THE EFFECT OF RENAL FUNCTION ON CLINICAL PHARMACOKINETICS IN THE NEWBORN

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THE EFFECT OF RENAL FUNCTION ON CLINICAL PHARMACOKINETICS IN THE NEWBORN

Het effect van de nierfunctie op de klinische farmacokinetiek bij de pasgeborene

Proefschrift

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Aan mijn ouders

Voor Elly en Deborah

Doctors treat patients of whom they know little,
for diseases of which they know even less,
with drugs of which they know almost nothing

Adapted from Voltaire (1694-1778)

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CHAPTER 1

INTRODUCTION

CHAPTER 1

INTRODUCTION

1.1 General introduction

The pharmacologic behaviour of drugs administered to newborns shows unique characteristics which in general cannot be extrapolated from data derived from older infants and adults. Rapidly changing physiological processes characteristic of the neonatal period may profoundly affect the pharmacokinetics of drugs and result either in subtherapeutic or toxic drug concentrations. Therefore, the pharmacokinetics but also the safety and efficacy of drugs need to be determined by trials specifically designed to include term and preterm infants. Since the 1950s investigators have reported serious side effects associated with the inadvertent use of drugs in newborns. Silverman et al.[1] described in 1956 the deleterious effects of sulfonamide as a prophylactic agent against neonatal sepsis. Sulfonamides displaced bilirubin from albumin-binding sites which resulted in an increased incidence of kernicterus in preterm infants. Subsequently, Sutherland[2] described the "grey baby syndrome" in three newborns treated with chloramphenicol. The occurrence of cardiovascular collapse and shock in these neonates was due to the accumulation of free drug caused by deficient glucuronidation in the presence of a reduction in glomerular filtration. More recent examples of the consequences of ignorance about the unique transitional metabolic and physiological characteristics of neonates are easily found. These include poisoning of very low birth weight infants by inadvertent exposure to toxic doses of benzyl alcohol contained in bacteriostatic water or saline used to reconstitute medications or to flush intravascular catheters[3], and the excessive mortality associated with the intravenous administration of vitamin E to low birth weight infants[4]. As a result of these adverse experiences both the pharmaceutical industry and pediatricians have become more careful with the introduction of new compounds in neonates. They have recognized that rational drug therapy for newborns is often confounded by a combination of poorly understood pharmacokinetic and pharmacodynamic interactions[5,6]. However, new drugs are currently

still introduced into neonatal intensive care units, even though most of these have neither been tested in neonatal animals nor studied in human infants. In addition most studies on pharmacokinetics, safety and efficacy of drugs in newborns have only included term infants. Nowadays neonatal intensive care units are increasingly occupied with preterm infants with gestational ages of less than 32 weeks and a birth weight below 1500 g. Even pharmacokinetic data on commonly used drugs such as penicillin G, flucloxacillin, dobutamine and tolazoline are not available in these infants.

Effective and safe drug therapy requires a thorough understanding of human developmental biology and of the dynamic ontogeny of drug absorption, drug disposition, drug metabolism, and drug excretion. It is apparent that maturation of organ system function and changes in body composition during gestation and during the neonatal period exert a significant effect on the disposition of drugs. Hence, specific dosage recommendations are required for newborn infants. These infants should be stratified according to gestational and postnatal age as will be illustrated in this thesis. In addition pathophysiological conditions such as asphyxia or hyaline membrane disease and the impact of in utero or postnatal exposure to drugs may necessitate further dosage adjustments.

1.2 Clinical pharmacokinetics

Pharmacokinetics is the mathematical description of the biologic rate processes in the body by which drug concentrations are altered. This includes the study of the plasma concentration versus time course of a drug after its administration and the development of mathematical models to predict these concentrations. Knowledge of a drug's physicochemical and pharmacokinetic properties allows the clinician to predict plasma concentrations at any given time after administration and to make fairly reliable estimates of the magnitude and duration of drug response. The application of pharmacokinetic principles provides an invaluable tool that will lead to optimal drug therapy in the individual patient.

Four pharmacokinetic parameters are critical to the characterization of plasma concentrations after drug administration and hence necessary for the determination

of appropriate drug dosing regimens: systemic availability, volume of distribution, clearance, and half-life.

Systemic availability

In order to accurately predict plasma concentrations and clinical response after administration of a drug to a patient, it is necessary to know the exact amount of drug in the body, i.e. the systemic availability. Administration by an intravenous bolus is assumed to provide 100 percent systemic availability. The systemic availability of other routes of administration is commonly calculated from the comparison of plasma concentration following administration of a single dose by intravascular and extravascular routes. In this thesis drugs were only administered by intravenous bolus injection. We therefore assume that 100 percent systemic availability was reached.

Volume of distribution

Drugs will not remain exclusively in the blood but may distribute into various tissues and other fluids. The rate at which a particular tissue-plasma concentration equilibrium is achieved depends on the blood perfusion to the organ. The extent to which a drug distributes extravascularly depends on its lipophilicity and its affinity for plasma and tissue proteins. The parameter volume of distribution (V) is used to identify the proportionality factor relating the amount of drug in the body (A) with the blood or plasma concentration (C). This can be expressed with use of the following equation: $A=V.C$.

Volume of distribution does not represent a true physiological volume[7]. The volume of distribution of a drug that is highly bound to plasma proteins with no significant tissue binding is equal to the volume of distribution of albumin. If a drug has a very low affinity for plasma proteins, the minimum volume of distribution would equal the extracellular fluid space. There is no upper limit for volume of distribution, and calculation of the volume of distribution frequently exceeds total body water. This would indicate significant storage of the drug in peripheral tissue sites.

Clearance

Just as volume of distribution relates the amount of drug in the body to the plasma

concentration, body clearance refers to the proportionality factor between the rate of elimination of the drug from the body and the plasma or blood concentration. Body clearance is a more precise measurement of the body's ability to eliminate drugs than half-life because it has a physiological basis. It directly reflects physiological processes of elimination. Clearance does not measure the quantity of drug eliminated by the body, but it quantifies the volume of blood or plasma that can be completely cleared of drug per unit time. Clearance is the most important pharmacokinetic parameter for calculation of maintenance doses. The kidney and liver are the major routes of elimination for most drugs. Renal clearance depends on renal blood flow, plasma drug-protein binding, and glomerular filtration, tubular secretion and reabsorption. Similarly, hepatic clearance depends on the hepatic blood flow, plasma drug-protein binding, and the intrinsic capability of the liver to metabolize a drug.

Half-life

The half-life ($t_{1/2}$) of a drug is defined as the amount of time necessary to decrease plasma drug concentrations by 50 percent. In order to be eliminated from the body, a drug must be present in the plasma without being bound to proteins. Plasma half-life depends on the physiologically based parameters volume of distribution and total body clearance (CL). This can be expressed with use of the following equation: $t_{1/2} = 0.693.V/CL$. Although half-life is not an independent pharma-cokinetic parameter, it is an useful estimation of the time required to eliminate the drug entirely from the body, as well as the time needed to reach steady state during a multiple-dosing regimen.

1.3 Developmental physiology and drug disposition

Disposition of drugs in preterm infants differs substantially from that in term infants as a result of differences in absorption, distribution, biotransformation, and excretion[6]. The unique characteristics of these processes in the small preterm infant are briefly reviewed below.

Drug absorption

Absorption of drugs from the gastrointestinal tract, skin, or an intramuscular injection site is significantly different in newborns as compared to older children and adults. The gastric and duodenal pH, gastro-intestinal motility, the maturational state of intestinal mucosa, concomitant feedings and fluctuating gastrointestinal perfusion have been implicated as factors contributing to the variability in the gastrointestinal absorption of enterally administered drugs[8,9,10,11,12]. For instance during hypochlorhydria the absorption of penicillin, ampicillin, nafcillin and erythromycin is enhanced, whereas the oral absorption of phenobarbitone, diphenylhydantoin, nalidixic acid, acetaminophen, rifampicin and ketoconazole is reduced. This variability and the limited data on the bioavailability of enterally administered drugs have restricted oral administration of many compounds in the preterm infant.

Transdermal absorption is increased in the preterm infant because of the relatively thin layer of epidermal tissue at birth[13]. In the past this has resulted in intoxications[3,14,15]. More recently attention has been given to potential beneficial effects. In a study of Evans et al.[16] therapeutic concentrations of theophylline were obtained after topical application of theophylline gel in preterm infants.

The systemic absorption of many intramuscularly administered drugs in newborns who are hemodynamically stable results in a similar therapeutic efficacy as intravenous administration[17]. However, the clinical condition of the patient must be taken into account since hemodynamically unstable newborns may lack adequate tissue perfusion to effectively absorb drugs given by the intramuscular route. In addition muscle activity may affect the rate of absorption and consequently the peak serum concentration of a drug. Sick, immobile newborns or those receiving a paralyzing agent such as vecuronium may show reduced absorption rates after intramuscular drug administration. Finally, intramuscular administration of drugs in very low birth weight infants is not practical because of their small muscle mass. Therefore intravenous administration remains the main route for drug therapy in this patient population.

Drug distribution

The distribution of most drugs in the body is influenced by several age-dependent

factors including protein binding, body compartment size, hemodynamic factors e.g. cardiac output and regional blood flow, and membrane permeability[18].

A. PROTEIN BINDING

The serum protein binding of drugs is dependent on the amount of binding proteins, the affinity constant of the drug for the protein, the number of available binding sites, and the presence of pathophysiological conditions or endogenous compounds which may alter the drug-protein binding interaction[19]. Acidic and uncharged compounds are primarily bound by albumin. Basic drugs bind to albumin, alpha-1-acid glycoprotein and lipoprotein[6]. Albumin concentrations are lower in term infants than in older children and adults and are further reduced with increasing prematurity[20]. Plasma concentrations of alpha-1-acid glycoprotein are significantly lower in term infants than in normal adults and are even lower in premature infants[21,22]. Substantial differences exist between the degree of drug-protein binding for various agents in newborn and adult serum[23]. Increased concentrations of unbound drug have been reported in neonatal or fetal plasma samples of antibiotics such as ampicillin, benzylpenicillin, chloramphenicol and sulfonamides[6]. Consequently the therapeutic and adverse effects of the drug may be accentuated. Protein binding may also be affected by endogenous competitors for binding sites. There are a number of endogenous molecules such as bilirubin which may bind to plasma proteins[18,24]. These may displace drugs from binding sites, and at least transiently increase the apparent volume of distribution of the drug. More importantly, the increase in the fraction of free drug, which occurs because of the displacement reaction, may result in a transiently enhanced pharmacological response. However, a clinically important protein binding displacement reaction will only occur if a drug is more than 80 to 90% protein bound[25]. Endogenous molecules may displace drugs from their binding sites, but there are also drugs which can displace endogenous molecules from their binding sites. This may lead to unacceptable high levels of for instance bilirubin with the potential risk of increasing the incidence of kernicterus[1]. Antibiotics that have been shown to significantly displace bilirubin from albumin-binding sites include sulfonamides, moxalactam, cefoperazone and ceftriaxone.

B. BODY WATER COMPARTMENT SIZES

Age dependent changes in the composition of various fluid compartments have recently been reviewed[26]. Total body water comprises nearly 92% of body weight in the young fetus, with the extracellular fluid volume accounting for 65% of body weight, and the intracellular fluid volume responsible for 25% of body weight. Body fat comprises less than 1%. At term total body water falls to approximately 75% of body weight, and the amount of fat increases to approximately 15%. Measurements of extracellular fluid volume ranged from 350 to 440 mL/kg body weight in neonates after a 40 week gestation[27]. As a consequence, the intracellular volume increases from 25% of body weight in the young fetus to 33% at birth.

In addition there is a 8 to 15% reduction of body weight during the first 3 to 5 days after birth. This weight loss is due to mobilization of both intracellular and extracellular fluid through urinary and transepidermal losses[28], and tissue loss due to low calory intake.

These issues may have important implications for optimal drug use in the tiny infant. Attainment of the same peak serum concentration of drugs which are primarily distributed in the extracellular fluid space may require twice the relative dose, on mg/kg basis, because the very low birth weight preterm infant has an extracellular fluid compartment more than twice the relative size of that of an adult. In contrast, a much smaller apparent volume of distribution would be expected for highly lipophilic compounds in the very low birth weight premature infant. In addition rapid changes in body composition, especially over the first days of life, may complicate pharmacokinetic calculations.

Drug biotransformation

The primary organ for drug metabolism is the liver, but the kidneys, intestines, lungs and skin are also capable of biotransformation[29]. Metabolites of most drugs are generally pharmacologically weak or inactive but parent compounds may be transformed into active metabolites. Furthermore, pharmacologically inactive compounds may be converted to their active moiety. The first step in drug metabolism is uptake of the drug by the metabolizing cell. Ligandin, or Y-protein, is a basic protein that binds bilirubin and organic anions such as drugs[30,31]. It is present in hepatocytes, as well as in proximal renal tubular cells and nongoblet, small

intestinal mucosal cells. The concentration of ligandin in the fetus and neonate is low but appears to approach adult values during the first 5-10 days of postnatal life[30]. Thus it is likely that the hepatic clearance of capacity-limited drugs will be lower in neonates than in older infants and children. Drug biotransformation within the hepatocyte involves two primary enzymatic processes: phase I, or nonsynthetic, and phase II, or synthetic, reactions.

A. PHASE I REACTIONS

Phase I biotransformation reactions, which include oxidation, reduction, hydrolysis and hydroxylation, transform compounds into more polar, less lipid-soluble molecules that may be more rapidly eliminated in the urine or bile. The hepatic cytochrome P450 oxidase system is responsible for many of the phase I reactions in the human liver. In the newborn the activity of the oxidative enzyme systems is markedly reduced[32]. Although this system matures rapidly after delivery at term[33], the rapidity of maturation in premature infants is unknown. Hydroxylation is decreased in both preterm and term newborns[34], and the activities of alcohol dehydrogenase[35] and aromatic nitro reduction pathways[36] are very low in both fetuses and neonates. In addition esterase activity, responsible for hydrolysis of chloramphenicol, is very low in the fetus and the neonate[37].

B. PHASE II REACTIONS

Phase II reactions, or conjugation reactions, synthesize more water-soluble compounds by combining a substance with an endogenous molecule in order to enhance excretion of that substance. Glucuronide, sulfate, and glycine are the common endogenous molecules to which drugs are bound. A drug must possess a specific functional group, such as a carboxyl, hydroxyl, amino, or sulphydryl group, in order to be conjugated. Alternatively, a drug may acquire one of these functional groups by undergoing phase I reactions.

Glucuronidation is the most common conjugation pathway, but it is also the most deficient immediately after birth[38]. In contrast, conjugation to sulfate[39] or glycine[36] does not appear to be decreased in the neonatal period, and methylation reactions, which are generally insignificant in adults, have a prominent role in drug metabolism during the neonatal period[40].

Drug excretion

Most drugs or their metabolites are excreted from the body by the kidneys. Renal excretion is dependent on glomerular filtration, tubular reabsorption, and tubular secretion. At birth, renal function is limited, because the kidney is anatomically and functionally immature[41,42,43]. The main factors involved in the development of renal function are the gestational age and the dramatic sequential hemodynamic changes in a situation initially dominated by high vascular resistance and extremely low blood flow. At birth the glomerular filtration rate is 2 to 4 mL/min in term neonates and it may be as low as 0.6 to 0.8 mL/min in preterm infants. The increase in glomerular filtration rate after birth is important and usually greater in term than in preterm infants[41,42,44]. The increase is due to the increase in cardiac output which is associated with specific changes in renal vascular resistances resulting in an increase in renal blood flow, changes in renal blood flow distribution, and a higher permeability of the glomerular membrane.

The low glomerular filtration rate may be partially compensated for by a relatively greater reduction in tubular reabsorption. This may be due to the relative immaturity of the renal tubule. Generally, the clearance of drugs such as gentamicin follows the renal maturation[45,46]. However, no significant changes were observed in the clearance of digoxin during the first 7 days of life in preterm infants[47].

Tubular secretory function is low compared with adults. Reasons for the reduced transport capacity are the low blood flow in peritubular regions, the immaturity of energy-supplying processes, the small mass of working tubular cells, and the small size of as yet undeveloped tubuli[48]. A similarly low capacity has been reported for drugs such as penicillins and sulphonamides[49]. The reduced renal elimination affects the disposition of many drugs. The rapid development of renal function during the first month of life therefore requires continuous monitoring and dosage adjustment of drugs that are dependent on renal elimination.

