the desired level thereafter. Patients were cardiovascularily stable, inotropic support was reduced and no adverse drug effects were observed during the furosemide therapy. However due to the retrospective nature of the study serum furosemide levels were not available to monitor furosemide toxicity.
Although with all regimens adequate urine output was achieved, the used furosemide regimens might not be the optimal regimen for infants treated with ECMO given the wide variety of doses used. Therefore it would be preferable when more standardized and efficacious dosing regimens are developed. It seems reasonable to assume that the PK/PD model developed for infants after CPB surgery might also be applicable for infants treated with ECMO, since the ECMO circuit, like the CPB circuit trigger an inflammatory reaction which is clinically associated with capillary leakage syndrome. [6]

The study to evaluate the efficacy and safety of the proposed furosemide regimen by the developed PK/PD model for infants after CPB surgery in neonates treated with ECMO. (chapter 8)

To obtain the desired urine output of 6 ml/kg per hour the PK/PD model developed for infants after CPB surgery suggested to start with an furosemide infusion rate between 0.2 and 0.3 mg/kg per hour. Based upon the relatively low doses of continuous furosemide doses (mean 0.08 mg/kg hour) used in the retrospective study, we decided to use the lowest dose suggested by the model.
The evaluated regimen consisted of a continuous furosemide infusion at a rate of 0.2 mg/kg per hour that was preceded by a loading bolus. The infusion rate was adjusted according to the observed urine output.
The furosemide dose had to be decreased in the vast majority of the patients indicating that the starting dose of 0.2 mg/kg per hour was too high for infants treated with ECMO. Why furosemide doses required in infants on ECMO are substantially less than in infants after CPB is hard to understand. Contributing factors to this phenomenon might be age and renal function of the patients in addition to the ECMO circuit. [18-24] The patients treated with ECMO were younger (median 3 days) than the patients after CPB surgery (median 12 weeks), and therefore by definition a less mature renal function. The renal function in the ECMO patients (median creatinine 30 µmol/l) was normal for age whereas (transient) renal failure

(median creatinine 95 µmol/l) was observed in the majority of the patients after CPB surgery. [25]
Therefore it can be hypothesised that the acute renal failure observed in the patients after CPB surgery had a major impact on renal clearance which is most closely related to drug response, since furosemide only acts after reaching the tubular lumen. [11,26-28] This might explain why higher doses were needed in the patients after CPB surgery. In addition phase II reactions are better developed in older infants and as a result the percentage of furosemide glucuronide will be higher. [18-24] Therefore it can be assumed that less unchanged furosemide will be available to interact with the furosemide receptor and consequently higher doses are needed to reach the same furosemide excretion rate. [26,27] This might clarify why higher doses were required in the patients after CPB surgery. On the other hand the lower continuous furosemide doses after the loading bolus used in the ECMO patients might be explained by the effects of the ECMO circuit on furosemide PK. [18,19]
Specifically, the furosemide loading bolus seems to compensate for the increased volume of distribution, due to the addition of a large exogenous blood volume for priming of the circuit and the possible absorption of furosemide onto the ECMO circuit components. [19,29] Since the effects of furosemide are dependent on renal function, the apparent need for lower continuous furosemide dose might be explained, by the absence of impaired renal function and consequently increased renal clearance in the patients studied on ECMO compared to the patients post CPB surgery. [11]
The forced diuresis was haemodynamically well tolerated and disturbances in serum electrolytes were not recorded, however a tendency to metabolic alkalosis was observed after 48 hours of continuous infusion. There was no clear explanation for the metabolic alkalosis after exclusion of contraction alkalosis and pre-renal failure. Serum furosemide concentration remained well below accepted safety level (50 µg/ml) for ototoxicity. [12]
The considerable faster attainment of the target urine production in the prospective study compared to the retrospective study may be explained by the loading bolus and the initially higher infusion rate. Differences observed in variance in urine output between the prospective and retrospective studies may suggest that strict protocols for diuretic therapies reduce variability in patients' response.
Our exploratory study suggests that the dose of the proposed furosemide regimen as used in infants after CPB is too high for infants treated with ECMO. Therefore a PK/PD model should be developed for infants on ECMO, recognizing the factors that influence drug disposition during ECMO.

Conclusion

- The evaluated furosemide regimens are safe and effective to augment urine production in critically ill infants after CPB surgery and infants treated with ECMO; however RCT's should be performed to find the optimal furosemide regimen.

- The PK/PD model developed for infants after CPB surgery should be used with caution in infants treated with ECMO since the suggested regimen might be too high. Therefore a novel PK/PD model should be developed for infants treated with ECMO, identifying the factors that influence drug disposition during ECMO.

- Furosemide serum concentrations remained well below toxic levels in the studies performed and therefore routine therapeutic drug monitoring (TDM) for toxicity might not be indicated. However when furosemide is used in infants with reduced renal excretion and/or in infants treated with prolonged administration of aminoglycosides or other ototoxic drugs, TDM should be considered.

- Development of tolerance to furosemide was not observed after prolonged furosemide administration in infants after CPB surgery. A possible explanation might be volume overload in infants after CPB.

Future prospects

Pharmacotherapy in critically ill infants
Furosemide is amongst the most frequently prescribed drugs, and is also part of the most frequently used unlicensed and/or off-label drugs in critically ill infants. [30,31] Furosemide is used off-label since no dose recommendation for furosemide administered as continuous infusion is available and no generally accepted indication for the continuous intravenous route based on (R)CT with adequate power. The off-label use of furosemide and other drugs in the different paediatric age groups are an undesirable situation and leads to adverse drug reactions. [32,33]
Therefore full and proper evaluation of furosemide is necessary and hopefully this will be stimulated by the implementation of the Paediatric Regulation in the European Union on 26 of January 2007 which aims to improve health of children of Europe.