1.4 Aims of the studies

The studies presented in this thesis were undertaken to investigate the effects of gestational and postnatal age on the pharmacokinetics of two antibiotics, ceftazidime

and amoxicillin. In addition the effect of changes in glomerular filtration rate on the pharmacokinetics of these primarily renally excreted antibiotics were studied. Finally, to enhance our understanding of the transfer across both the blood-cerebrospinal fluid barrier and across the placenta, the penetration of ceftazidime into the cerebrospinal fluid of preterm infants and the transplacental passage of ceftazidime in the second half of pregnancy were studied.

Chapter 2 reviews the clinical pharmacokinetics of antibacterial agents in the preterm infant. Dosage guidelines for drugs are presented and recommendations for future research are suggested.

Chapter 3 describes a study on the effects of gestational age, and prenatal exposure to betamethasone and indomethacin on the glomerular filtration rate in 147 preterm infants on day 3 of life.

Chapter 4 describes a study that compares the assessment of glomerular filtration rate by two different methods: inulin clearance versus serum creatinine in 144 preterm infants on day 3 of life. The results of this study demonstrate the usefulness of serum creatinine measurements in the assessment of renal function.

Chapter 5 and 6 describe studies on the effects of gestational age and glomerular filtration rate on the pharmacokinetics of ceftazidime and amoxicillin in preterm infants on day 3 of life. Based on these data dosage recommendations for ceftazidime and amoxicillin are presented.

Chapter 7 describes a study that compares once-daily versus twice-daily administration of ceftazidime in preterm infants with gestational ages of less than 32weeks. The usefulness and limitations of once-daily dosing are discussed.

Chapter 8 describes a study on the effect of postnatal age and postnatal exposure to indomethacin on the pharmacokinetics of ceftazidime. Based on these data the need for dosage adjustments during the second week of life is addressed.

Chapter 9 describes a study on the effect of asphyxia on the pharmacokinetics of ceftazidime in the term newborn. Based on these data dosage adjustments for asphyxiated term newborns are presented.

Chapter 10 describes a study on the penetration of ceftazidime into the cerebrospinal fluid of preterm infants. The data suggest that the blood-cerebrospinal fluid barrier in these infants is easily permeable, leading to high cerebrospinal fluid concentrations of ceftazidime even in the absence of meningitis.

Chapter 11 describes a study on the transplacental passage of ceftazidime in the second half of pregnancy. Based on these data dosage recommendations for pregnant women are presented.

Chapter 12 summarizes the results of the studies presented in Chapters 3 to 11. The major conclusions are briefly discussed and recommendations for future research are proposed.

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CHAPTER 2

CLINICAL PHARMACOKINETICS OF ANTIBACTERIAL AGENTS IN PRETERM INFANTS

Submitted

CHAPTER 2

CLINICAL PHARMACOKINETICS OF ANTIBACTERIAL AGENTS IN PRETERM INFANTS

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2.1 Introduction

Bacterial infections continue to be a major cause of morbidity and mortality in preterm infants admitted to neonatal intensive care units[1,2]. Nosocomial infections including septicemia, meningitis, pneumonia or urinary tract infection occur in approximately 18% of neonates with a very low (<1500 g) birth weight[3]. Major pathogens responsible for bacterial infections during the first month of life are *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, group B streptococcus, *Escherichia coli*, klebsiella, enterobacter, pseudomonas and other gram-negative bacteria[3,4,5]. The combination of prolonged hospitalization, multiple invasive procedures, prolonged positive-pressure ventilation and parenteral nutrition, and an impaired host defence is largely responsible for the increased susceptibility of preterm infants for bacterial, viral and fungal infections.

An early diagnosis of invasive infections remains difficult since signs and symptoms are frequently nonspecific. Between 4.4% and 10.5% of all newborn infants therefore receive systemic antibiotic therapy before the results of bacterial cultures are known[6]. In preterm infants admitted to a neonatal intensive care unit even more than 60% are treated with antibiotics during the first week of life[7]. The most commonly used drugs are penicillins, aminoglycosides and cephalosporins (53, 43 and 16%, respectively)[7]. The extensive use of antibiotics in infants of whom renal and liver function and metabolic processes are not yet well developed underscores the necessity to perform pharmacokinetic and pharmacodynamic studies which

will lead to optimal therapy and minimize drug-related toxicity and cost of therapy. The purpose of this review is to summarize the available pharmacokinetic data for antibiotics in preterm infants. The current policy not to reduce antibiotic dosage intervals in preterm infants with gestational ages of less than 32 weeks until after the fourth week of life will be discussed. Dosage recommendations, recommendations for dosage adjustments in the face of renal or hepatic immaturity, and recommendations for the monitoring of toxicity will be presented. Disease-specific therapy and pharmacologic principles underlying neonatal drug therapy are beyond the scope of this article since they have recently been addressed in reviews[1,8,9,10].

2.2 Aminoglycosides

Gentamicin, tobramycin, netilmicin and amikacin have adequate antibacterial activity against most gram-negative bacteria isolated from preterm infants with nosocomial infections. Renal excretion accounts for the elimination of approximately 80% of the aminoglycoside dose. The risk of toxicity therefore increases when drug elimination is impaired by a reduction in renal function. Nephro- and ototoxicity are the major side effects of aminoglycosides in adults. Two studies on treatment of newborns with aminoglycosides did not demonstrate significant nephrotoxic effects[11,12]. In contrast, Adelman et al.[13] reported that treatment with amikacin led to a delayed postnatal maturation in the glomerular filtration rate (GFR) of 56 preterm infants. In other studies, reversible increases in serum creatinine were reported[14], particularly when aminoglycosides were combined with nephrotoxic drugs such as indomethacin[15]. Increases in enzymuria and beta-2-microglobulin excretion were also observed in newborns treated with gentamicin.
However, these changes were transient and not predictive of glomerular function impairment[11,12,14,16,17]. The differences in nephrotoxicity of aminoglycosides between newborns and adults are similar to those reported in animal models. The lower nephrotoxicity in newborn as compared to adult rats has been attributed to factors such as lower blood perfusion and a reduced uptake by proximal tubular cells[18]. Peak and serum trough concentrations and cumulative dose are factors involved in the ototoxicity of aminoglycosides. Comparative studies in adults did

Table 1. Pharmacokinetics of aminoglycosides

Reference	Antibiotic	No	GA (weeks)	PNA (days)	Weight (g)	CL (mL/h/kg)	V (mL/kg)	$t_{1/2}$ (h)
Kildoo[24]	gentamicin	15	<33	<7	<1500	23	530	11.1
		15	<33	8-30	<1500	27	500	10.8
		6	<33	>31	<1500	71	500	4.4
Koren[25]	gentamicin	12	–	2	<1000	31	350	7.9
		20	<31	2	–	35	–	7.4
Landers[26]	gentamicin	6	28	–	<1000	32	480	11.4
Nahata[27]	tobramycin	5	31-32	2-6	1000-1499	74	930	9.5
Nahata[28]	tobramycin	9	28-30	2-6	–	67	840	9.3
		7	–	2-6	1000-1250	63	1020	11.3
		6	–	2-6	1260-1500	67	740	8.2
Nahata[29]	tobramycin	8	<30	<7	<1000	41	590	9.9
Kuhn[30]	netilmicin	12	28-33	<28	770-2050	50	630	8.6
Kenyon[31]	amikacin	28	31	–	1380	50	570	8.4

Abbreviations: No, number; GA, gestational age; PNA, postnatal age;
CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life

not reveal significant differences in ototoxicity between amikacin, gentamicin, and tobramycin[19,20]. However, in adults netilmicin was shown to be less ototoxic in comparison with other aminoglycosides[21,22]. Controversy exists as to whether the aminoglycosides are a significant cause of early-onset hearing impairment in infants. Confirmation of the cause of ototoxicity in newborns is confounded by other potentially ototoxic factors such as meningitis, prematurity, intracranial hemorrhage, and otitis media. Nevertheless, several well-conducted studies detected only a few cases (0-3%) of permanent injury in infants treated with high dosages of these drugs[11,12,23]. This suggests that the ototoxicity of aminoglycosides is less prevalent in newborns (0-3%) than in adults (2-24%). However, in only one study auditory function was evaluated longitudinally[23]. Long-term follow-up studies are necessary to detect the possible presence of ototoxicity in preterm infants treated with aminoglycosides.

Studies on the pharmacokinetics of aminoglycosides in preterm infants are summarized in Table 1[24,25,26,27,28,29,30,31]. Gentamicin is the most extensively documented aminoglycoside in preterm infants. The serum half-life correlates inversely with the rates of creatinine clearance, gestational age (GA), birth weight and postnatal age[32,33,34,35]. During the first week of life, serum half-life values up to 14 h have been observed in infants with birth weights between 800 and 1500 g. The serum half-life of gentamicin is significantly lower in term infants: 4-5 h. After the first two weeks of life, serum half-life is approximately 3 h irrespective of actual weight. Both perinatal asphyxia and a patent ductus arteriosus are associated with prolongation of the serum half-life values[36,37]. Tobramycin serum half-life is also inversely related to birth weight, GA, postnatal age and creatinine clearance[38]. In infants who weigh less than 1500 g at birth and are younger than 1 week of age, serum half-life values may be as long as 9 to 17 h whereas serum half-life values of 3 to 4.5 h are reported in infants larger than 2500 g at birth and 1 to 4 weeks of age. The serum half-life of netilmicin is inversely related to birth weight, GA and postnatal age. Serum half-life values between 4.6 and 11.5 h were reported in 12 preterm infants (mean weight: 1335 g)[30]. Accumulation of netilmicin has been documented in preterm infants[39]. Serum half-life values of amikacin are inversely related to GA and postnatal age[40]. The serum half-life in preterm infants between 1 and 3 days of age is 7 to 8 h. In term infants older than 1 week of age serum half-life is 4 to 5 h. Serum half-life is prolonged in hypoxemic newborns[41]. These data suggest that there are only slight differences in pharmacokinetic behaviour between the different aminoglycosides.

Cerebrospinal fluid (CSF) concentrations of gentamicin in newborn infants with meningitis vary between 0.3 and 3.7 mg/L (mean 1.6 mg/L) after a dose of 2-2.5 mg/kg[42,43]. Peak values observed 4 to 6 h after the dose directly correlate with the degree of meningeal inflammation and the dosage of gentamicin. CSF concentrations of amikacin measured between 1 and 4 h after a 10 mg/kg dose vary between 0.2 and 2.7 mg/L[40].

The available data on the disposition of aminoglycosides in preterm infants indicate that serum half-life values are inversely related to GA, postnatal age and renal function. There is a rapid GA and postnatal age dependent increase of the GFR[44,45,46]. This enhances the capacity to eliminate these drugs from the body. GFR values are

also significantly lower in preterm infants with GAs of less than 28 weeks in comparison with preterm infants with GAs between 28 and 32 weeks. In addition GFR values increas rapidly after birth irrespective of GA[44]. Based on these data investigators have proposed to prolong the dosing interval of gentamicin to 24 h in newborns weighing less than 1000 g[25,47,48]. Others have recommended tobramycin dosage intervals of 18 to 24 h in infants with GAs of less than 30 weeks[29].

Twice daily administration of 2.5 mg/kg of netilmicin to infants younger than 1 week of age will result in potentially toxic trough levels in 25-50% of preterm infants[12,30,49,50].

We conclude that the current policy not to reduce antibiotic dosage intervals in preterm infants with GAs of less than 32 weeks until after the fourth week of life should therefore be revised[10]. Dosage guidelines should be stratified according to GA and postnatal age. We propose a stratification based both on GA (<28 weeks; 28-32 weeks) and on postnatal age (<7 days; 1-4 weeks), which takes into account both GA and postnatal age dependent changes in total body clearance and apparent volume of distribution (Table 2).

Table 2. **Suggested and currently used dosage schedules for aminoglycosides**

	Dosage (mg/kg) and interval of administration			
Antibiotics	GA <28 weeks PNA (days)		GA 28-32 weeks PNA (days)	
	0-7	7-28	0-7	7-28
gentamicin	3.5 q 36h (2.5 q 18h)	3.0 q 24h (2.5 q 18h)	3.0 q 24h (2.5 q 18h)	2.5 q 18h (2.5 q 18h)
tobramycin	3.5 q 36h (2.5 q 18h)	3.0 q 24h (2.5 q 18h)	3.0 q 24h (2.5 q 18h)	2.5 q 18h (2.5 q 18h)
netilmicin	3.5 q 36h (2.5 q 18h)	3.0 q 24h (2.5 q 18h)	3.0 q 24h (2.5 q 18h)	2.5 q 18h (2.5 q 18h)
amikacin	12 q 24h (7.5 q 12h)	10 q 18h (7.5 q 12h)	10 q 18h (7.5 q 12h)	7.5 q 12h (7.5 q 12h)

Abbreviations: GA, gestational age; PNA, postnatal age
Values given between parentheses represent currently recommended dosages[1]

The reduced renal capacity to eliminate aminoglycosides, especially during the first week of life, warrants a prolongation of the dosing interval from 18 h to 36 h in preterm infants with GAs of less than 28 weeks and from 18 h to 24 h in preterm infants with GAs between 28 and 32 weeks. The rapid postnatal changes in GFR suggest that a prolongation of the dosing interval from 18 h to 24 h is only indicated after the first week of life in preterm infants with GAs of less than 28 weeks. The increased apparent volume of distribution of aminoglycosides warrants an increase of the dosage from 2.5 mg/kg to 3.5 mg/kg in preterm infants with GAs of less than 28 weeks and from 2.5 mg/kg to 3.0 mg/kg in preterm infants with GAs between 28 and 32 weeks. The rapid postnatal changes in apparent volume of distribution suggest that a higher dosage is only indicated after the first week of life in preterm infants with GAs of less than 28 weeks (Tabel 2).
Prenatal exposure to indomethacin, perinatal asphyxia, and a patent ductus arteriosus may necessitate prolongation of the suggested dosing intervals. Careful monitoring of renal function is indicated to further adjust these dosing schedules as well as to detect nephrotoxicity. Whether these guidelines need to be changed in the presence of signs of meningitis is not determined. There is a lack of data on CSF penetration of the aminoglycosides, especially in preterm infants. However, there is some evidence that the transfer across the blood-CSF barrier may be higher in these infants than in full-term infants[51,52,53]. If the penetration is higher the current recommendation to increase drug dosage in patients with meningitis should be reconsidered, especially in view of the poor outcome in neonates with gram-negative meningitis treated with intraventricular gentamicin[54].

2.3 Penicillins

Penicillins have been used for more than 30 years in the treatment of neonatal bacterial infections. These drugs are very safe and effective against most streptococci, pneumococci, *Listeria monocytogenes*, and *Treponema pallidum*. Other penicillins are also active against *Staphylococcus aureus* (methicillin, nafcillin, cloxacillin) and *Pseudomonas aeruginosa* (carbenicillin, ticarcillin, piperacillin).
Penicillins are mainly eliminated by the kidney. In adults tubular secretion accounts

Table 3. **Pharmacokinetics of penicillins**

Reference	Antibiotic	No	GA (weeks)	PNA (days)	Weight (g)	CL (mL/h/kg)	V (mL/kg)	$t_{1/2}$ (h)
Dahl[55]	ampicillin	11	26-33	–	–	–	–	8-9.5
Huisman[56]	amoxicillin	17	29	3	1175	66	671	6.7
Banner[57]	nafcillin	7	–	–	<1200	44-75	250-500	2-5
Nelson[58]	ticarcillin	14	<32	1-3	<1500	2.01[a]	545	3.7
Kacet[59]	piperacillin	6	29-31	3-5	1000-1520	100	633	4.3
		6	29-31	9-12	850-1400	181	822	3.2

[a]mL/min

Abbreviations: No, number; GA, gestational age; PNA, postnatal age;
CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life

for approximately 90% of the urinary excretion of penicillin, whereas glomerular filtration contributes the remaining 10%. In newborns glomerular filtration is the major determinant of renal elimination, but tubular processes may play an important role in the renal handling of some of the penicillins. There is little information in preterm infants on the elimination of penicillins by tubular secretion or reabsorption. Excretion by tubular secretion may be different from that in full-term infants because of the limited tubular function in preterm infants[52,53]. Tubular secretion capacity matures more slowly during the first 6 months of life than glomerular filtration. Thus clearance of drugs such as penicillins may be reduced in comparison with that in adults. Paradoxically, because the tubular reabsorption capacity is also reduced, certain drugs may be eliminated more rapidly. For compounds like nafcillin and perhaps mezlocillin hepatic clearance is important. Hepatic biotransformation is also limited in the preterm infant. This may result in a delayed clearance of the parent drug or a delayed transformation from a prodrug to the active compound. Penicillins have a wide ratio between therapeutic effect and toxicity, but nevertheless acute interstitial nephritis (methicillin), hepatic dysfunction (oxacillin), neurotoxicity (penicillin G) and transient hematologic effects (methicillin, nafcillin, oxacillin) have been reported. Data on the pharmacokinetics of penicillins in preterm infants are summarized in Table 3[55,56,57,58,59].