Randomized controlled trials in critically ill infants
RCT's to compare different furosemide regimens should be performed to find the optimal furosemide therapy for infants after CPB surgery and for infants treated with ECMO.
The primary objective of the RCT's should be the attainment of adequate urine production without cardiovascular instability and other adverse effects. With the implementation of the Paediatric Regulation paediatric age categories are redefined based upon growth and development. As a result RCT's should be performed for the 'the newborn category (< 1 month) and the infants/ toddler category (1-23 months). The secondary objective of the RCT's should be reduction in mechanical ventilation time. Reduction in ventilation time will reduce the ventilation associated morbidity/ mortality and consequently ICU and hospital length of stay, and last but not least a reduction in costs. [34-38]

Development of furosemide regimens in critically ill infants
Furosemide therapy is frequently used in critically ill infants other than after CPB and on ECMO, to improve haemodynamics, facilitate weaning form mechanical ventilation and obtain an adequate urinary output. [39-43] Therefore the use of continuous furosemide regimens should be evaluated in this group of infants and if applicable furosemide regimens for continuous administration should be developed.

Individual variability in fluid balances in critically ill infants treated with continuous IV furosemide therapy
The obtained fluid balances in the critically infants studied in this thesis were

acceptable but showed substantial variability. Differences in the fluid balances cannot fully be explained by the administration of additional volume and/or urine production. Polymorphisms of renal drug transporters and of molecular targets of diuretics, as they may affect drug delivery to the site of action and drug effects should be considered responsible for this phenomenon, and therefore be the subject of further research. [44,45]

Alternative administration routes of furosemide in critically ill infants
Lung mechanics are often compromised in critically ill infants after CPB surgery. Decreased lung compliance and increased airway resistance due to increased total body, including lung water content are considered to be responsible for weaning difficulties in these patients. The management in post CPB surgery patients is focused on a negative total body water balance and therefore diuretics are administered. [46] It is reasonable to assume that selective reduction of lung water content could have a major impact on the weaning process. It has indeed been demonstrated that intra-tracheally applied furosemide in infants after CPB surgery improved static lung compliance. In addition a short and significant diuretic effect was observed. [47] Since the improvement in compliance was observed parallel with the highest increase in urine output it is not clear if intratracheally administered furosemide exerts its effect as a topical effect and/or systematic effect after rapid absorption into the pulmonary circulation. Since little is known about the effectively delivered amount of furosemide with the various application devices research should focus first on the effectively delivered amount of furosemide in order to perform PK/PD studies.

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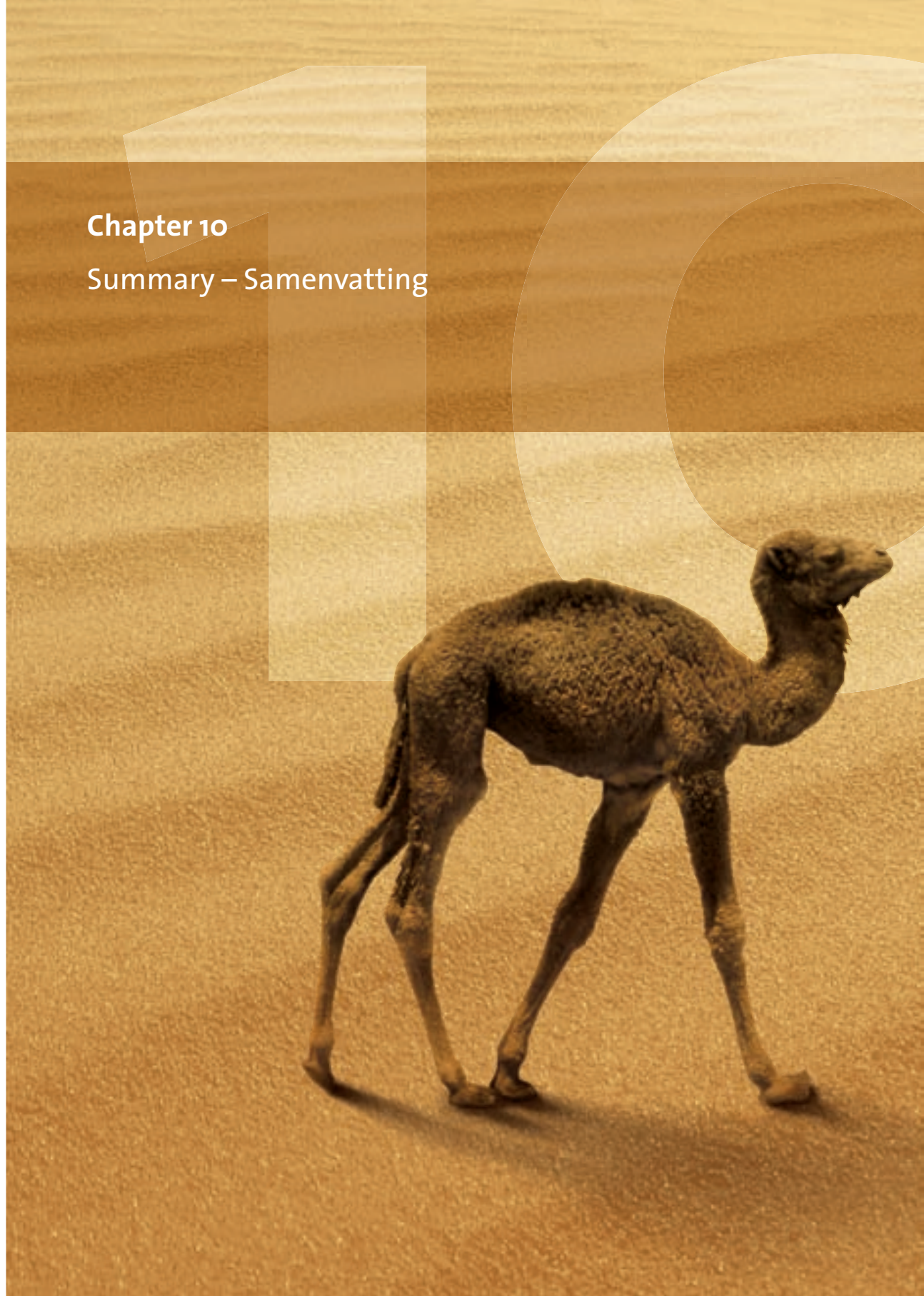
Chapter 10