The serum half-life of penicillin is inversely correlated with birth weight, postnatal age and creatinine clearance.

Serum half-life values of 1.5 to 10 h are observed in the first week of life[60]. The larger values are usually seen in infants with a birth weight of less than 1500 g. The serum half-life of ampicillin is inversely correlated with GA and postnatal age. Steady state serum half-life values are approximately 9.5 h in preterm infants with GAs of 26 to 33 weeks and approximately 7 h for infants with GAs of 34 to 40 weeks[55]. Steady state serum half-life values of amoxicillin in preterm infants with GAs of less than 32 weeks have a mean value of 6.7 h[56]. The serum half-life of methicillin is inversely correlated with birth weight, GA and postnatal age[61,62]. The serum half-life of nafcillin is inversely correlated with postnatal age. Values range between 2.2 and 5.5 h[57]. Renal excretion of nafcillin varies between 8 and 25%. This suggests that hepatic metabolism is the primary route of elimination in neonates[63]. The serum half-life values of carbenicillin are inversely correlated with birth weight, postnatal age and rate of creatinine clearance[64]. The serum half-life values of ticarcillin during the neonatal period are similar to those of carbenicillin[58]. When ticarcillin combined with clavulanic acid was given to preterm neonates only 7.5% of the administered dose was recovered in the urine[65]. It is not known whether clavulanic acid affects the renal clearance or apparent volume of distribution of ticarcillin in neonates. The serum half-life of mezlocillin is inversely related to GA and postnatal age. It decreases from 4.5 h in premature infants aged 1 week or less to 1.6 h in full-term neonates older than 7 days[66]. Mezlocillin is eliminated by both renal and nonrenal mechanisms, although this has only been studied in 4 preterm infants[67]. The mean serum half-life values of piperacillin are inversely related to GA, postnatal age and birth weight, and ranged from 1.7 to 4.3 h[59].

Penetration of penicillin into the CSF varies significantly depending on the sodium concentration of the penicillin, the degree of maturation of the blood-CSF barrier and the presence or absence of meningeal inflammation. CSF penetration of penicillins is poor, even when meninges are inflamed[68]. Data on CSF penetration of penicillin G are not available in preterm infants. CSF concentrations of ampicillin vary greatly. In 8 infants with meningitis mean CSF concentrations 2 and 6 h after intravenous dosing were 13.6 and 15.2 mg/L, respectively, which represented 11 to 65% of the corresponding serum concentrations[69].

Table 4. Suggested and currently used dosage schedules for penicillins

	Dosage (mg/kg) and interval of administration			
Antibiotics	GA <28 weeks PNA (days)		GA 28-32 weeks PNA (days)	
	0-7	7-28	0-7	7-28
ampicillin	25 q 18h (25 q 12h)	25 q 12h (25 q 12h)	25 q 12h (25 q 12h)	25 q 8h (25 q 12h)
amoxicillin	25 q 18h (25 q 12h)	25 q 12h (25 q 12h)	25 q 12h (25 q 12h)	25 q 8h (25 q 12h)
nafcillin	25 q 12h (25 q 12h)	25 q 12h (25 q 12h)	25 q 12h (25 q 12h)	25 q 12h (25 q 12h)
ticarcillin	75 q 18h (75 q 12h)	75 q 12h (75 q 12h)	75 q 12h (75 q 12h)	75 q 8h (75 q 12h)
piperacillin	75 q 18h	75 q 12h	75 q 12h	75 q 8h

Abbreviations: GA, gestational age; PNA, postnatal age
Values given between parentheses represent currently recommended dosages[1]

Information on the CSF penetration of mezlocillin is also limited. In one study values between 0 and 13.7 mg/L were measured[70], whereas in another study values between 20 and 90 mg/L were found[71]. CSF concentrations of piperacillin were approximately 8 to 30% of the corresponding serum concentrations. Detectable CSF concentrations were observed up to 7 hours after dosing, regardless of meningeal inflammation[51]. Data on CSF penetration of methicillin, nafcillin, oxacillin, cloxacillin, carbenicillin, ticarcillin, and azlocillin are not available.

We conclude that there are insufficient data on the pharmacokinetics of penicillins in preterm infants with GAs of less than 32 weeks. The data available on older penicillins are derived from previous studies in which neonates were only stratified according to their weight (<2000-2500 g; >2000-2500 g). Pharmacokinetic and pharmacodynamic studies with penicillins in preterm infants are urgently needed in view of the frequent use of penicillin derivatives. Suggested and currently recommended dosing regimens for ampicillin, amoxicillin, nafcillin, ticarcillin, and piperacillin are presented in Table 4.

The reduced renal capacity (both glomerular filtration and tubular secretion) to eliminate ampicillin, amoxicillin, ticarcillin and piperacillin, especially during the first week of life, warrants a prolongation of the dosing interval from 12 h to 18 h in preterm infants with GAs of less than 28 weeks. The rapid postnatal changes in renal clearing capacity warrants a shortening of the dosing interval of the aforementioned penicillins from 12 h to 8 h in preterm infants with GAs between 28 and 32 weeks (Table 4). Nafcillin is eliminated by hepatic metabolism. It seems likely that hepatic clearance of nafcillin is also reduced. However, since there are no experimental data to justify dosage adjustments we still recommend to use the current dosage guidelines.

2.4 Third generation cephalosporins

Third generation cephalosporins (cefoperazone, cefotaxime, ceftizoxime, ceftriaxone, ceftazidime) have adequate antibacterial activity against a wide range of gram-positive and gram-negative microorganisms. We will limit the discussion to cefotaxime, ceftazidime and ceftriaxone since neonatal studies on the pharmacokinetics of the other agents are lacking. Approximately 80% of a cefotaxime dose is excreted in the urine. However, only a third is eliminated in unchanged form. Cefotaxime is rapidly metabolized to desacetyl-cefotaxime through the action of esterases in the liver, erythrocytes and other tissues[72]. In preterm infants approximately 70% of cefotaxime will be metabolized to its active metabolite desacetyl-cefotaxime[73]. This metabolite retains, depending on the pathogen, 10 to 100% of the antimicrobial activity of its parent compound[74]. Seventy to 90% of a ceftazidime dose is eliminated in unchanged form by the kidneys. About 70% of a ceftriaxone dose is excreted in unchanged form in the urine. The remainder is eliminated by the liver.
Cephalosporins are frequently used in the empiric treatment of neonatal septicemia and generally well-tolerated by the newborn[75]. Alterations of the bowel bacterial flora are most pronounced with third-generation agents, especially ceftriaxone and cefoperazone, and may lead to intestinal colonization by resistant organisms. Subsequent superinfections by drug-resistant pathogens have been described[76]. High biliary concentrations of ceftriaxone have been associated with reversible bile

Table 5. **Pharmacokinetics of third generation cephalosporins**

Reference	Antibiotic	No	GA (weeks)	PNA (days)	Weight (g)	CL (mL/h/kg)	V (mL/kg)	$t_{1/2}$ (h)
Aujard[77]	cefotaxime	3	<32	<7	–	65	340	3.5
Kearns [78]	cefotaxime	18	<32	<8	<1500	50-100	310-790	3.4-6.4
Gouyon[79]	cefotaxime	10	28-37	3-8	–	36-192	219-636	1.9-6.8
Kearns[78]	desacetyl-cefotaxime	17	<32	<8	<1500	–	–	3.1-35.8
McCracken[80]	ceftriaxone	10	–	1-4	<1500	60	610	7.7
		3	–	6-8	<1500	44	530	8.4
McCracken[81]	ceftazidime	7	<33	<22	–	59	530	6.7
Anker[82]	ceftazidime	136	24-37	3	1413	37	350	7.0
Anker[83]	ceftazidime	11	29	3	1052	31	363	8.7
		11	29	10	1163	42	292	5.0
Anker[84]	ceftazidime	15	<32	3	1141	31	323	8.2
		13	<32	3	1168	28	305	7.1

Abbreviations: No, number; GA, gestational age; PNA, postnatal age;
CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life

sludging (pseudolithiasis) in children receiving this drug. High doses of ceftazidime may result in neurotoxicity because of interference with cerebral enzyme activity. Bleeding disorders due to hypoprothrombinemia have been observed after therapy with moxalactam and cefamandole but are rare in patients treated with cefotaxime and ceftriaxone. Hypoprothrombinemia is associated with the presence of the N-methylthiotetrazole side chain that appears to be capable of interfering with hepatic vitamin K metabolism.

The available data on the pharmacokinetics of cefotaxime, ceftriaxone and ceftazidime in preterm infants are presented in Table 5[77,78,79,80,81,82,83,84]. The serum half-life of cefotaxime is inversely related with GA and postnatal age[77,85,86]. Because desacetyl-cefotaxime is biologically active it is important to study the pharmacokinetics of desacetyl-cefotaxime as well. The pharmacokinetic parameters of this metabolite were not correlated with postnatal age, GA or birth weight[78], and were

not affected by in utero exposure to betamethasone[87]. The serum half-life of ceftazidime is inversely related to GA and postnatal age[81,82,83,88,89]. Both perinatal asphyxia and a patent ductus arteriosus treated with indomethacin are associated with prolonged serum ceftazidime half-life values[83,90]. The serum half-life of ceftriaxone is inversely related with GA[91,92]. Serum half-life values ranged from 8 to 34 h[92]. In another study the mean serum half-life was 15.5 h[93].

Cefotaxime and desacetyl-cefotaxime penetrate well into the CSF of infants with meningitis[85]. Ceftazidime also penetrates well into the CSF, especially in the presence of meningitis[94]. In another study penetration into the CSF was independent of meningeal inflammation[95], which is in agreement with recent data in preterm infants without meningeal inflammation[96]. Penetration of ceftriaxone into the CSF was higher in patients with bacterial meningitis (17%) in comparison with that observed in infants with aseptic meningitis (4.1%)[91]. The CSF penetration of ceftriaxone is substantially less in older infants and children with bacterial meningitis (2 to 7%)[97,98].

We conclude that GA, postnatal age, renal and hepatic function are important determinants for the clinical pharmacokinetics of the three most frequently used cephalosporins. The currently recommended dosing regimens for cefotaxime, ceftriaxone and ceftazidime are presented in Table 6. The reduced capacity to eliminate cephalosporins, especially during the first week of life, warrants a prolongation of the dosing interval of cefotaxime and ceftazidime from 12 h to 24 h in preterm infants with GAs of less than 28 weeks, and from 24 h to 36 h for ceftriaxone. The rapid postnatal changes in clearing capacity warrant a shortening of the dosing interval of cefotaxime from 12 h to 8 h in preterm infants with GAs between 28 and 32 weeks. For ceftriaxone a shortening of the dosing interval from 24 h to 18 h seems indicated (Table 6).

Once-daily administration of 25 mg/kg of ceftazidime in preterm infants with GAs of less than 32 weeks leads to serum levels well above the minimal inhibitory concentration of major neonatal pathogens during the entire dosing interval[84]. Alternatively this can also be achieved by twice-daily administration of 10 mg/kg of ceftazidime in preterm infants with GAs of less than 28 weeks during the first week, or twice daily 15 mg/kg of ceftazidime in preterm infants with GAs between 28 and 32 weeks[82]. In the second week this should be adapted to twice daily 15

Table 6. **Suggested and currently used dosage schedules for third generation cephalosporins**

	Dosage (mg/kg) and interval of administration			
Antibiotics	GA <28 weeks PNA (days)		GA 28-32 weeks PNA (days)	
	0-7	7-28	0-7	7-28
cefotaxime	50 q 24h	50 q 12h	50 q 12h	50 q 8h
	(50 q 12h)	(50 q 12h)	(50 q 12h)	(50 q 12h)
ceftriaxone	50 q 36h	50 q 24h	50 q 24h	50 q 18h
	(50 q 24h)	(50 q 24h)	(50 q 24h)	(50 q 24h)
ceftazidime	25 q 24h	25 q 24h	25 q 24h	25 q 12h
	10 q 12h	15 q 12h	15 q 12h	25 q 12h
	(50 q 12h)	(50 q 12h)	(50 q 12h)	(50 q 12h)

Abbreviations: GA, gestational age; PNA, postnatal age
Values given between parentheses represent currently recommended dosages[1]

mg/kg of ceftazidime in preterm infants with GAs of less than 28 weeks, or twice daily 25 mg/kg in preterm infants with GAs between 28 and 32 weeks (Table 6)[83]. Therefore not only prolongation of the dosing interval but also reduction of the dosage will lead to optimal therapy with this agent. There is a need to obtain more information on desacetyl-cefotaxime and ceftriaxone to be able to further specify dosage recommendations for these preterm infants.
Prenatal exposure to indomethacin, perinatal asphyxia, and a patent ductus arteriosus may necessitate prolongation of the dosing intervals.

2.5 Miscellaneous antibiotics

Vancomycin
Vancomycin has a good antibacterial activity against methicillin-resistant staphylococci. Vancomycin is not metabolized and is excreted unchanged in the urine.

Although vancomycin was originally thought to be ototoxic and nephrotoxic, recent animal experimental studies did not show any evidence of toxicity[99,100]. It is likewise difficult to document that vancomycin is ototoxic or nephrotoxic in humans[101]. Vancomycin is well-tolerated and safe particularly in newborn and young infants[102]. When administered in a less than 30-minute infusion, patients may develop the red man syndrome, a histamine reaction characterized by an erythematous, pruritic rash on the upper part of the body and arms and on the neck and face. Such reactions have not been reported in newborns.

The available data on the pharmacokinetics of vancomycin in preterm infants are presented in Table 7[103,104,105,106,107,108]. The serum half-life of vancomycin correlates inversely with GA and postnatal age in neonates during the first week after birth[108]. It is also inversely correlated with serum creatinine[106,107,108,109], and with post-conceptional age in older neonates[103,104,106,108,110].

CSF concentrations of vancomycin vary between 1.2 and 4.8 mg/L and represent 7 to 21% of the corresponding serum concentrations in infants with ventriculo-peritoneal shunt infections[102].

In adults routine monitoring of serum vancomycin concentrations is not indicated[111]. However, there are a number of clinical settings in which the determination of vancomycin levels in serum or other body fluids is advocated[112]. These include patients who receive vancomycin/aminoglycoside combinations, patients undergoing hemodialysis, patients receiving higher-than-usual-doses, and patients with rapidly changing renal function like preterm infants[112]. Monitoring to achieve therapeutic and non-toxic concentrations of vancomycin was originally based upon models used to direct aminoglycoside therapy, in which peaks were assumed to be therapeutically important. Current understanding of both agents makes such a comparison inappropriate. Optimal vancomycin therapy requires the maintenance of therapeutic concentrations and avoidance of unnecessary high peaks. Trough levels should ideally be maintained between 5 and 12 mg/L, and concentrations above 10 mg/L should be thought of as early signs of accumulation[113]. Recent data show that peak vancomycin concentrations do not need to be measured routinely in preterm infants if trough concentrations are below 12 mg/L[114].

We conclude that GA, postnatal age, and renal function are major determinants of the pharmacokinetics of vancomycin.

Table 7. **Pharmacokinetics of miscellaneous antibiotics**

Reference	Antibiotic	No	GA (weeks)	PNA (days)	Weight (g)	CL (mL/h/kg)	V (mL/kg)	$t_{1/2}$ (h)
Reed[103]	vancomycin	12	28	21	1069	74	520	6.6
Lisby-Sutch[104]	vancomycin	5	30-34	13-42	–	43	470	7.8
Gross[105]	vancomycin	3	24-27	27-32	<1000	66	970	9.9
		6	26-28	26-62	>1000	62	450	5.3
Leonard[106]	vancomycin	19	24-29	20	<1000	48	680	10.6
Kildoo[107]	vancomycin	15	29	29	1297	64	480	5.6
James[108]	vancomycin	17	25-35	–	880	36-78	–	6-17
Cuzzolin[117]	aztreonam	14	27.6	–	1061	91	639	5.3
Reed[122]	imipenem	39	22-37	1-6	670-1890	150	500	2.5
Reed[122]	cilastatin	39	22-37	1-6	670-1890	30	400	9.1
Jager-Roman[128]	metronidazole	3	–	–	<1200	0.12[a]	650	75.0
Hall[129]	metronidazole	24	25-40	–	780-2480	–	–	22.0
Koren[130]	clindamycin	12	26-39	1-24	640-2700	22-135	153-1137	3.5-9.8
Waites[134]	erythromycin	14	–	<15	<1500	79	2400	2.1

[a] μmol/L
Abbreviations: No, number; GA, gestational age; PNA, postnatal age;
CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life

The suggested and currently recommended dosing regimens for vancomycin are presented in Table 8. The reduced renal capacity to eliminate vancomycin, especially during the first week of life, warrants a prolongation of the dosing interval from 24 h to 36 h in preterm infants with GAs of less than 28 weeks. The rapid postnatal changes in GFR warrants a shortening of the dosing interval from 24 h to 18 h in preterm infants with GAs between 28 and 32 weeks (Table 8). Alternatively, a reduction of the dosage to 5 mg/kg twice daily will probably maintain therapeutic concentrations and avoid high peak values (Table 8). Prenatal exposure to indomethacin, the concomitant prescription of an aminoglycoside, and asphyxia may necessitate further dosage adjustments.

Aztreonam

Aztreonam is the first synthetic monocyclic beta-lactam (monobactam) antibiotic. It has good activity against a broad spectrum of aerobic gram-negative bacteria, but its activity against gram-positive or anaerobic organisms is poor. Aztreonam is excreted primarily in unchanged form in the urine. Aztreonam contains 780 mg of arginine per gram of antibiotic. Therefore concern has been raised regarding possible adverse effects such as an arginine-induced hypoglycemia[115]. A study addressing this issue indicated that aztreonam was well-tolerated and safe in preterm infants when a glucose solution (>5 mg/kg per minute) was concomitantly infused[116]. The available data on the pharmacokinetics of aztreonam are presented in Table 8[117]. The serum half-life of aztreonam is inversely related with GA, postnatal age and renal function[118,119]. Aztreonam penetration into the CSF (3-19%) was studied in a small number of infants with bacterial meningitis[118]. The results of this study indicate that CSF concentrations were higher at the beginning of therapy[118]. Both the currently available dosage regimen and the suggested dosage schedule that takes into account the important changes in renal function are presented in Table 8.

Carbapenems

Carbapenems constitute a relatively new class of beta-lactam antibiotics. Its spectrum of activity includes most aerobic and anaerobic gram-positive and gram-negative bacteria.

A. IMIPENEM-CILASTATIN

Imipenem is the first of this new class of beta-lactam antibiotics[120]. Imipenem has an exceptionally broad spectrum of activity. Imipenem treatment may be associated with drug-related seizure activity[121]. Of interest is that imipenem has been shown to induce seizure activity in mice at serum concentrations two- to three-fold lower than those of penicillin and cefotaxime. Imipenem is normally hydrolyzed by dehydropeptidase I (DHP-I), a renal tubular enzyme. To inhibit this renal metabolism of imipenem, cilastatin is co-administered. As a result 70 to 80% of an imipenem dose can be recovered in the urine in unchanged form. Cilastatin is primarily excreted in unchanged form in the urine, but about 12% appears as the metabolite N-acetyl cilastatin.

Table 8. Suggested and currently used dosage schedules for miscellaneous antibiotics

	Dosage (mg/kg) and interval of administration			
Antibiotics	GA <28 weeks PNA (days)		GA 28-32 weeks PNA (days)	
	0-7	7-28	0-7	7-28
vancomycin	15 q 36h	15 q 24h	15 q 24h	15 q 18h
	5 q 12h	7.5 q 12h	7.5 q 12h	10 q 12h
	(15 q 24h)	(15 q 24h)	(15 q 24h)	(15 q 24h)
aztreonam	30 q 18h	30 q 12h	30 q 12h	30 q 8h
	(30 q 12h)	(30 q 12h)	(30 q 12h)	(30 q 12h)
imipenem	20 q 18h	20 q 12h	20 q 12h	20 q 8h
metronidazole	7.5 q 72h	7.5 q 48h	7.5 q 48h	7.5 q 36h
	(7.5 q 48h)	(7.5 q 48h)	(7.5 q 48h)	(7.5 q 48h)
clindamycin	5 q 18h	5 q 12h	5 q 12h	5 q 8h
	(5 q 12h)	(5 q 12h)	(5 q 12h)	(5 q 12h)
erythromycin	10 q 8h	10 q 6h	10 q 6h	--

Abbreviations: GA, gestational age; PNA, postnatal age
Values given between parentheses represent currently recommended dosages[1]

The available pharmacokinetic data are presented in Table 7[122]. The serum half-life values for both drugs are inversely related to birth weight and GA[122,123,124]. Clearance of cilastatin is much slower than clearance of imipenem. This may lead to accumulation in newborns. Freij et al.[123] suggested that an imipenem-cilastatin ratio of 1:0.25 rather than the currently available 1:1 ratio may achieve a minimum of cilastatin accumulation. CSF concentrations of imipenem in 2 neonates were 4 to 10% of the corresponding serum concentrations[124]. It was not indicated whether meningitis was present in these infants. Dosage modifications are presented that take into account the importance of renal elimination (Table 8).

B. MEROPENEM

Meropenem is a recently developed carbapenem antibiotic. In comparison with

imipenem, meropenem is relatively stable to hydrolysis by the enzyme DHP-I, thus precluding the need for co-administration with an inhibitor of DHP-I, such as cilastatin. Furthermore meropenem seems to be less neurotoxic than imipenem. In preterm infants serum half-life is inversely related to GA and renal function[125]. The penetration ratio into the CSF in infants and children, aged between 1 month and 17 years, was around 20%, but showed large interindividual variations[126]. Data on CSF penetration in the newborn are missing.

Metronidazole

Metronidazole has a adequate antiparasitic and antibacterial activity against *Trichomonas vaginalis, Entamoeba histolytica, Giardia lamblia,* and a variety of anaerobic bacteria including *Bacteroides fragilis.* Metronidazole is frequently used in newborns with suspected or documented anaerobic infections. The liver is the main site of metabolism, accounting for over 50% of the systemic clearance of metronidazole. It is hydroxylated, conjugated, and excreted by the liver[127]. Interestingly, the major hydroxy-metabolite is only detectable in newborns with GAs of more than 35 weeks and in those newborns with GAs of less than 35 weeks who had in utero exposure to betamethasone, suggesting that the hydroxylation pathway was not developed in preterm infants but could be induced by prenatal exposure to betamethasone[128].

The prolonged use of high doses is associated with reversible sensory neuropathy. The available pharmacokinetic data are presented in Table 7[128,129]. Serum half-life is inversely related to GA and body weight[128,129]. In 24 newborns with a median GA of 29.5 weeks the serum half-life of metronidazole was 23.4 h[129]. Metronidazole concentrations in the CSF are approximately 100% of the corresponding serum concentrations[128]. The currently advised dosing regimen is presented in Table 8. The reduced hepatic capacity to eliminate metronidazole warrants prolongation of the dosing interval from 48 h to 72 h in preterm infants with GAs of less than 28 weeks during the first week of life. Presumably hepatic capacity improves rapidly postnatally indicating the need for shortening of the dosing interval from 48 h to 36 h in preterm infants with GAs between 28 and 32 weeks after the first week of life (Table 8). Prenatal exposure to betamethasone might necessitate further dosage adjustments.

Clindamycin

Clindamycin is active against gram-positive cocci and anaerobic bacteria, especially members of the bacteroides group. Clindamycin is primarily eliminated by the liver, with only about 10% excreted in unchanged form in the urine. Hepatotoxicity, bone marrow depression and the Stevens-Johnson syndrome are reported. However, in adults pseudomembranous colitis is the most frequent complication. This side effect is seldomly seen in newborns and young infants. The available data on the pharmacokinetics are presented in Table 7[130]. The serum half-life of clindamycin is inversely related to GA and birth weight[130,131]. Penetration into the CSF is poor. Both the currently advised dosing regimen and the modified dosage schedule that takes into account the important changes in the primarily reduced hepatic capacity to eliminate clindamycin are presented in Table 8.

Erythromycin

Erythromycin is active against most gram-positive bacteria, including many penicillin-resistant strains of staphylococci. In addition, most strains of neisseria species, *Treponema pallidum, Mycoplasma pneumoniae, Ureaplasma urealyticum, Bordetella pertussis,* and *Chlamydia trachomatis* are susceptible to this agent. Although this antibiotic has been used for almost 40 years, little is known about its activity in the preterm infant. Erythromycin is excreted for only 12 to 15% in active form in the urine. The antibiotic is concentrated in the liver and excreted in active form in the bile, which may contain as much as 250 mg/L when plasma concentrations are very high. Some of the drug may be inactivated by demethylation in the liver. Despite reports of ototoxicity associated with administration of erythromycin to adults with impaired renal and/or hepatic function, no ototoxicity or other adverse effects, including hepatotoxicity and phlebitis, could be demonstrated in newborns[132]. Recently cardiorespiratory disturbances were reported in association with the intravenous administration of erythromycin[133]. This side effect was probably related to the rate of infusion because in another study which used an infusion time of 60 minutes no side effects were noticed[134]. Erythromycin has been reported to potentiate the effects of carbamazepine, corticosteroids and digoxin probably by interfering with their cytochrome P450-mediated metabolism. In addition, high and potentially toxic concentrations of theophylline may result when erythromycin

is administered concomitantly[135]. The available data on the pharmacokinetics of erythromycin are presented in Table 7[134]. Serum half-life did not show any relation with GA, body weight or postconceptional age after oral or intravenous administration[136]. Concentrations in CSF are low, even in the presence of meningeal inflammation[137]. Revised dosage recommendations are summarized in Table 8.

2.6 Perspectives

The pharmacokinetics and pharmacodynamics of antibiotics are insufficiently studied in newborns with GAs of less than 32 weeks, whereas antibiotic pharmacokinetic data in preterm infants with GAs of less than 28 weeks are almost completely absent. The few available studies show that the absorption, distribution, protein-binding, biotransformation and excretion of antibiotics in preterm infants are significantly different from those in older children and adults[8,10,138]. The metabolism and renal excretion of several antibiotics are initially severely impaired, but show a rapid development in the first month of life. These rapid developmental processes in the first month of life have a major impact on the pharmacokinetics of antibiotics in preterm infants as is illustrated in this review. In addition a great variety of underlying diseases and metabolic disturbances may further influence the pharmacokinetic behaviour of antibiotics and other drugs.

The dependence of many antibiotics on renal elimination underscores the need to obtain specific data in preterm infants whose renal function at birth depends on both GA and prenatal exposure to drugs such as betamethasone or indomethacin[44,45,46,58,82]. Moreover renal function is subject to rapid changes after birth[44,45,46]. Therefore in studies in which the pharmacokinetics of antibiotics are evaluated the infants should be stratified according to postnatal age. The rapid changes in GFR may be counteracted by perinatal asphyxia, respiratory disturbances, prenatal exposure to the aforementioned drugs, persistence of a ductus arteriosus, and concurrent treatment with other nephrotoxic drugs[13,15,36,37,41,44,90]. Antibiotics which are dependent on hepatic metabolism and/or elimination, such as clindamycin, cefotaxime and nafcillin, also need to be studied in these newborns in whom hepatic biotransformation capacities are reduced in the first weeks of life[57,63,78,87,130].

Ideally data should be obtained for any antibiotic used in these preterm infants, even if the compound is presumed to be relatively safe like penicillins and cephalosporins. In this way dosing guidelines can be rationalized and unanticipated toxicities may be rapidly identified. In the design of such pharmacokinetic studies attention should be given to the confounding factors as previously mentioned. This review demonstrates that all these parameters influence drug disposition considerably.

In the USA the National Institute of Health (NIH) tries to encourage the study of drugs in pediatric populations by the funding of 6 Pediatric Pharmacology Research Units[139]. The funding of such units, which certainly will stimulate the performance of pediatric clinical trials, should also be encouraged in Europe.

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CHAPTER 3

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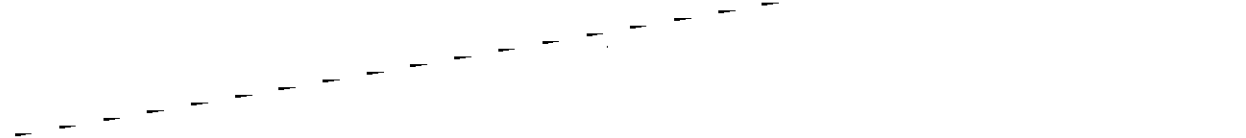

CHAPTER 3

EFFECTS OF PRENATAL EXPOSURE TO BETAMETHASONE AND INDOMETHACIN ON THE GLOMERULAR FILTRATION RATE IN THE PRETERM INFANT

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3.1 Abstract

The effects of gestational age (GA), body weight, and prenatal exposure to betamethasone and indomethacin on the glomerular filtration rate (GFR) on day 3 of life in preterm infants were studied. GFR measurements were performed in 147 preterm infants with a GA between 23.4 and 37.0 weeks by means of the continuous inulin infusion technique. Mean GFR values increased significantly with GA ($r=0.60$, $p<0.001$) and with body weight ($r=0.44$, $p<0.001$). Multivariate analysis indicated that GA was the most important determinant for this increase. Prenatal exposure to indomethacin resulted in significantly lower GFR values (-0.15 ± 0.03 mL/min, $p<0.001$) at day 3 after birth. Prenatal administration of betamethasone and indomethacin significantly ($p<0.001$) increased the GFR in comparison with exposure to indomethacin alone to levels not different than those seen in patients who were not prenatally exposed to betamethasone or indomethacin. GFR measurements were repeated in 40 preterm infants on day 10 after birth. During this 7-day period a significant increase in GFR values (0.17 ± 0.03 mL/min, $p<0.001$) was detected. This postnatal increase in GFR values was independent of GA and

was not influenced by prenatal exposure to betamethasone or indomethacin. We conclude that prenatal exposure to betamethasone or indomethacin exerts significant effects on the renal function of preterm infants in the first days of life.

3.2 Introduction

Developmental changes in the GFR of preterm infants have been the subject of many studies[1,2,3,4,5,6,7]. Most reports indicated the presence of a GA-dependent increase in the GFR[1,2,3,4,5,6]. In contrast, Aperia et al.[7] could not confirm these findings. Most studies included only a limited number of infants with a wide variation in postnatal age, and several different techniques were used to measure the GFR. Previous reports did not consider the possible effect of prenatal exposure to different drugs on these developmental changes of the GFR.

Betamethasone and indomethacin are potent drugs that are frequently used during pregnancy. Betamethasone is a synthetic glucocorticoid with a potency equivalent to dexamethasone. The drug is prescribed to pregnant women with an increased risk of preterm delivery before the 32nd week of gestation. The objective of this treatment is to accelerate maturation of the alveolar epithelium and stimulate synthesis of lipid and protein components of the pulmonary surfactant complex to prevent hyaline membrane disease. We hypothesized that prenatal exposure to betamethasone might accelerate the maturation of the GFR. Indomethacin is prescribed to inhibit preterm uterine contractions before the 32nd week of gestation. Short-term exposure to indomethacin leads to a reduction of the GFR, whereas conflicting data exist about the effect on the GFR after long-term exposure[8,9,10]. We therefore studied the effects of GA, body weight, and prenatal exposure to betamethasone and indomethacin on the GFR in a large population of preterm infants on days 3 and 10 of life.