Summary – Samenvatting



Summary

The aim of this thesis is to contribute to the development of safe and effective regimens for continuous intravenous furosemide in critically ill infants after cardiopulmonary bypass surgery and infants treated with extracorporeal membrane oxygenation.

Chapter 1 gives a general introduction to the loop diuretic, furosemide.
The principal site of action of furosemide is the thick ascending limb of the loop of Henle, with a minor additional inhibitory effect on sodium reabsorption in the proximal tubule attributable to its sulfonamide structure.
Furosemide blocks the site of chloride in the Na^+-K^+- $2Cl^-$ -membrane carrier in the thick ascending limb of the loop of Henle, and consequently reabsorption of sodium and chloride is diminished. In addition decreased potassium secretion and chloride reabsorption will impede tubular cell polarization, and as a result paracellular reabsorption of sodium, calcium and magnesium is abolished. (Figure 2 – chapter 1) Increased sodium delivery to the distal and collecting tubules results in compensatory increased sodium reabsorption and potassium secretion via the Na^+/K^+ countertransport system and hydrogen excretion is stimulated by the K^+/H^+ countertransport system.
Renal clearance is most closely related with drug response since furosemide has to reach the tubular lumen, by glomerular filtration and/or proximal tubular secretion to interact with the tubular receptor sites. Therefore urinary sodium excretion and diuresis are more correlated with urinary furosemide excretion than with serum furosemide concentration.
The cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) circuit trigger an important inflammatory reaction which is clinically associated with a capillary leakage syndrome, resulting in intravascular hypovolaemia and renal hypoperfusion. Therefore (transient) renal insufficiency may occur and consequently influences furosemide delivery to the site of action. In addition, the ECMO circuit itself may induce changes in the volume of distribution and elimination time of furosemide.
The use of furosemide may lead to disturbances in serum electrolytes and acid-base balance. Furosemide can cause both temporary and permanent hearing loss. The development of ototoxicity depends on high serum furosemide concentration. Furosemide induced interstitial nephritis is most likely an allergic or hypersensitivity reaction and not a direct toxic effect.
The shortage in availability of licensed drugs in an appropriate formulation has lead to the use of unlicensed and/or off-label drugs in children, and consequently to adverse drug reactions. Furosemide is one of the most frequently used off-label drugs in critically ill infants.
Furosemide therapy as continuous infusion is used in infants after CPB surgery and infants treated with ECMO to treat pathological fluid retention. Dosing schedules used in this group of critically ill infants are largely empirical and might not be optimal.
In **Chapter 2** the current knowledge on pharmacology, pharmacokinetics (PK), pharmacodynamics (PD) and clinical application of the most commonly used diuretics in infants and children are reviewed.
The main indication of diuretics is to reduce fluid overload in acute and chronic disease states. All diuretics, except spironolactone have to reach the tubular lumen, by glomerular filtration and/or proximal tubular secretion, to exert their action. Therefore renal development and function influence drug delivery and consequently the PD of diuretics.
As with most drugs used in children, optimal dosing schedules are largely unknown and empirical. Therefore additional PK/PD studies for the different paediatric age groups are necessary to develop dosing regimens.
The retrospective study described in **chapter 3** investigated renal function and renal replacement therapy after CPB surgery. Serum creatinine concentration before, and peak values after, CPB surgery were used to assess the renal function. Acute renal insufficiency was observed in 17% of the patients and 2.3% of the patients' required renal replacement therapy (peritoneal dialysis). The incidence of acute renal insufficiency is often related to the complexity of the operation. In conclusion acute renal insufficiency is a frequent complication after CPB surgery however renal replacement therapy is seldom necessary.
In **Chapter 4** an observational study evaluating PK/PD of continuous intravenous (IV) furosemide in haemodynamically unstable infants after CPB surgery is described. The currently used furosemide regimens for continuous IV furosemide administration are largely empirical in infants after CPB surgery and may not be optimal.
The study confirmed that sodium excretion, hence urine output, increases with decreasing serum creatinine concentrations. It can therefore be hypothesized that, contrary to the currently used regimens in which furosemide is gradually increased over time, it may be more effective to start with higher doses, and adapt these doses (downwards) guided by the urine production. A starting dose of 0.2 mg/kg per hour was suggested.
The development of a PK/PD model to simulate various furosemide regimens that adapt according to urine output is described in **chapter 5**. The PK/PD model describes the relation between furosemide dose, furosemide serum concentrations, and urinary furosemide excretion leading to urine output. Various dosing regimens were

simulated with the model for a predefined urine production of 4 ml/kg per hour.
The simulation results suggested that a combination of a 1 - 2 mg/kg loading bolus followed by an infusion rate at 0.2 mg/kg per hour leads to rapid and adequate urine production.
The suggested furosemide regimen was evaluated in a prospective study in haemodynamically unstable infants after CPB surgery and is described in **Chapter 6**.
The furosemide doses (0.2 mg/kg per hour) needed hardly to be adapted within each day. The obtained urine production was satisfactory concerning volume, time target urine production was obtained and deviation from target urine production.
The forced diuresis was well tolerated and produced negative fluid balances.
Development of tolerance to furosemide was not observed and serum furosemide levels were well below the toxic level.
In summary, the results suggest that a high-dose continuous IV furosemide is an effective means to reduce volume overload in haemodynamically unstable infants after CPB surgery.
In **chapter 7** the retrospective study evaluating currently used furosemide regimens in neonates treated with ECMO are discussed.
With the observations in infants after CPB surgery, and as ECMO and CPB are 'comparable' procedures the use of continuous IV furosemide in infants treated with ECMO is increasing. The advantage of continuous IV furosemide over intermittent furosemide therapy could not be demonstrated in this retrospective study.
Continuous IV furosemide regimens were frequently used and varied widely and on top additional loop diuretics were often administered prior or during the continuous infusion. Although, the target urine output (6 ml/kg per hour) was attained within 24 hours and remained at the target level throughout the study, the use of additional loop diuretics suggests that the applied infusion rates were not optimal. Therefore dosing regimens should be developed. It was suggested that the developed PK/PD model for infants after CPB surgery might also be applicable for patients treated with ECMO.
In **chapter 8** a prospective study exploring an adaptive continuous IV furosemide regimen in infants treated with ECMO is described. The regimen consisted of a loading bolus 1-2 mg/kg followed by a continuous infusion starting at 0.2 mg/kg per hour.
The dose needed to be decreased from the first to the second day in the majority of the patients, indicating that this furosemide dose was too high for infants treated with ECMO. The time to target urine production (6 ml/kg per hour) and the urine production achieved was satisfactory over the entire observation period.
The furosemide doses required in infants on ECMO are substantially lower than in infants after CPB surgery. Contributing factors might be the ECMO circuit, the age and renal function of the patients.
The forced diuresis was well tolerated and produced acceptable fluid balances. Toxic serum furosemide levels were not observed. The observed variance in urine output was small, 4.1 – 8.8 ml/kg per hour which suggests that strict protocols for diuretic therapies reduce variability in patients' response.
In summary, the results of the study suggest that the dose of proposed furosemide regimen is too high for infants on ECMO and therefore a PK/PD model should be developed, identifying the factors that influence drug disposition during ECMO.
In **chapter 9** the studies performed to contribute to the development of safe and effective furosemide regimens are discussed and suggestions are given for future research.
The observational study evaluating the PK/PD of continuous IV furosemide in haemodynamically unstable infants after CPB surgery confirmed that the effects of furosemide are dependent on renal function. (Chapter 4) Therefore it was hypothesized that furosemide therapy may be more effective when continuous IV furosemide is started at a higher dose and adapt the dose (downward) according to the observed urine production.
Based upon the maximum dose used and the observed serum furosemide levels a dose of 0.2 mg/kg per hour seems to be rational.
A population PK/PD model was developed that linked furosemide dose to serum furosemide concentration, renal function (creatinine clearance) and urine output. In this model creatinine clearance has been used as surrogate for renal function and a linearly increasing creatinine clearance over time was assumed. Various regimens were simulated with the model. (Chapter 5)
The suggested furosemide regimen, starting dose of 0.2 mg/kg per hour, by the PK/PD model was evaluated in haemodynamically unstable infants after CPB surgery. (Chapter 6)
The furosemide regimen seems rational since adaptation of the furosemide doses was hardly needed. In addition the obtained urine production was satisfactory concerning volume, time to target urine production and deviation from the target urine.
The variability in the observed fluid balances might be due to differences in drug delivery and effects.
The maximum serum furosemide concentration (28.5 µg/ml) remained well below the accepted safety level (50 µg/ml) for ototoxicity as predicted by the observational study and PK/PD model.
The volume overload of the patients after CPB surgery is a possible explanation that development of tolerance to furosemide was not observed. Superiority of the high dose furosemide regimen could not be confirmed over a low dose furosemide regimen. However, important parameters indicative of a faster onset and more controlled urine production favoured the furosemide regimen starting at the higher rate.
In a retrospective study furosemide regimens were evaluated in neonates treated