3.3 Methods

Patients

One hundred and forty-seven preterm infants admitted to the neonatal intensive care unit of the Sophia Children's Hospital between October 1989 and October 1991 were included in this study. Eighty-seven infants were male and 60 were female. Infants who were born in our hospital at less than 37 weeks of gestation were eligible for inclusion. The infants were hemodynamically stable (diuresis > 1mL/kg/h; systolic and diastolic blood pressure above the third percentile adjusted for GA), had normal liver function, had not received inotropic or nephrotoxic drugs, did not have an intracranial hemorrhage beyond grade II, and had an indwelling arterial catheter. The partial pressure of oxygen in arterial blood was kept at greater than 50 mmHg or oxygen saturation greater than 92%, and hematocrit values were maintained above 0.35 by packed erythrocyte transfusions. Infants were excluded from the study if they had life-threatening illnesses or became hemodynamically unstable (systolic and diastolic blood pressure below the third percentile adjusted for GA; diuresis < 1 mL/kg/h). The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. Patients were only enrolled after informed consent was obtained from the parents.

The GA of the 147 children was estimated from the mother's menstrual history, early ultrasound examinations if available, and physical examination using the criteria of Dubowitz et al.[11]. Ninety-four children were not prenatally exposed to betamethasone or indomethacin (group A). Twenty-six children were prenatally exposed to indomethacin, but not to betamethasone (group B). Only six children were prenatally exposed to betamethasone, but not to indomethacin (group C). Twenty-one children were prenatally exposed to both betamethasone and indomethacin (group D). Betamethasone had been administered in two intravenous doses of 12 mg each on 2 consecutive days. This dose was repeated every week until delivery or until the 32nd week of gestation. Indomethacin had been administered in suppositories of 100 mg each, which were repeatedly given in the presence of preterm uterine contractions. In 40 infants, GFR measurements were repeated at day 10 after birth. Eighteen children were not prenatally exposed to betamethasone or indomethacin (group A). Thirteen children were prenatally exposed to indo-

methacin, but not to betamethasone (group B). Two children were prenatally exposed to betamethasone, but not to indomethacin (group C). Seven children were prenatally exposed to both betamethasone and indomethacin (group D).

Laboratory studies

GFR values were determined by means of the continuous inulin infusion technique on the third day of life[5,6,12]. Inulin was obtained from Laevosan Gesellschaft mbH (Lienz, Austria) and was administered as a glucose 10%-inulin solution containing 25 g inulin/L, at an infusion rate of 0.6 mL/kg/h. After 24 h the inulin clearance (CL_{in}) was calculated from the infusion rate (R), the inulin concentration in the infusate (I) and the serum inulin concentration (P_{in}) with the following equation: $CL_{in}=I.R/P_{in}$. The determination of inulin in serum was performed after acid hydrolysis in 0.3 mmol/L perchloric acid for 15 minutes at 70°C. The fructose thus formed was measured enzymatically according to Beutler[13].

Statistical analysis

Data given are mean ± SEM unless indicated otherwise. Correlation coefficients given are Pearson's. Comparison of groups was done using the t-test. Multiple regression was used to evaluate various factors simultaneously with respect to GFR. P-values ≤ 0.05 (two-tailed) were considered significant.

3.4 Results

The GA of the 147 preterm infants varied between 23.4 and 37 weeks (mean 30.2 weeks). The birth weight was between 560 and 3685 g (mean 1425 g). One hundred and thirty (88%) of the children were appropriate for GA. One hundred and seven (73%) were ventilated at day 3. GFR values at day 3 after birth ranged from 0.45 to 1.30 mL/min (mean 0.85 mL/min). GFR values increased significantly with GA ($r=0.60$, $p<0.001$). Multiple regression analysis showed the presence of a significant correlation between GFR and GA ($p<0.001$). The percentage of explained variation of GFR considering only GA was 35.6%. Body weight did not exert a significant effect on the GFR ($p=0.21$). Artificial ventilation ($p=0.50$), respiratory

Table 1. Clinical parameters of the study infants[a]

	group A (n = 94)	group B (n = 26)	group C (n = 6)	group D (n = 21)
	Indo – Beta –	Indo + Beta –	Indo – Beta +	Indo + Beta +
GA (weeks)	31.4[b] (2.7)	28.9 (2.3)	30.4 (2.0)	29.2 (1.3)
Weight (g)	1534[b] (592)	1156 (349)	1093 (266)	1174 (265)
AGA	79 (84%)	25 (96%)	5 (83%)	21 (100%)
Ventilation	73 (78%)	17 (65%)	3 (50%)	14 (67%)
RDS	28 (30%)	5 (19%)	2 (33%)	4 (19%)

[a]Values are mean (± SD) or numbers (%) of patients
Abbreviations: Indo, indomethacin; Beta, betamethasone; GA, gestational age; AGA, appropriate for gestational age; RDS, respiratory distress syndrome
Symbols: –, no prenatal exposure; +, prenatal exposure
[b]Significantly different ($p < 0.005$) from groups B and D

distress syndrome ($p=0.93$) or small weight for GA ($p=0.33$) also did not have a significant effect.

Timing before birth and cumulative dose of both indomethacin and betamethasone were analyzed. The median dose of indomethacin was 200 mg (range 100-2200 mg). The median dose of betamethasone was 24 mg (range 24-120 mg). We could not detect an effect of the dose and timing before birth of both drugs given to the mother on the GFR values measured on day 3 of life.

The neonates were divided in four groups. Ninety-four infants were not prenatally exposed to betamethasone or indomethacin (group A). Twenty-six children were prenatally exposed to indomethacin alone (group B). Six children were prenatally exposed to betamethasone alone (group C). Twenty-one children were prenatally exposed to both betamethasone and indomethacin (group D).

Table 1 shows the clinical parameters including GA, birth weight, and the percentage of children who were appropriate for GA, ventilated, or had respiratory distress syndrome. The GA of children who were prenatally exposed to indomethacin with

Table 2. GFR values at day 3 after birth according to prenatal exposure to betamethasone, indomethacin, or both[a]

	group A (n = 94)	group B (n = 26)	group C (n = 6)	group D (n = 21)
	Indo – Beta –	Indo + Beta –	Indo – Beta +	Indo + Beta +
GFR (mL/min)	0.91 ± 0.02	0.66 ± 0.02 (-0.17 ± 0.03)[b]	0.93 ± 0.06 (0.05 ± 0.06)[b]	0.81 ± 0.03 (-0.02 ± 0.04)[b]

[a]Values are mean ± SEM
Abbreviations: Indo, indomethacin; Beta, betamethasone; GFR, glomerular filtration rate
Symbols: –, no prenatal exposure; +, prenatal exposure
[b]The GFR values given between parentheses represent the difference between the GFR in group A and the gestational age adjusted GFR values in groups B, C and D

or without betamethasone (groups B and D) was significantly lower compared with the GA of the infants who were not prenatally exposed to betamethasone or indomethacin (group A).

Table 2 delineates the relation between GA and GFR on day 3 of life after prenatal exposure to different combinations of betamethasone and indomethacin. After adjustment for the difference in GA between groups, the GFR values of the patients in group B (only prenatal exposure to indomethacin) were still significantly lower (-0.17 ± 0.03 mL/min, $p<0.001$) compared with the GFR values of the patients in group A (not exposed to indomethacin or betamethasone). No significant difference was present between the GA-adjusted GFR values of the patients in group D (prenatal exposure to both betamethasone and indomethacin) and group A (not exposed to indomethacin or betamethasone). GA-adjusted GFR values of the patients in group D (prenatal exposure to both betamethasone and indomethacin) were significantly higher (+0.15 ± 0.04 mL/min, $p<0.001$) compared with the GA-adjusted GFR values of the infants in group B (prenatal exposure to indomethacin alone). A multivariate analysis was performed to analyze the impact of prenatal exposure to betamethasone and indomethacin on GFR values at day 3.

Table 3. The effect of gestational age and prenatal exposure to betamethasone or indomethacin on GFR values at day 3 after birth[a]

	regression coefficient			p-value
Gestational age (weeks)	+0.035	(± 0.005)	mL/min/week	p <0.001
Indomethacin[b]	-0.15	(± 0.03)	mL/min	p <0.001
Betamethasone[b]	+0.11	(± 0.03)	mL/min	p <0.001

[a]Values are mean increase (± SEM)
[b]prenatal exposure versus no prenatal exposure

Indomethacin use was associated with significantly lower (-0.15 ± 0.03 mL/min, p<0.001) GFR values, whereas betamethasone use was associated with significantly higher (+0.11 ± 0.03 mL/min, p<0.001) GFR values (Table 3).
At day 10 after birth, GFR measurements were repeated in 40 children. During this 7-day period, a significant increase in GFR values (0.17 ± 0.03 mL/min, p<0.001) to normal levels was detected. This postnatal increase in GFR values was independent of GA and was not influenced by prenatal exposure to betamethasone or indomethacin.

3.5 Discussion

The data presented in this paper demonstrate the presence of a GA-dependent increase of the GFR in preterm infants. These findings are consistent with the results of most previous reports[1,2,3,4,5,6]. The increase of the GFR was also associated with an increase in body weight. However, multivariate analysis showed that GA but not body weight was the major determinant for the development of the GFR. Our results do not support the presence of a significant effect of clinical variables such as artificial ventilation, respiratory distress syndrome, and small size for GA on the development of the GFR. This is in accordance with some published studies[6,14]. However, other studies showed a marked decrease in GFR in infants with respiratory distress syndrome[15,16]. Our patients were hemodynamically stable (diuresis >1mL/kg/h; systolic and diastolic blood pressure above the third percentile

adjusted for GA), and had no hypoxemia or hypercapnia. The lack of hypoxemia and especially hypercapnia in our patients probably explains our findings, indicating that not respiratory distress syndrome itself downregulates GFR, but perhaps hypoxemia or hypercapnia does.

In this study, most pregnant women who were treated with betamethasone were also treated with indomethacin to inhibit preterm uterine contractions. The number of patients exposed to betamethasone alone was therefore too small to do a separate analysis. However, our analysis indicates that the GA-adjusted GFR of the children who were prenatally exposed to both betamethasone and indomethacin was significantly higher compared with the GFR of the children who were prenatally exposed to indomethacin alone. In addition, the GA-adjusted GFR values of the children who were prenatally exposed to both drugs were not different from the GFR values of the children who were not exposed at all (group A). The use of multivariate analysis allowed us to detect an association between prenatal exposure to betamethasone and GFR values, showing significantly higher GFR values (+0.11 ± 0.03 mL/min) at day 3 after birth after prenatal exposure to betamethasone. The effect of prenatal exposure to betamethasone on the development of the GFR at day 3 was independent of the GA and could no longer be detected at day 10 after birth. The effects of exposure to betamethasone on the GFR have also been studied in several animal models. These studies suggested that administration of glucocorticoids results either in an increase in renal blood flow or in direct vasodilation of the renal vasculature[17,18]. Baylis and Brenner[19] provided evidence in a carefully delineated micropuncture study that values for single-nephron GFR were 25% higher in rats treated with methylprednisolone. Values for glomerular plasma flow rate were also 25% higher in the treatment group, whereas values of the transglomerular hydraulic pressure difference, afferent and efferent oncotic pressures and filtration pressure equilibrium were similar between control animals and rats treated with methylprednisolone. These results indicated that the rise in single-nephron GFR was entirely due to an increase in glomerular plasma flow probably mediated by renal arteriolar vasodilation.

The effects of prenatal exposure to betamethasone on the GFR of preterm infants have been studied by three groups[20,21,22]. These studies did not show an increase of the GFR during the first week of life after prenatal exposure to glucocorticoids.

However, in these three studies creatinine clearance was used as a less reliable marker for the GFR in preterm infants and a small number of children was studied. This might have prevented the authors from demonstrating an increase in the GFR in the first week of life after prenatal exposure to glucocorticoids. We hypothesize that prenatal exposure to betamethasone may lead to a direct vasodilating effect of the renal arterioles in preterm infants, which is probably mediated by glucocorticoid receptors.

Prenatal exposure to indomethacin resulted in significantly lower GFR values (-0.15 ± 0.03 mL/min) at day 3 of life. This effect was independent of the cumulative dose of indomethacin given to the pregnant women, although 94% had received indomethacin within a period of 48 h before delivery. This effect of prenatal exposure to indomethacin on the development of the GFR at day 3 was independent of the GA and could no longer be detected at day 10 after birth. Animal studies have indicated that the inhibition of prostaglandin synthesis by indomethacin increases renal vascular resistance. This subsequently results in an impaired renal blood flow and a concomitant reduction in the GFR[23]. This holds also for short-term exposure in the human neonate. Some case reports show that prolonged prenatal use of indomethacin can lead to deleterious renal and extrarenal effects[8,9,24,25,26], whereas other reports could not detect any serious side effects[10,27].

In summary, prenatal exposure to indomethacin significantly reduces GFR values at day 3 after birth. Betamethasone significantly increases GFR when coadministered prenatally with indomethacin. Our data suggest that betamethasone increases the GFR irrespective of the use of indomethacin. Some authors previously showed that prenatal exposure to indomethacin may lead to a decrease in GFR. However, we could not demonstrate a decrease in GFR when both drugs were given simultaneously. We suggest that an increase in renal plasma flow due to betamethasone may overcome intrarenal vasoconstriction secondary to the decreased synthesis of intrarenal prostaglandins by indomethacin. Additional studies are needed to delineate the proposed effects of both drugs.

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CHAPTER 4

ASSESSMENT OF GLOMERULAR FILTRATION RATE IN PRETERM INFANTS BY SERUM CREATININE: COMPARISON WITH INULIN CLEARANCE

Pediatrics, in press

CHAPTER 4

ASSESSMENT OF GLOMERULAR FILTRATION RATE IN PRETERM INFANTS BY SERUM CREATININE: COMPARISON WITH INULIN CLEARANCE

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4.1 Introduction

Dosage regimens of drugs that are cleared mainly by glomerular filtration as well as fluid management in preterm infants should be based on the glomerular filtration rate (GFR) of the individual patient. However, GFR measurements and collection of urine in newborns are difficult to perform. The 24-48 h continuous inulin infusion technique does not require the collection of urine and is considered the most reliable indicator of the GFR[1,2]. This method is invasive, time-consuming and expensive. In contrast, serum creatinine measurements can be obtained easily and determined quickly in the clinical chemistry laboratory. Most laboratories use an automated kinetic Jaffé method which is subject to negative interference by plasma hemoglobin above 0.06 mmol/L, and to negative interference by bilirubin (about 35 µmol/L by a serum bilirubin of about 100 µmol/L). Ketones and cephalosporins exert a positive interference[3]. This may explain why serum creatinine, determined by the Jaffé methodology, has never gained wide use as an indicator of the GFR in the preterm infant. The availability of enzymatic methods to determine serum creatinine concentrations with significantly less interference by bilirubin and other compounds stimulated us to investigate whether serum creatinine

measurements determined by an enzymatic method are reliable enough to be used as an indicator of GFR in the preterm infant. We therefore investigated the relation between GFR and gestational age (GA) and compared serum creatinine concentrations, measured by the enzymatic method according to Schoenmakers et al.[4] to inulin clearances in blood samples from 144 preterm infants on day 3 of life.

4.2 Methods

Study population

One hundred and fourty-four preterm infants admitted to the neonatal intensive care unit of the Sophia Children's Hospital between October 1989 and October 1991 were included in this study. The infants were hemodynamically stable (diuresis >1 mL/kg/h; systolic and diastolic blood pressure above the third percentile adjusted for GA), had never received drugs which could possibly have influenced the GFR (aminoglycosides, anti-epileptic drugs, caffeine, dobutamine, dopamine, midazolam, vecuronium), and had an indwelling radial artery catheter. The partial pressure of oxygen in arterial blood was kept at greater than 50 mmHg or oxygen saturation greater than 92%. The GA of the 144 children was estimated from the mother's menstrual history, early ultrasound examinations if available and from physical examination using the criteria of Dubowitz et al.[5]. Inulin clearances, serum creatinine and serum bilirubin concentrations were determined on day 3 of life. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. Infants were only enrolled after informed consent was obtained from the parents.

Laboratory studies

Inulin clearances were determined by means of the continuous inulin infusion technique. Inulin was obtained from Laevosan Gesellschaft mbH (Lienz, Austria) and was administered as a glucose 10%-inulin solution containing 25 g inulin/L, at an infusion rate of 0.6 mL/kg/h. After 24 h the inulin clearance (CL_{in}) was calculated from the infusion rate (R), the inulin concentration in the infusate (I), and the serum inulin concentration (P_{in}) with the following equation: $CL_{in}=I.R/$

P_{in}. The validity of the infusion time was verified as described previously[2]. The determination of inulin in serum was performed after acid hydrolysis in 0.3 mmol/L perchloric acid for 15 minutes at 70°C. The fructose thus formed was measured enzymatically. Glucose did not show any interference with this determination. Serum samples for creatinine were taken at the same time as those for inulin determination. Serum creatinine was measured on a Cobas Mira Clinical Chemistry Analyzer (Hoffman La Roche, Basel, Switzerland) using the Boehringer Mannheim Creatinine PAP method, based on an amidohydrolase coupled reaction, adapted to contain potassium hexacyanoferrate in reagent 2 for further reduction of bilirubin interference (BM3)[4]. The test profile of the BM3 enzymatic method showed linearity up to 2000 µmol/L, a constant stability, low variation, and no interference with lipids, hemoglobin, bilirubin or ditauro-bilirubin. Furthermore the correlation with the HPLC-assay for creatinine showed a constant test outcome with the use of BM3.

Statistical analysis

Data given are mean ± SD unless indicated otherwise. Correlation coefficients given are Pearson's. Multiple regression was used to evaluate various factors simultaneously with respect to inulin clearance and serum creatinine. P-values ≤ 0.05 (two-tailed) were considered significant. The relationship between inulin clearances and the reciprocal of the serum creatinine concentrations was calculated using least squares linear regression.

4.3 Results

The GA of the 144 preterm infants varied between 23.4 and 36.9 weeks (mean 30.2 weeks). The birth weight was between 560 and 3685 g (mean 1425 g). One hundred and seven (73%) of the infants were ventilated at day 3 of life. Inulin clearances at day 3 of life increased significantly with GA ($r=0.60$, $p<0.001$), whereas serum creatinine values decreased significantly with GA ($r=-0.50$, $p<0.001$) (Figure 1). Multiple regression analysis showed the presence of a significant correlation between GFR, measured by both the inulin clearance and the reciprocal of

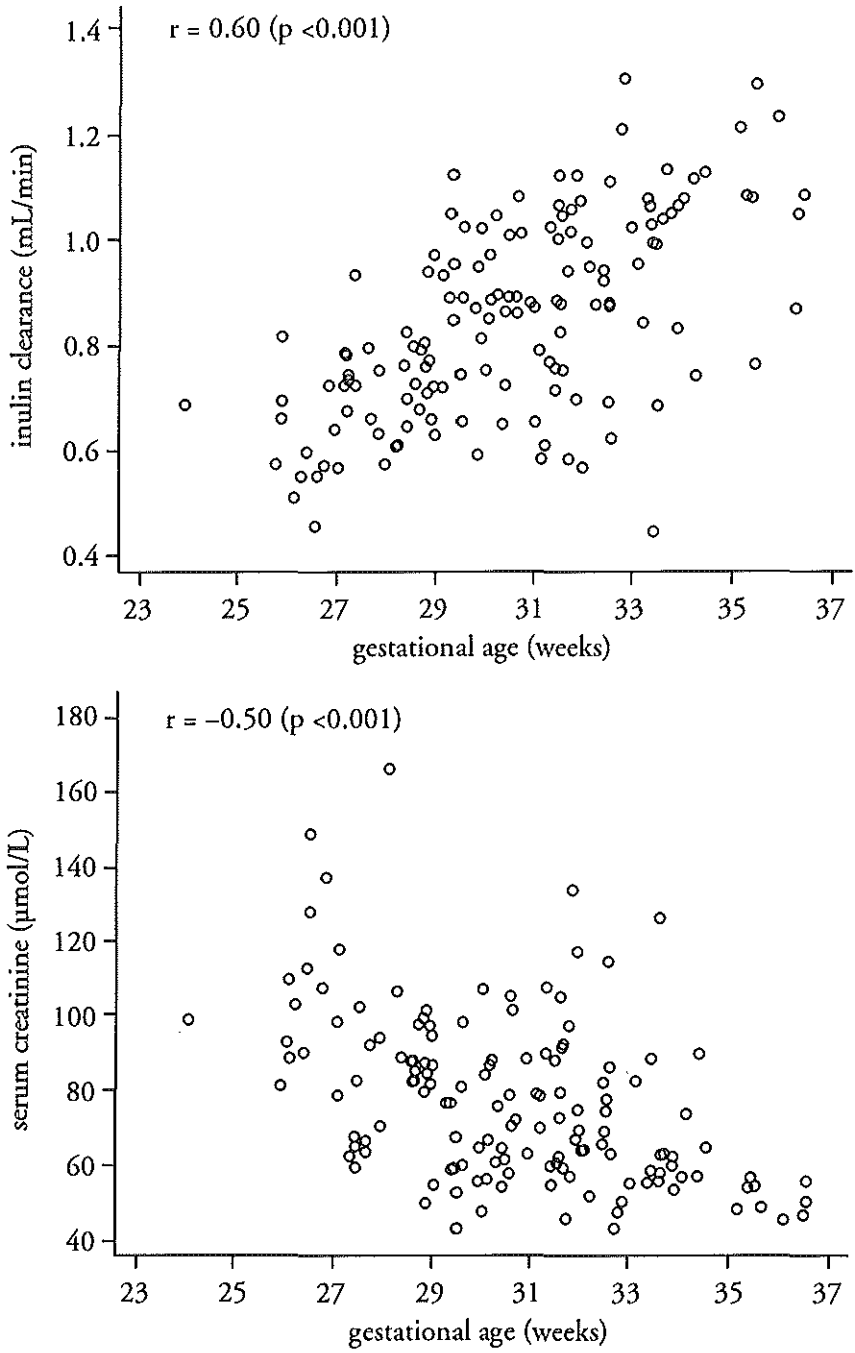

Figure 1. **Inulin clearances (mL/min) and serum creatinine values (µmol/L) versus gestational age (weeks) on day 3 after birth**

Table 1. **Inulin clearances and serum creatinine concentrations (mean ± SD) according to gestational age categories on day 3 of life**

Gestational age (weeks)	No	Inulin clearance (mL/min)	Serum creatinine μmol/L	mg/dL
<28	26	0.67 ± 0.11	92 ± 24	1.05 ± 0.27
28-32	76	0.84 ± 0.15	77 ± 21	0.88 ± 0.24
32-37	42	0.97 ± 0.19	64 ± 19	0.73 ± 0.22
Total	144	0.85 ± 0.19	76 ± 23	0.86 ± 0.26

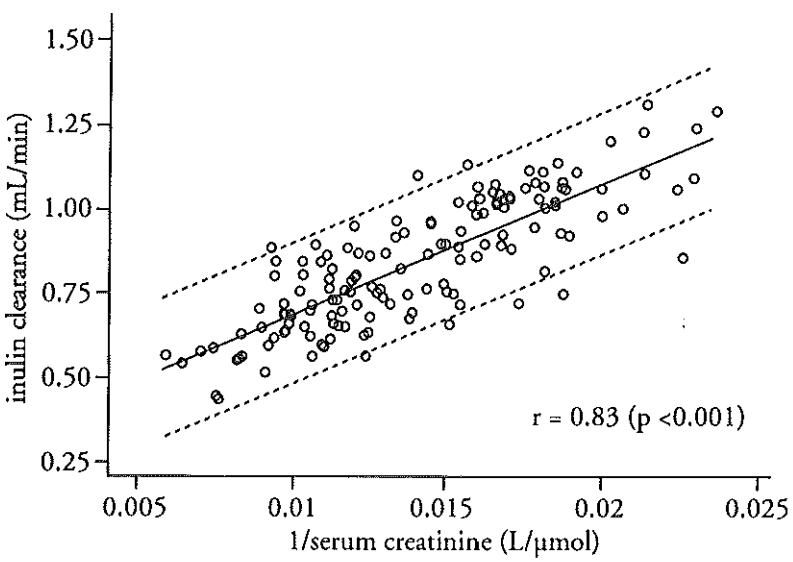

Figure 2. **Inulin clearance (mL/min) on day 3 after birth versus the reciprocal of serum creatinine (L/μmol). Drawn line (GFR = 0.29 + 38.99 x creat^{-1}) denotes the least-squares regression line. Dotted lines represent 95% prediction limits**

the serum creatinine, and GA (p<0.001). However, body weight did not exert a significant effect on the GFR (p=0.21). Artificial ventilation (p=0.50) or respiratory distress syndrome (p=0.93) also did not have a significant effect on the GFR values. The use of the reciprocal of the serum creatinine, a useful index of glomerular filtration in clinical practice, showed a positive linear relationship between this measure of the GFR and the inulin clearance (r=0.83, p<0.001) (Figure 2).

For practical purposes, we divided the infants in three groups (GAs of less than 28 weeks, GAs between 28 and 32 weeks, GAs between 32 and 37 weeks). Values for serum creatinine and inulin clearances are indicated in Table 1. These values may be regarded as reference values, because all infants were stable with normal blood pressure and did not receive any drug that potentially could have influenced GFR.

4.4 Discussion

The capacity of the kidney to clear certain drugs is to a great extent dependent on the total amount of fluid filtered. This study shows a positive linear relation between GFR expressed in mL/min and GA, demonstrating a GA-dependent increase of the GFR. The increase of the GFR was also associated with an increase in body weight. However, multivariate analysis showed that GA but not body weight was the major determinant for the development of the GFR. Therefore we propose to express GFR values in mL/min in stead of mL/min/kg. Our results do not support the presence of a significant effect of clinical variables such as artificial ventilation and respiratory distress syndrome on the GFR values. This is in agreement with previous reported data[2,6]. Other studies showed a marked decrease in GFR in infants with respiratory distress syndrome[7,8]. Our patients were hemodynamically stable and had no hypoxemia or hypercapnia, which may explain the absence of an effect on the GFR.

Secondly, we show a positive linear relation between inulin clearance and the reciprocal of serum creatinine. Drugs that are cleared mainly by glomerular filtration should be dosed according to GFR. As it is impossible however to perform inulin clearances in all infants, the positive relationship between GA and GFR indicate that drugs can be dosed according to GA. Serum creatinine can than be used to evaluate whether kidney function is within or outside the normal range for that particular GA and further adjustments of dosing is needed.

Manzke et al.[9] previously reported that serum creatinine measurements in newborns do not reliably predict GFR. They hypothesized that serum creatinine concentrations in the initial days after birth are a reflection of maternal serum creatinine. Our results, however, show that serum creatinine concentration is inversely related

with GA. If the serum concentration in the days after birth are indeed a reflection of maternal serum creatinine, the youngest infants should have had the lowest concentrations because maternal serum creatinine is lowest at the beginning of the last trimester[10]. The elevated levels of serum creatinine in these infants on day 3 of life probably reflect the difficulty these infants have to eliminate the excess creatinine transferred from their mother. Their GFR is probably too low during the first postnatal days to eliminate this excess. Also, the possibility that creatinine is reabsorbed by the immature tubular cells must be considered. If such a reabsorption, as has been demonstrated in immature animals, is present in preterm infants it could account for the elevated levels of serum creatinine[11].

Sensibility to interfering substances of serum creatinine measurements may be the main reason for the observed limited predictive value of serum creatinine as a measure for GFR. Creatinine is usually measured in the routine laboratory by a modification of the alkaline picrate method first described by Jaffé[3] more than 100 years ago. High serum levels of serum bilirubin, ketoacids and cephalosporins interfere with the Jaffé reaction. Automated enzymatic methods for creatinine determination, either based on a amidohydrolase- or on a iminohydrolase-coupled reaction, that are much less influenced by these substances have recently been introduced.

Wilkins[12] used a resin adsorption assay in 39 preterm infants and reported a 50% reduction in the variability of reference ranges of serum creatinine concentrations. In our study we also showed a 50% reduction in the reference ranges of serum creatinine compared with the data of Rudd et al.[13].

In summary, our results indicate that, for clinical practice, GA may be used as a guide to prescribe drugs that are primarily cleared by glomerular filtration. Secondly, regarding the good correlation between serum creatinine and GFR, serum creatinine values can be used to further adjust the dosage when creatinine is outside the normal range for that particular GA.

4.5 References

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CHAPTER 5

CEFTAZIDIME PHARMACOKINETICS IN PRETERM INFANTS: EFFECT OF RENAL FUNCTION AND GESTATIONAL AGE

Clinical Pharmacology and Therapeutics, in press

CHAPTER 5

CEFTAZIDIME PHARMACOKINETICS IN PRETERM INFANTS: EFFECT OF RENAL FUNCTION AND GESTATIONAL AGE

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5.1 Abstract

Purpose

The objectives of this study were (1) to determine the effects of gestational age (GA) on ceftazidime (CAZ) pharmacokinetics in the preterm infant, (2) to relate these effects to changes in glomerular filtration rate (GFR) and (3) to establish appropriate dosage recommendations for preterm infants on day 3 of life.

Patients and methods

Multiple-dose pharmacokinetics of CAZ (administered twice daily in a 25 or 50 mg/kg of body weight intravenous dose) were evaluated in 136 preterm infants on day 3 of life. Blood samples were collected from an arterial catheter at 0, 0.5, 1, 2, 4, 8, and 12 h after the intravenous dose. A high-performance liquid chromatography method was used to determine CAZ concentrations in serum. The GFR was simultaneously studied by means of the 24 h continuous inulin infusion technique.

Results

The total body clearance, apparent volume of distribution, and serum half-life of

CAZ (mean ± SD) were 55.7 ± 34.4 mL/h (37.3 ± 11.9 mL/h/kg), 496 ± 228 mL (350 ± 96 mL/kg), and 6.95 ± 2.32 h, respectively. The mean ± SD peak and trough levels were 114.9 ± 39.4 and 33.9 ± 17.8 mg/L. All infants had a serum trough level above 5 mg/L. Clearance and apparent volume of distribution of CAZ and GFR increased significantly with increasing GA, whereas serum trough levels and serum half-life of CAZ decreased significantly with increasing GA. CAZ clearance increased significantly with increasing GFR. Prenatal exposure to indomethacin resulted in significantly lower GFR values and CAZ clearances.

Conclusions

Dosage recommendations for CAZ administration in preterm infants during the first week of life should be based on GA and GFR. Additional dosage adjustments are indicated in preterm infants who are prenatally exposed to indomethacin.

5.2 Introduction

CAZ, a third generation cephalosporin, is frequently used for the treatment of bacterial infections in newborn infants. It is active against common gram-positive neonatal pathogens such as *Streptococcus agalactiae* (MIC_{90} <0.25 mg/L) and against gram-negative bacilli, including *Escherichia coli* (MIC_{90} <0.25 mg/L)[1,2,3]. Despite the widespread use of CAZ in neonatal intensive care units, the pharmacokinetics of CAZ in preterm infants with GAs of less than 30 weeks have not been studied. The pharmacokinetic parameters of CAZ in preterm infants with GAs above 30 weeks show a large variability in kinetic parameters [4,5,6,7,8]. The currently recommended dosage for CAZ in preterm infants less than 4 weeks of life with a birth weight below 1200 g is 25-50 mg/kg of body weight every 12 h[4,5,6,7,8,9]. Dosage recommendations for CAZ are derived from studies which did not stratify patients according to GA or postnatal age. However, the GFR of preterm infants increases significantly with advancing GA and postnatal age[10,11]. This has a major effect on the pharmacokinetics of antibiotics which are mainly eliminated by glomerular filtration, as was demonstrated for amoxicillin[12]. In addition, prenatal exposure to betamethasone (a drug prescribed to pregnant women with an increased risk of

preterm delivery with the intention to prevent hyaline membrane disease) or indomethacin (a drug prescribed to pregnant women in order to inhibit preterm uterine contractions) exert significant effects on the GFR of preterm infants in the first days of life [11]. CAZ has a low level of serum protein binding and is eliminated primarily by glomerular filtration[13,14]. We therefore hypothesized that the pharmacokinetic behaviour of CAZ in preterm infants in the first days of life would be influenced by GA and GFR, and that this might result in higher concentrations of CAZ in the more preterm infants. The purpose of the present study was to determine the effects of GA and GFR on the multiple-dose pharmacokinetics of CAZ in preterm infants with GAs between 24 and 37 weeks on day 3 of life and to establish appropriate dose and dose-interval recommendations for CAZ administration in preterm infants during the first week of life.