with ECMO. (Chapter 7) The advantage of continuous IV furosemide therapy over intermittent furosemide therapy could not be demonstrated, since only limited number of patients was available for comparison. The dose of continuous IV furosemide therapy varied widely and additional loop diuretics were frequently administered what suggest that the used regimens might not be the optimal. It seems reasonable to assume that the PK/PD model developed for infants after CPB surgery might also be applicable for infants treated with ECMO.
A prospective study in infants treated with ECMO was conducted to explore a suggested furosemide regimen by a PK/PD model. (Chapter 8) To obtain a urine output of 6 ml/kg per hour the PK/PD model developed for infants after CPB surgery suggested to start with a furosemide dose between 0.2 and 0.3 mg/kg per hour. Based upon the retrospective study the lowest dose suggested by the model was evaluated.
The furosemide dose had to be decreased in the majority of the patients indicating that the starting dose of 0.2 mg/kg per hour was still too high for infants treated with ECMO. The age and renal function of the patients, in addition to the ECMO circuit might be responsible for the fact that the furosemide doses required in infants on ECMO are substantial less than in infants after CPB. The maximum serum furosemide concentration observed in patients on ECMO was 12.9 µg/ml what is far below the accepted safety level (50 µg/ml).
The forced diuresis was haemodynamically well tolerated and toxic furosemide serum levels were not reached,however a tendency to metabolic alkalosis was observed after 48 hours which could not be explained after excluding contraction alkalosis and pre-renal failure.
Differences observed in variance in urine output between the prospective and retrospective studies may suggest that strict protocols for diuretic therapies reduce variability in patients' response. The results of the prospective study suggest that the proposed furosemide dose is too high and therefore a PK/PD model should be developed for infants on ECMO, identifying the factors that influence drug disposition during ECMO.

Conclusion

- The evaluated continuous IV furosemide regimens are safe and effective to augment urine production in critically ill infants after CPB surgery and infants treated with ECMO; however RCT's should be performed to find the optimal furosemide regimen.

- The PK/PD model developed for infants after CPB surgery should be used with caution in infants treated with ECMO since the furosemide dose suggested regimen might be too high. Therefore a novel PK/PD model should be developed for infants treated with ECMO, identifying the factors that influence drug disposition during ECMO.

- Furosemide serum concentrations remained well below the toxic levels in the studies performed and therefore routine therapeutic drug monitoring (TDM) for toxicity might not be indicated.

- After prolonged furosemide administration development of tolerance to furosemide was not observed in infants after CPB surgery. A possible explanation might be the volume overload observed in infants after CPB.

Future prospects

Pharmacotherapy in critically ill infants: The off-label use of furosemide in critically ill infants is an undesirable situation and leads to adverse drug reactions and therefore full and proper evaluation of furosemide is necessary.

Randomized controlled trials in critically ill infants: RCT's to compare different furosemide regimens should be performed. The primary objective of the RCT's is to obtain an adequate urine production without cardiovascular instability and other adverse effects. The secondary objective of the RCT's should be the reduction in mechanical ventilation time.

Development of furosemide regimens in critically ill infants: Furosemide regimens should be evaluated in critically ill infants other than infants after CPB and infants treated with ECMO and if applicable furosemide regimens should be developed.

Inter-individual variability in fluid balances in critically ill infants: The fluid balances obtained in critically infants studied after CPB and on ECMO were acceptable but

showed substantial variability. Polymorphisms of renal drug transporters and of molecular targets of diuretics, should be considered responsible for this phenomenon, and be subject of research.

Alternative administration routes of furosemide in critically ill infants: The effects observed in pulmonary mechanics after intratracheally applied furosemide are promising. However research should focus first on the effectively delivered amount of drug with the various application devices in order to study the PK/PD parameters.

Samenvatting

Het doel van dit proefschrift is om een bijdrage te leveren aan de ontwikkeling van veilige en effectieve toedieningsschema's voor continue intraveneuze furosemide bij ernstige zieke zuigelingen na open hartchirurgie en tijdens extracorporele membraanoxygenatie.

In **hoofdstuk 1** wordt het loop diureticum, furosemide beschreven. Het belangrijkste aangrijpingspunt van furosemide ligt in de opstijgende lis van Henle, een tweede aangrijpingspunt, ten gevolge van de sulfonamide stuctuur van furosemide, ligt in de proximale tubulus. Furosemide bezet de chloride plaats in het Na^+-K^+-$2Cl^-$ -cotransport systeem in de opstijgende lis van Henle en remt daarmee de terugresorptie van natrium en chloor. Polarisatie van de tubulus cel zal niet ontstaan door de verminderde kalium secretie en chloor terugresorptie met als gevolg dat er geen paracelulaire terugresorptie van natrium, calcium en magnesium zal plaatsvinden (figure 2 - hoofdstuk1). Het toegenomen aanbod van natrium aan de distale tubuli en verzamelbuizen resulteert in een compensatoire verhoogde natrium resorptie en kalium secretie via het Na^+/K^+ countertransport systeem, daarnaast wordt de waterstof uitscheiding gestimuleerd door het K^+/H^+ countertransport systeem. Het furosemide effect is zeer nauw gerelateerd aan de renale klaring omdat furosemide eerst het tubulus lumen moet bereiken, via glomerulaire filtratie en/of proximale tubulaire secretie, om een interactie aan te gaan met de tubulaire receptoren. Dit verklaart dat de natrium excretie in de urine, en de urine productie, sterker gerelateerd is aan de furosemide excretie in de urine dan aan de plasma furosemide concentratie.
Het circuit van de hart-long machine en van de extracorporele membraanoxygenatie (ECMO) initieert een belangrijke ontstekingsreactie die klinisch is geassocieerd met een capillair lek syndroom, wat resulteert in intravasculaire ondervulling en verminderde doorstroming van de nier. Hierdoor kan (tijdelijke) nierinsufficientie ontstaan, met als gevolg een verminderde aanvoer van furosemide naar het tubulus lumen. Bovendien beinvloedt het ECMO circuit het verdelingsvolume en de eliminatietijd van furosemide.
Het gebruik van furosemide kan verstoringen in de electrolieten en het zuur-base evenwicht geven. Furosemide kan leiden tot zowel tijdelijk als permanent gehoorverlies. De ontwikkeling van gehoorschade is afhankelijk van de hoogte van de plasma furosemide concentratie. De door furosemide geinduceerde interstitiële nephritis is zeer waarschijnlijk eerder een allergische of overgevoeligheidsreactie dan een direct toxich effect.
Het tekort aan geregistreerde geneesmiddelen voor kinderen heeft geleid tot het unlicensed en off-label gebruik bij kinderen, en daarmee tot bijwerkingen.