5.3 Methods

Patients

One hundred and thirty-six preterm infants with GAs between 24 and 37 weeks, admitted to the neonatal intensive care unit with suspected or documented septicemia, were eligible for this study. The inclusion criteria were: postnatal age of 3 days, stability of hemodynamic function (diuresis >1 mL/kg of body weight per h; systolic and diastolic blood pressure above the third percentile adjusted for GA), and a normal liver function. Infants receiving nephrotoxic or inotropic drugs were excluded. All patients had an indwelling arterial catheter. The partial pressure of oxygen in arterial blood was kept at greater than 50 mmHg or oxygen saturation was greater than 92%. The GAs of the 136 infants were estimated from the mother's menstrual history, early ultrasound if available and from physical examination using the criteria of Dubowitz et al.[15]. Preterm infants with GAs of less than 34 weeks were given CAZ (25 mg/kg intravenously) every 12 h and amoxicillin (25 mg/kg intravenously) every 12 h. Preterm infants with GAs between 34 and 37 weeks assigned to receive therapy were given CAZ (50 mg/kg intravenously) every 12 h and amoxicillin (50 mg/kg intravenously) every 12 h. Patients with documented

invasive bacterial infections received at least 10 days of intravenous therapy. Patients with sterile blood cultures and with only a suspicion of infection received a total of 72 h of therapy.

Eighty-four infants (group A) were not prenatally exposed to betamethasone or indomethacin. Twenty-five infants were prenatally exposed to indomethacin but not to betamethasone (group B). Only six infants were prenatally exposed to betamethasone, but not to indomethacin (group C). Twenty-one infants were prenatally exposed to both betamethasone and indomethacin (group D).

Betamethasone was administered in two intravenous doses of 12 mg each on 2 consecutive days. This dose was repeated every week until delivery or until the 32nd week of gestation. Indomethacin was administered in suppositories of 100 mg each, which were repeatedly given in the presence of preterm uterine contractions. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. Patients were only enrolled after informed consent was obtained from the parents.

Pharmacokinetic study

The multiple-dose pharmacokinetics of CAZ were studied on day 3 after birth. Blood samples were taken from indwelling arterial lines before administration of an intravenous bolus injection (t=0) and at 0.5, 1, 2, 4, 8, and 12 h after the administration. These sampling times were selected based on the known disposition profile for CAZ. Serum samples obtained after centrifugation (Merck-type Eppendorf 5414, 3000 x g for 1 minute) were stored at -70°C.

Measurement of the glomerular filtration rate

The GFR was measured by the continuous inulin infusion technique on day 3 after birth[10,11]. A 10% glucose-inulin solution containing 25 g of inulin per liter was infused at a rate of 0.6 mL/kg/h, beginning at time (t) zero of the pharmacokinetic study. After 24 h, the inulin clearance (CL_{in}) was calculated from the infusion rate (R), the inulin concentration in the infusate (I), and the serum inulin concentration (P_{in}) by the equation $CL_{in} = I.R/P_{in}$. Determination of the inulin in serum was performed after acid hydrolysis in 0.3 mmol/L perchloric acid for 15 minutes at 70°C. The fructose thus formed was measured enzymatically.

Ceftazidime assay

Analysis of serum CAZ concentrations was performed according to the method described by Ayrton[16] with minor modifications. HPLC-grade acetonitrile was purchased from Rathburn (Walkerburn, Scotland). The other chemicals were purchased from Aldrich-Chemie (Steinheim, Germany). All chemicals applied were of the highest grade commercially available. Chromatographic analysis was performed with a glass-prepacked C_{18} column (100 by 8 mm, Resolve Radial Pak, Waters, USA) combined with a guard column. A Waters Chromatography pump (model 6000 A, Waters, USA) was used to deliver the eluent: 4.8% (vol/vol) acetonitrile, 13.5% methanol in 20 mM sodium acetate buffer (pH 3.6) at a flow rate of 2 mL/min. The separations were carried out at room temperature.

The eluate was monitored with two Waters Absorbance Detectors (Model 440/ wavelength of 254 nm and Model 484/wavelength 265 nm, Waters, USA).

To a 50-µL aliquot of the serum sample, an equal volume of 6% (vol/vol) perchloric acid containing 50 mg/L cephaloridine as an internal standard was added. Samples were centrifuged at 1500 g for 5 minutes (Eppendorf Centrifuge 5412). Subsequently, 25 µL was injected into the column by a WISP (Waters Intelligent Sample Processor) sample injector.

A calibration curve was made by dissolving 4, 12, 25, 50, 100, 200, and 400 mg CAZ per liter in serum. These spiked standard samples were processed according to the procedure mentioned above. A linear calibration curve was obtained over a range of 4 to 400 mg of CAZ per liter. Because the spiked samples of the calibration curve underwent the same processing procedure as the clinical samples, the clinical samples were directly converted from the calibration curve to actual CAZ concentrations per liter of serum. The lower limit of detection of CAZ in serum was 0.5 mg/L. The coefficients of interassay variation at different concentrations were less than 7%. The intraassay values were less than 5%. Recovery of 95% of CAZ, which had been incubated for 24 h at room temperature, was established.

Pharmacokinetic analysis

Pharmacokinetics were studied on the third day after birth. Kinetic data were described using a one-compartment open model. Visual inspection of individual model fits gave no indication that a model more complex than a one-compartment

model was required. Pharmacokinetic parameters were calculated with the multiple-dose equations described by Rowland and Tozer[17]. The basic equation used was C_t = dose/V x $(1-r^N)/(1-r)$ x e^{-kt}. In this equation, C_t is the plasma concentration of CAZ at times t after each dose, V is the apparent volume of distribution, N is the dose number, $r = e^{-k\tau}$, in which k is the elimination rate constant and τ the dosing interval. Because doses were given twice daily, the CAZ concentration-versus-time curve was assumed attributable to the 7th dose (and the trough level at t = 0 was assumed to be attributable to the 6th dose). Total body clearance (CL) was calculated with the following equation: CL = k.V. Concentration time plots showed linear decrease over time and no indication of levelling off. Scatter was evenly distributed on log-scale indicating the need for $1/(Ycal)^2$ weighting. All calculations were carried out with the non-linear regression module of SPSS/PC + V 4.0.1 (SPSS, Inc., Chicago, Ill.), which uses a Levenberg-Marquardt algorithm.

In order to examine the different dosing strategies, based on the assumption that serum trough levels should never drop below 5 mg/L, dosage recommendations for CAZ were calculated using the following equation:

$$5 < C_\tau = \frac{D.wt.e^{-k\tau}}{V}$$

In this equation C_τ is the serum trough concentration, D the prescribed dose in mg/kg, wt the weight in kg, k the elimination rate constant, τ the dosing interval, and V the apparent volume of distribution of CAZ.

Statistical analysis

Data given are mean ± SD unless indicated otherwise. Correlation coefficients given are Pearson's. Comparison of groups was done using the t-test. Least-squares regression was used to evaluate linear relations between variables. In most of these analyses the dependent variable had to be transformed logarithmically to obtain approximate normal distributed residuals. P-values ≤ 0.05 (two-sided) were considered significant.

5.4 Results

One hundred and thirty-six neonates were enrolled in the study. Fifty-five infants (40%) had GAs of less than 30 weeks. The demographic and clinical parameters of all patients are shown in Table 1. The pharmacokinetic parameters of CAZ before and after normalization for weight and the inulin clearances are indicated in Table 2. The mean ± SD of total body clearance, apparent volume of distribution, and the serum half-life of CAZ were 55.7 ± 34.4 mL/h, 496 ± 228 mL, and 6.95 ± 2.32 h, respectively. After correction for body weight the mean ± SD of clearance and volume of distribution of CAZ were 37.3 ± 11.9 mL/h/kg, and 350 ± 96 mL/kg, respectively. The mean ± SD peak and trough levels were 114.9 ± 39.4 and 33.9 ± 17.8 mg/L, respectively. All neonates had serum trough concentrations above 5 mg/L. The serum trough levels of CAZ were high (>40 mg/L) especially in infants with GAs of less than 28 weeks. Clearance of CAZ (r=0.83, p<0.001) (Figure 1) as

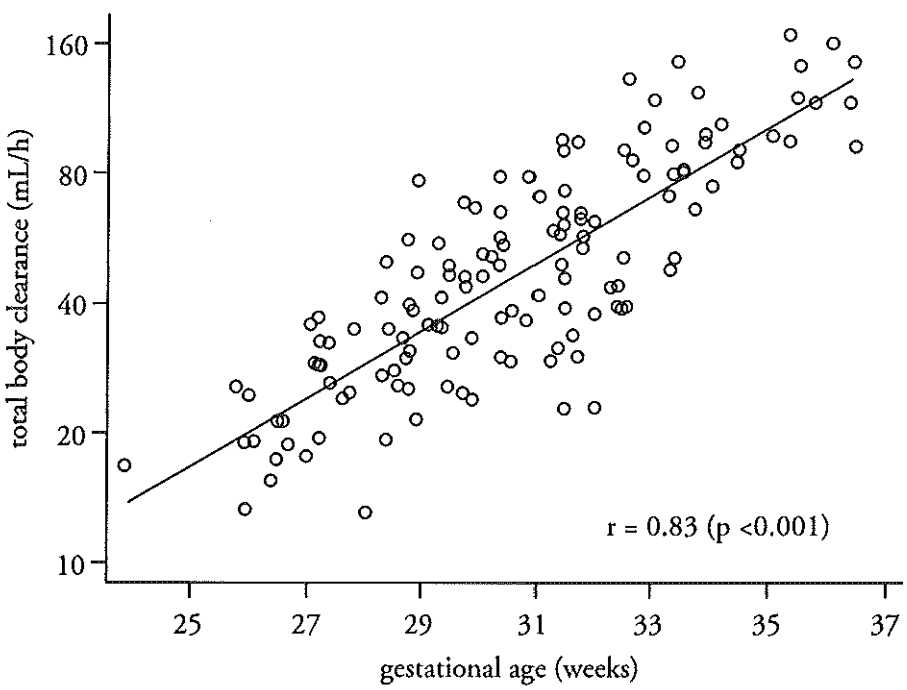

Figure 1. **Linear regression analysis of total body clearance of ceftazidime (mL/h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth. Note the logarithmically transformed vertical axis**

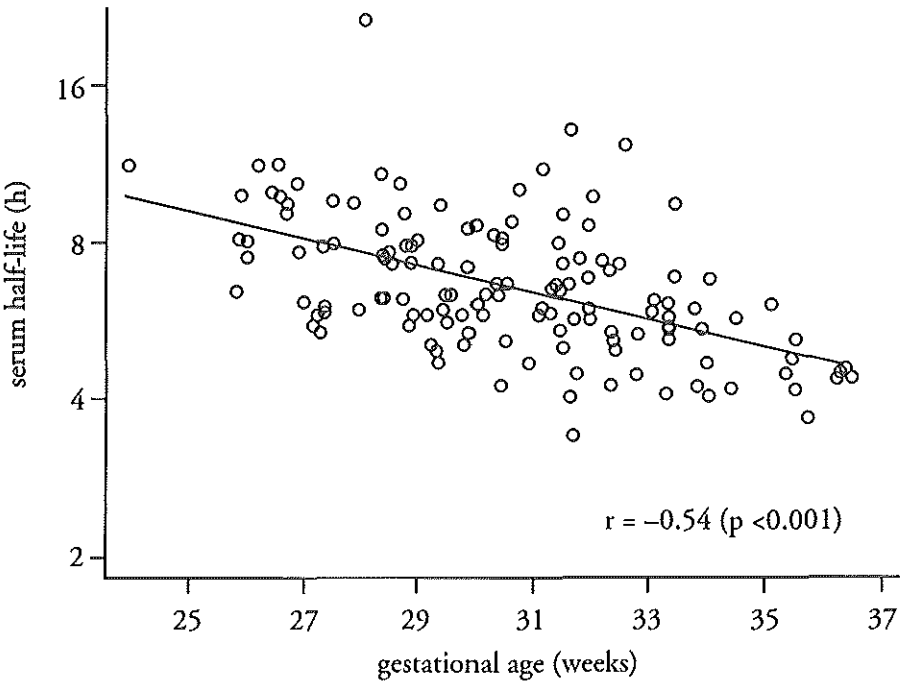

Figure 2. **Linear regression analysis of serum half-life of ceftazidime (h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth**

well as volume of distribution of CAZ (r=0.74, p<0.001) increased significantly with increasing GA. Clearance of CAZ (r=0.88, p<0.001) as well as volume of distribution of CAZ (r=0.84, p<0.001) also increased significantly with weight. The correlation between GA and volume of distribution disappeared (p=0.588) after normalization of volume of distribution for weight. Clearance of CAZ per kg still increased significantly with GA (r=0.56, p<0.001). The serum half-life of CAZ decreased significantly with GA (r=–0.54, p<0.001) (Figure 2) as well as with weight (r=–0.50, p<0.001). Inulin clearance (as a parameter of the GFR) increased significantly with increasing GA (r=0.63, p<0.001). The clearance of CAZ increased significantly with increasing inulin clearance (r=0.73, p<0.001) (Figure 3), whereas serum half-life of CAZ decreased significantly with increasing inulin clearance (r=–0.70, p<0.001). The reciprocal of the serum creatinine, a useful index of glomerular filtration in clinical practice, showed a positive linear relationship with the clearance of CAZ (r=0.72, p<0.001) (Figure 4).

Table 1. **Clinical parameters of infants with or without prenatal exposure to betamethasone or indomethacin**[a]

	Group A (n = 84) (Indo–/Beta–)	Group B (n = 25) (Indo+/Beta–)	Group C (n = 6) (Indo–/Beta+)	Group D (n = 21) (Indo+/Beta+)	Total (n = 136)
GA (weeks)	31.5 ± 2.8[b]	28.9 ± 2.3	30.4 ± 2.0	29.2 ± 1.3	30.6 ± 2.7
Weight (g)	1579 ± 597[b]	1133 ± 334	1093 ± 266	1174 ± 265	1413 ± 545
AGA	72 (86%)	24 (96%)	5 (83%)	21 (100%)	122 (90%)
Ventilation	66 (79%)	17 (68%)	3 (50%)	14 (67%)	100 (74%)
RDS	26 (31%)	5 (20%)	2 (33%)	4 (19%)	37 (27%)

[a]Values are mean ± SD or numbers (%) of patients
Abbreviations: Indo, indomethacin; Beta, betamethasone; GA, gestational age; AGA, appropriate for gestational age; RDS, respiratory distress syndrome
Symbols: –, no prenatal exposure; +, prenatal exposure
[b]Significantly different ($p<0.005$) from groups B and D

Table 2. **Pharmacokinetic parameters of ceftazidime and inulin clearances at day 3 after birth in infants with or without prenatal exposure to betamethasone or indomethacin**[a]

	Group A (n = 84) (Indo–/Beta–)	Group B (n = 25) (Indo+/Beta–)	Group C (n = 6) (Indo–/Beta+)	Group D (n = 21) (Indo+/Beta+)	Total (n = 136)
CL (mL/h)	67.9 ± 37.6	32.6 ± 15.9[b]	37.9 ± 13.0	39.9 ± 11.0	55.7 ± 34.4
CL (mL/h/kg)	41.0 ± 12.2	28.2 ± 9.5[b]	34.5 ± 7.2	34.0 ± 6.2	37.3 ± 11.9
V (mL)	560 ± 241	416 ± 196	315 ± 54	386 ± 120	496 ± 228
V (mL/kg)	356 ± 94	366 ± 130	294 ± 38	326 ± 53	350 ± 96
$t_{1/2}$ (h)	6.32 ± 1.72	9.39 ± 3.15[b]	6.05 ± 1.10	6.83 ± 1.57	6.95 ± 2.32
CL_{in} (mL/min)	0.90 ± 0.19	0.66 ± 0.11	0.93 ± 0.16	0.81 ± 0.12	0.85 ± 0.19

[a]Values are mean ± SD
Abbreviations: Indo, indomethacin; Beta, betamethasone; CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life; CLin, inulin clearance
Symbols: –, no prenatal exposure; +, prenatal exposure
[b]Significantly different from group A after adjustment for differences in gestational age