Furosemide is een van de meeste off-label gebruikte geneesmiddelen die aan ernstig zieke zuigelingen worden toegediend. Furosemide, als continu-infuus wordt gebruikt bij zuigelingen na open hartchirurgie en tijdens ECMO behandeling om overtollig vocht af te drijven.
In **hoofdstuk 2** wordt de huidige kennis van de farmacologie, farmacokinetiek (PK) en farmacodynamiek (PD), alsmede wordt de klinische toepassing van de meest gebruikte diuretica bij zuigelingen en kinderen beschreven. De voornaamste indicatie voor diuretica is het verminderen van volume overbelasting bij acute en chronische ziektes. Alle diuretica, uitgezonderd spironolactone moeten het tubulus lumen bereiken, via glomerulaire filtratie en/of proximale tubulaire secretie om te kunnen werken. Dit verklaart dat de ontwikkeling en funktie van de nier van invloed zijn op de PK van diuretica en daardoor op het effekt.
Zoals met de meeste geneesmiddelen bij kinderen, zijn optimale doseringen van diuretica over het algemeen niet bekend en empirisch. Daarom is het noodzakelijk dat aanvullende PK/PD studies worden verricht in de verschillende leeftijdsklassen om doseringsschema's te ontwikkelen.
De retrospectieve studie, die in **hoofdstuk 3** wordt beschreven onderzocht de nier-functie en nierfunctie vervangende behandeling na open hartchirurgie bij kinderen. De plasma kreatinine concentratie vóór en de maximale concentraties ná open hartchirurgie werden gebruikt om de nierfunktie te beoordelen. Acute nierinsufficientie werd gezien bij 17% van de kinderen en bij 2.3 % van de kinderen was nierfunctie vervangende behandeling noodzakelijk (peritoneaal dialyse). De incidentie van acute nierinsufficientie is vaak gerelateerd aan de complexiteit van de operatie. Deze studie toonde aan dat acute nierinsufficientie een vaak voorkomende complicatie is na open hartchirurgie, maar dat nierfunctie vervangende behandeling slechts zelden nodig is.
In **hoofdstuk 4** wordt een observationele studie beschreven, die de PK/PD van continue intraveneuze (IV) furosemide bij hemodynamisch instabiele zuigelingen na open hartchirurgie evalueert. Deze studie bevestigde dat de natrium uitscheiding, en dus de urine productie, toeneemt met het dalen van de plasma kreatinine waarde. Daarom kan men stellen, in tegenstelling tot de huidige gebruikte doseringsschema's waarin de furosemide dosis geleidelijk wordt opgehoogd in de tijd, dat het starten met een hogere aanvangsdosering en deze aan te passen (naar beneden) op geleide van de urine productie misschien effektiever is. Een aanvangsdosering van 0.2 mg/kg per uur werd gesuggereerd.
In **hoofdstuk 5** wordt de ontwikkeling van een PK/PD model beschreven dat verschillende furosemide doseerschema's kan simuleren, die zich aanpassen aan de urine productie. Het PK/PD model beschrijft de relatie tussen de furosemide dosis, de furosemide plasma concentratie en de furosemide excretie in de urine leidend tot urine productie. Met het PK/PD model werden verschillende doseerschema's gesimuleerd met een vooraf gedefineerde urine productie van 4 ml/kg per uur. Op basis van de simulaties werd, voor een snelle en goede urine productie een doseerschema opgebouwd uit een oplaaddosis van 1-2 mg/kg gevolgd door een continue infusie van 0.2 mg/kg per uur, voorgesteld.
Het voorgestelde furosemide doseerschema werd geëvalueerd in een prospectieve studie in hemodynamisch instabiele zuigelingen na open hartchirurgie en is beschreven in **hoofdstuk 6**. Het aanpassen van de furosemide dosering (0.2 mg/kg per uur) was nagenoeg niet nodig. De urine productie was goed ten aanzien van het volume en de tijd dat de gewenste urine productie van 4 ml/kg per uur werd gehaald. De geforceerde diuresis werd goed verdragen en resulteerde in negatieve vochtbalansen. De ontwikkeling van tolerantie voor furosemide werd niet waargenomen en de plasma furosemide concentraties bleven ver onder de toxiche grens. De resultaten van deze studie suggereren dat een hoge dosis van continue IV furosemide een effektieve manier is om volume overbelasting in hemodynamisch instabiele zuigelingen na open hartchirurgie te bestrijden.
In **hoofdstuk 7** wordt een retropectieve studie beschreven, die de furosemide therapie bij neonaten tijdens ECMO behandeling evalueerd. Sinds de bevindingen met continue IV furosemide therapie bij zuigelingen na open hartchirurgie en het feit dat de hart-longmachine en ECMO vergelijkbare procedures zijn, is ook het gebuik van continue furosemide infuzen bij zuigelingen tijdens ECMO behandeling toegenomen. Het voordeel van continue versus intermitterende furosemide toediening kon in de retrospective studie niet worden aangetoond. De furosemide doses van continue infuzen varieerden sterk en tevens werden extra (bolus) loop diuretica toegediend, dit impliceert dat de gebruikte doseringen niet optimaal waren. Daarom zullen toedieningsschema's moeten worden ontwikkeld. Het werd gesuggereerd dat het ontwikkelde PK/PD model voor zuigelingen na open hartchirurgie ook van toepassing zou kunnen zijn bij patiënten behandeld met ECMO.
In **hoofdstuk 8** wordt een prospectieve studie beschreven die de effekten van een adaptief continu furosemide doseerschema bij zuigelingen tijdens ECMO behandeling onderzocht. Het doseerschema bestond uit een oplaaddosis gevolgd door een infuus met een aanvangsdosis van 0.2 mg/kg per uur. Bij het merendeel van de patiënten moest de dosis verminderd worden van de eerste naar de tweede dag, wijzend op het feit dat deze furosemide dosis voor zuigelingen behandeld met ECMO te hoog was. De tijd om een urine productie van 6 ml/kg per uur te behalen en de urine productie over de gehele observatie periode waren acceptabel. De furosemide doses in zuigelingen tijdens ECMO waren substantieel lager dan in zuigelingen na open hartchirurgie. Faktoren, die hierbij een rol spelen zijn waarschijnlijk het ECMO circuit, de leeftijd en de nierfunctie van de patiënten. De geforceerde diurese werd goed verdragen en bereikte acceptabele vochtbalansen. Toxische plasma furosemide

waarden werden niet waargenomen. De variabiliteit in de urine productie was gering, 4.1 – 8.8 ml/kg per uur wat suggereert dat strakke richtlijnen voor diuretica behandelingen tot minder variabilteit in de urine productie leiden.
De resultaten van deze studie suggeren dat de furosemide dosis van het voorgestelde doseerschema te hoog was voor zuigelingen tijdens ECMO behandeling. Daarom zal een nieuw PK/PD model ontwikkeld moeten worden, die de faktoren die de geneesmiddelen dispositie beinvloeden gedurende ECMO behandeling identificeert.
In **hoofdstuk 9** worden de studies die uitgevoerd zijn om een bijdrage te leveren aan de ontwikkeling van veilige en effectieve furosemide doseerschema's beproken en worden voorstellen gedaan voor verder onderzoek.
De observationele studie, die de PK/PD van continue IV furosemide evalueerde in hemodynamisch instabiele zuigelingen, bevestigde dat de effecten van furosemide afhankelijk zijn van de nierfunctie. Daarom werd gesuggereerd dat furosemide therapie effectiever zou kunnen zijn wanneer met een hogere aanvangsdosering gestart zou worden en deze vervolgens zou worden aangepast (naar beneden) opgeleide van de geobserveerde urine productie. Op basis van de maximale toegediende dosis en de gemeten plasma furosemide concentraties lijkt een (aanvangs)dosis van 0.2 mg/kg per uur rationeel. (hoofdstuk 4)
Het ontwikkelde populatie PK/PD model beschreef de relatie tussen de furosemide dosis en de plasma furosemide concentratie, de nierfunctie (kreatinine klaring) en de urine productie. In dit PK/PD model werd de kreatinine klaring gebruikt als surrogaat voor de nierfunctie en werd een lineaire toename in de tijd van de kreatinine klaring aangenomen. Verschillende doseerschema's met een vooraf gedefineerde urine productie werden gesimuleerd met het model. (hoofdstuk 5)
Het door het PK/PD model gesuggereerde furosemide doseerschema, met een aanvangsdosering van 0.2 mg/kg per uur, werd in hemodynamisch instabiele zuigelingen na open hartchirurgie geëvalueerd. Het geëvalueerde furosemide doseerschema lijkt rationeel omdat het aanpassen van de furosemide dosis nagenoeg niet nodig was. Bovendien was de urine productie bevredigend wat betreft het volume, de tijd tot het bereiken van de gewenste urine productie (4 ml/kg per uur) en het afwijken van de gewenste urine productie.
De variabiliteit van de vochtbalansen wordt waarschijnlijk veroorzaakt door het verschil in geneesmiddel aanbod en effect. Zoals voorspeld in de observationele studie en door het PK/PD model, bleef de maximale plasma furosemide concentratie (28.5 µg/ml) onder het geaccepteerde veiligheidsniveau (50 µg/ml) voor gehoorschade.
De volume overbelasting in de patiënten na open hartchirurgie is mogelijk een verklaring dat de ontwikkeling van tolerantie voor furosemide niet werd waargenomen.
Het voordeel van een hoge dosis furosemide ten opzichte van een lage dosis furosemide konden niet worden bevestigd. Alhoewel belangrijke factoren, het sneller bereiken van de gewenste urine productie en een meer gecontroleerde urine productie, wijzen op de voordelen van een doseerschema met een hoge dosis furosemide. (hoofdstuk 6)
In een retrospectieve studie werden furosemide doseerschema's in neonaten tijdens ECMO behandeling geëvalueerd. (hoofdstuk 7) Het voordeel van continue boven intermittterende furosemide therapie kon niet worden aangetoond omdat er slechts een beperkt aantal patiënten beschikbaar was voor vergelijking. De doses van de furosemide infuzen varieerden aanzienlijk en tevens werden frequent extra loop diuretica toegediend hetgeen suggereert dat de gebruikte furosemide doseerschema's zeer waarschijnlijk niet optimaal zijn. Het lijkt aannemelijk vanwege de overeenkomsten tussen ECMO en de hart-longmachine dat het PK/PD model, ontwikkeld voor zuigelingen na open hartchirurgie ook toepasbaar zou zijn voor zuigelingen tijdens ECMO behandeling.
Een prospectieve studie in zuigelingen tijdens ECMO behandeling werd verricht om een furosemide doseerschema op basis van het PK/PD model te exploreren. Het PK/PD model ontwikkeld voor zuigelingen na open hartchirurgie suggereerde een furosemide aanvangsdosering tussen 0.2 en 0.3 mg/kg per uur om de gewenste urine productie van 6 ml/kg per uur te verkrijgen. Op grond van de resultaten van de retrospectieve studie werd de laagste furosemide dosering geëvalueerd. (hoofdstuk 8) De furosemide dosis moest bij het overgrote deel van de patiënten verlaagd worden, wat aangeeft dat de aanvangsdosering van 0.2 mg/kg per uur nog steeds te hoog was voor zuigelingen aan ECMO. De leeftijd en de nierfunctie van de patiënten, naast het ECMO circuit, zijn waarschijnlijk verantwoordelijk voor het feit dat de benodigde furosemide doses in zuigelingen tijdens ECMO behandeling substantieel lager zijn dan de doses in zuigelingen na open hartchirurgie.
De maximale gemeten furosemide plasma concentratie was 12.9 µg/ml wat ver beneden de geaccepteerde veiligheidsconcentratie (50 µg/ml) voor ototoxiciteit is.
De geforceerde diurese werd hemodynamisch goed verdragen en toxiche plasma furosemide werden niet bereikt, echter wel werd een neiging tot metabole alkalose waargenomen na 48 uur. Er werd geen verklaring gevonden voor de metabole alkalose, nadat een contractie alkalose en een pre-renale nierinsufficientie als mogelijke oorzaken waren uitgesloten.
De verschillen, waargenomen in de variabiliteit van de urine productie tussen de prospectieve en retropsectieve studie suggereren dat strikte protocollen voor diuretica behandelingen de variabliteit van de urine productie doet afnemen.
De resultaten van de prospectieve studie suggereren dat de voorgestelde furosemide dosis te hoog is. Daarom zou een nieuw PK/PD model ontwikkeld moeten worden voor zuigelingen tijdens ECMO behandeling, die de factoren die van invloed zijn op de furosemide dispositie tijdens ECMO identificeert.

Conclusie

- De geëvalueerde continue IV furosemide doseerschema's zijn veilig en effectief om de urine productie te stimuleren bij ernstige zieke zuigelingen na open hartchirurgie en tijdens ECMO behandeling. Echter, gerandomiseerde gecontroleerde studies (RCT's) zullen moeten worden verricht om het optimale furosemide doseerschema te vinden.

- Het PK/PD model ontwikkeld voor zuigelingen na open hartchirurgie moet met enige voorzichtigheid gebruikt worden bij zuigelingen behandeld met ECMO omdat de gesuggereerde furosemide dosis te hoog zou kunnen zijn. Een nieuw PK/PD model zal daarom ontwikkeld moeten worden voor zuigelingen tijdens ECMO behandeling, die de factoren die de furosemide dispositie beinvloeden indentificeert.

- In de verrichtte studies waren de gemeten plasma furosemide waarden ver beneden de grens voor ototoxiciteit, en daarom is het routinematig meten van plasma furosemide spiegels voor toxiciteit misschien niet geindiceerd.

- Bij zuigelingen na open hartchirurgie werd de ontwikkeling van tolerantie voor furosemide niet waargenomen na langdurige toediening van furosemide. Een mogelijke verklaring kan de volume overbelasting bij zuigelingen na open hartchirurgie zijn.

Voorstellen voor verder onderzoek

Farmacotherapie bij ernstige zieke zuigelingen: Het off-label gebruik van furosemide bij ernstige zieke zuigelingen is een ongewenste situatie en leidt tot bijwerkingen. Goede en volledige evaluatie van furosemide is daarom noodzakelijk.

Gerandomiseerde gecontroleerde studies bij ernstig zieke zuigelingen: RCT's moeten worden verricht om de verschillende furosemide doseerschema's met elkaar te vergelijken. Het eerste doel van de RCT's is het verkrijgen van een optimale urine productie zonder cardiovasculaire instabiliteit en andere bijwerkingen. Het tweede doel van de RCT's zal zijn de vermindering van de de mechanische ventilatietijd.

De ontwikkeling van furosemide doseerschema's voor ernstige zieke zuigelingen: Furosemide therapie bij ernstig zieke zuigelingen anders dan na open hartchirurgie en tijdens ECMO behandeling zal geëvalueerd moeten worden. En indien van toepassing zullen furosemide doseerschema's ontwikkeld moeten worden.

Inter-individuele variabiliteit in de vochtbalansen van ernstige zieke zuigelingen: De vochtbalansen, die bereikt werden bij ernstig zieke zuigelingen na open hartchirurgie en tijdens ECMO behandeling waren acceptabel, maar vertoonden substantiele variabiliteit. Polymorfisme van renale transporteurs van diuretica en van moleculaire aangrijpingspunten van diuretica, kunnen verantwoordelijke geacht worden voor dit fenomeen, en daarom onderwerp zijn van onderzoek.

Alternatieve toedieningswegen van furosemide bij ernstig zieke zuigelingen: De geobserveerde effecten in pulmonale mechanica na intra-thracheaal toegediende furosemide zijn veelbelovend. Maar het onderzoek zal zich eerst moeten concentreren op de werkelijk toegediende hoeveelheid geneesmiddel met de verschillende toedieningsapparaten, om PK/PD parameters te kunnen bestuderen.

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