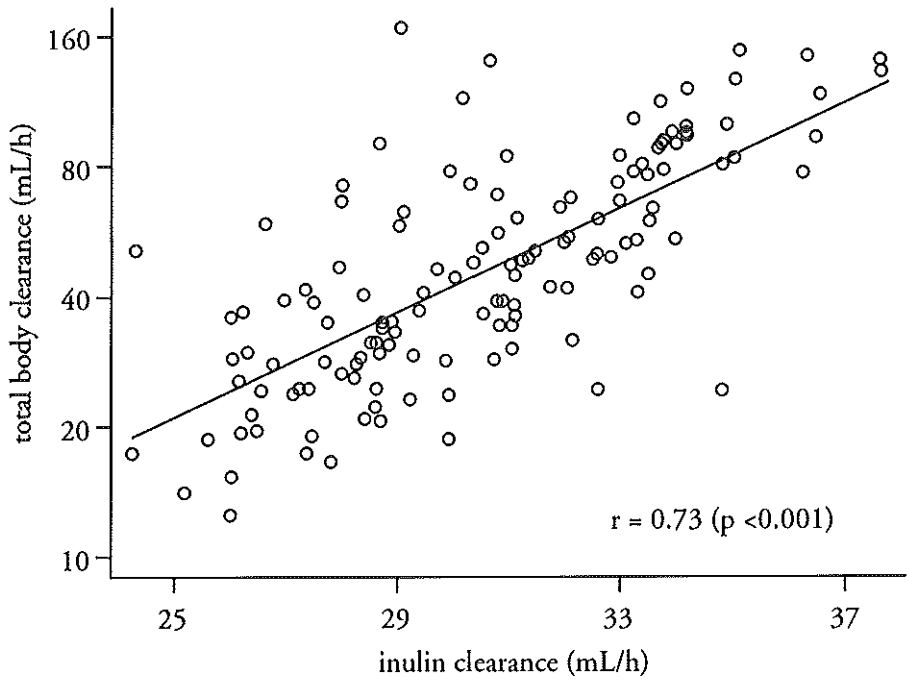

Figure 3. **Linear regression analysis of total body clearance of ceftazidime (mL/h) versus inulin clearance (mL/h) in 136 preterm infants on day 3 after birth**

Assuming that serum concentrations should not be lower than 5 mg/L appropriate dosing can be achieved by administration of 10 mg/kg CAZ twice daily to infants with GAs of less than 28 weeks, 15 mg/kg twice daily to infants with GAs between 28 and 32 weeks, and 25 mg/kg twice daily to infants with GAs above 32 weeks (Figure 5). Alternatively, appropriate dosing may also be achieved by prolonging the dosing interval to 24 h in preterm infants with GAs of less than 32 weeks using 25 mg/kg. These recommendations may be applied to all preterm infants on a neonatal intensive care unit irrespective of prenatal exposure to betamethasone or indo-methacin.

To study the impact of prenatal exposure to betamethasone or indomethacin on the pharmacokinetic parameters of CAZ the infants were divided into four groups. Table 1 shows the clinical parameters of the infants in these four groups. The GAs of the infants who were prenatally exposed to indomethacin with or without beta-methasone (groups B and D) were significantly lower compared with the GAs of

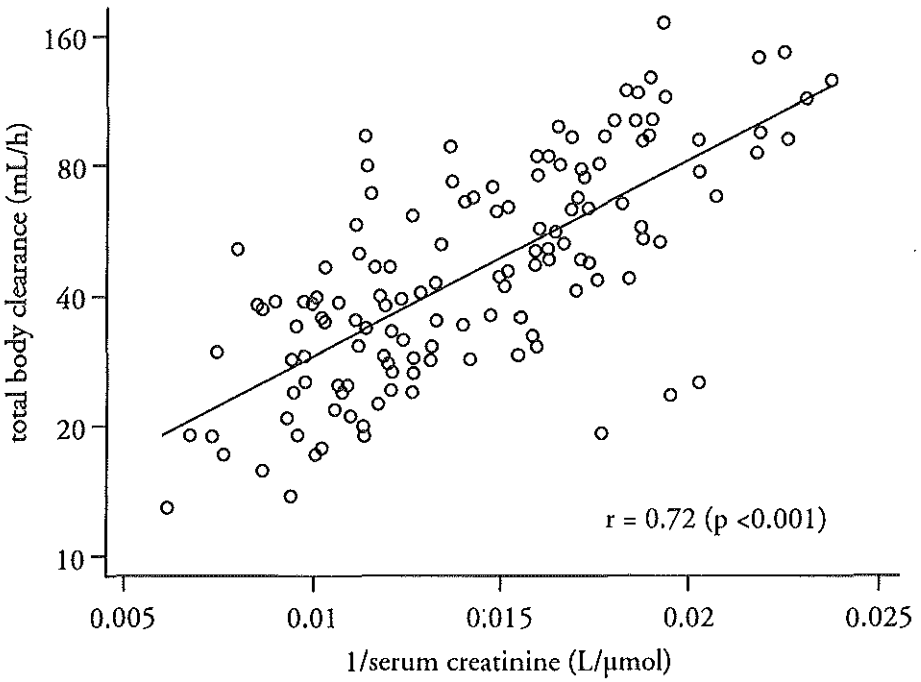

Figure 4. **Linear regression analysis of total body clearance of ceftazidime (mL/h) versus the reciprocal of serum creatinine (L/µmol) in 136 preterm infants on day 3 after birth**

the infants who were not prenatally exposed to betamethasone or indomethacin (group A). Table 2 shows the pharmacokinetic parameters of CAZ and inulin clearances at day 3 after birth in infants with or without prenatal exposure to betamethasone or indomethacin. After adjustment by multiple regression for the difference in GA between groups the clearance of CAZ of the patients in group B (prenatal exposure to indomethacin) was still significantly decreased and the serum half-life of CAZ significantly prolonged compared with the clearance and serum half-life values of the patients in group A (not exposed to indomethacin or betamethasone). The effect of prenatal exposure to indomethacin was not dependent on the GA or on the severity of illness. No significant difference was present between the CAZ clearance or serum half-life of the patients in group D (prenatal exposure to both betamethasone and indomethacin) and group A (not exposed to indomethacin or betamethasone) when adjusted for GA. The number of children in group C (n=6) was considered too small for reliable statistical analysis.

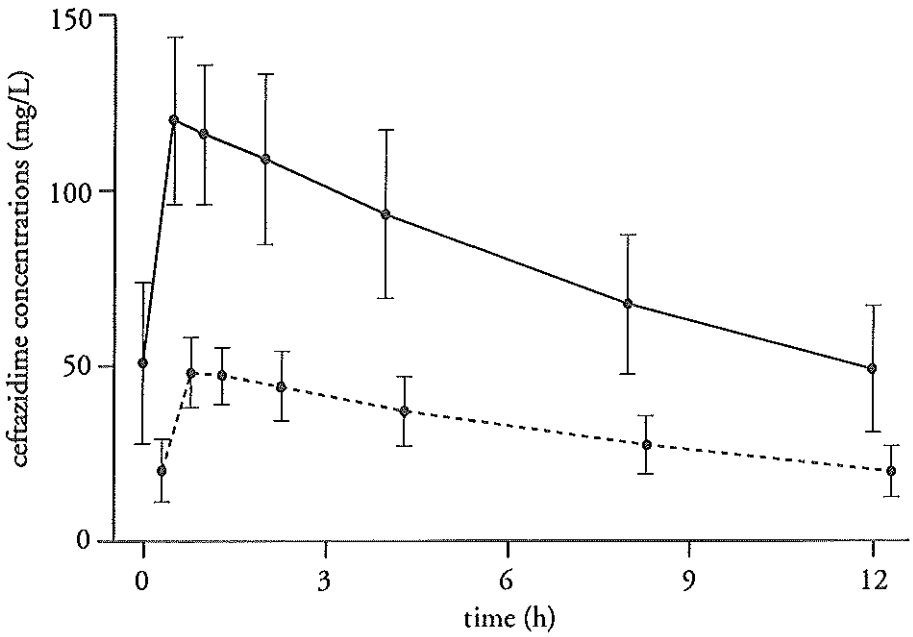

Figure 5. Serum drug concentration-versus-time profiles of ceftazidime (25 mg/kg of body weight) in 27 preterm infants with gestational ages of less than 28 weeks on day 3 after birth (continuous line) versus predicted serum drug concentration-versus-time-profiles of ceftazidime (10 mg/kg of body weight) in the same infants (dotted line)

5.5 Discussion

CAZ is predominantly eliminated from serum by glomerular filtration. Even at relatively high concentrations the tubular excretion of CAZ is negligible[18]. The pharmacokinetics of CAZ in adults are dose independent over a dose range of 0.5-2.0 gram intravenously and unaltered by repeated dosing[14,19].

The pharmacokinetic parameters of CAZ are different in the newborn in comparison with those in other pediatric age groups and adults[20,21]. Furthermore, in preterm infants with GAs of more than 30 weeks, a large variability in these parameters has been reported[4,6,8,22,23,24]. The major reasons for this variability are differences in GA and postnatal age, the route of antibiotic administration and an insufficient number of postdose samples to reliably calculate pharmacokinetic parameters.

The currently recommended dosing guidelines are based on these data. We questioned the validity of these recommendations and designed this study to establish appropriate dosage recommendations.

Our results indicate that twice daily administration of 25 mg/kg CAZ to infants with GAs of less than 34 weeks and 50 mg/kg to infants with GAs of more than 34 weeks results in high serum levels during the entire dosing interval. The values for serum half-life were markedly increased in the less mature preterm infants and showed a GA-dependent decrease. These values were similar to those previously reported by others[4,5,6], whereas one study reported lower values[8]. However, the latter study included only small numbers of slightly older neonates. This relationship between GA and serum half-life was also seen for cefotaxime, but the mechanism of the decrease of the serum half-life of cefotaxime with increasing GA remained speculative[25]. Gouyon et al.[26] postulated that cefotaxime clearances and serum half-life were closely dependent on the normal maturation of renal function in newborn infants. However, they could not provide evidence for this assumption. Other studies on the disposition of cefotaxime did not provide sufficient data to document possible effects of renal development on cefotaxime pharmacokinetics[27,28,29,30,31].

The second aim of our study was to relate the effects of GA on the pharmacokinetics of CAZ to changes in GFR. Our results demonstrate the presence of a GA-dependent increase of the GFR in these preterm infants. These data are in agreement with those from other studies in which a positive linear relationship between the GA and the GFR was demonstrated [10,11,32]. The positive relationship ($r=0.73$, $p<0.001$) between the GFR and the clearance of CAZ indicates that glomerular filtration has an important effect on the clearance of CAZ. However, the variability in the clearances of CAZ exceeds that of the inulin clearance (Figure 3). This indicates that CAZ is not eliminated by glomerular filtration alone. We propose that tubular reabsorption and/or tubular secretion are involved in the renal handling of CAZ in preterm infants.

The third aim of this study was to calculate dose recommendations for CAZ that may be used during the first week of life. An optimal dose regimen should result in a high clinical efficacy and a minimal chance on toxicity. To ensure clinical efficacy serum concentrations of CAZ should be above the MIC of CAZ for major neonatal

pathogens such as *Streptococcus agalactiae* (MIC_{90} <0.25 mg/L) and *Escherichia Coli* (MIC_{90} <0.25 mg/L)[2,3]. In our preterm infants serum concentrations of CAZ are sufficiently high to obtain maximal clinical efficacy. However, beta-lactam antibiotics are all neurotoxic to some extent[33,34]. In adults CAZ has been reported to cause encephalopathy, hallucinations, confusion, and neuromuscular excitability[35,36,37,38,39]. In the rat model, a dose dependent suppressive effect of beta-lactam antibiotics has been demonstrated on the differentiation and proliferation of oligodendrocytes[40]. In addition to this potential neurotoxic side effect, high concentrations of CAZ may also result in inhibition of cell proliferation in cultured human myeloid precursor and lymphoid cells[41]. This may lead to neutropenia and impairment of cellular and humoral immune responses. The above described toxicity profile indicates that modification of the dose of CAZ in the preterm infant should be considered to prevent potential drug-induced toxicity. However, CAZ-related side effects or differences in efficacy could not be demonstrated despite the large variability in levels of CAZ.

The presence of high serum trough concentrations and a prolonged serum half-life suggest that dosage adjustments are needed in this patient population. Our data indicate that the low GFR is primarily responsible for the decreased CAZ clearance. However, CAZ clearance is also dependent on GA. As the determination of GA is much easier than the measurement of the GFR we suggest that dose recommendations of CAZ in the preterm infant should be primarily based on GA. This approach is supported by the stronger correlation between CAZ clearance and GA (r=0.83) in comparison with the correlation between CAZ clearance and GFR (r=0.73).

To calculate dosage recommendations infants were stratified in three groups: GAs of less than 28 weeks, GAs between 28 and 32 weeks, GAs between 32 and 37 weeks. We used a model in which a trough level of 5 mg/L was chosen as the minimum level desired for appropriate bacterial killing of the major neonatal microorganisms. Two different strategies were used for the calculations. First, dosage recommendations were calculated using a fixed dosing interval of 12 h. Alternatively, appropriate dosing may also be achieved by prolonging the dosing interval to 24 h in infants with GAs of less than 32 weeks. These recommendations may be applied to a broad population of preterm infants because they are derived from results

obtained from all preterm infants on a neonatal intensive care unit irrespective of prenatal exposure to betamethasone or indo-methacin. Further studies will be necessary to determine if invasive bacterial infections have a significant effect on the pharmacokinetics of CAZ in the first two weeks of life.

We recently reported that prenatal exposure to betamethasone or indomethacin exerted significant effects on the GFR of preterm infants in the first days of life[11]. We therefore studied the effects of prenatal exposure to betamethasone and indomethacin on the pharmacokinetics of CAZ. Most pregnant women who were treated with betamethasone were also treated with indomethacin to inhibit preterm uterine contractions. The number of patients exposed to betamethasone alone was therefore too small to perform a separate analysis. Our analysis indicates that the GA-adjusted CAZ clearance of the infants who were prenatally exposed to both betamethasone and indomethacin was significantly higher compared with the clearance of CAZ of the infants who were prenatally exposed to indomethacin alone. In addition, the GA-adjusted clearance of CAZ of the infants who were prenatally exposed to both drugs was not different from the clearance of CAZ of the infants who were not exposed at all (group A). The GA-adjusted volume of distribution of CAZ did not show any significant difference between groups A, B and D. Consequently, the GA-adjusted serum half-life of CAZ of the infants who were prenatally exposed to both betamethasone and indomethacin was significantly shortened compared with the serum half-life of CAZ of the infants who were prenatally exposed to indomethacin alone. Additionally, the GA-adjusted serum half-life of the infants who were prenatally exposed to both drugs were not different from the serum half-life of the infants who were not exposed at all (group A).

These results clearly indicate that prenatal exposure to indomethacin alone significantly decreases CAZ clearance and increases serum half-life of CAZ. The co-administration of betamethasone prevents these changes. We therefore advocate that additional dosage adjustments in the first week of life are needed after prenatal exposure to indomethacin, when this is not combined with the use of betamethasone. The recommended dosage for infants with GAs of less than 28 weeks should be adjusted to 7.5 mg/kg of body weight every 12 h, and for infants with GAs between 28 and 32 weeks this should be adjusted to 10 mg/kg of body weight every 12 h. Prescription of indomethacin as a tocolytic agent is much more restricted in the

USA than in the Netherlands. This has been caused by reports about negative effects on fetal and neonatal renal and cardiovascular function[42,43,44]. Our data demonstrate that there is an effect of maternally administered indomethacin on renal function in the newborn during the first three days of life. At day 10 after birth this effect could no longer be detected. Although renal toxicity was reversible it may result in metabolic and volume derangements in addition to potential drug overdosing. These data are in agreement with the lower urine output and higher serum creatinine concentrations that were seen during the first three days of life in preterm infants delivered at or before 30 weeks' gestation whose mothers had been treated with indomethacin[45]. Other complications seen after prenatal exposure to indomethacin are: necrotizing enterocolitis, intracranial hemorrhage and a patent ductus arteriosus[45]. Indomethacin is an effective tocolytic drug that unfortunately also increases the risk of complications associated with preterm birth. Prospective studies are needed to investigate if the efficacy of indomethacin as a tocolytic agent outweighs the risk of these complications.

In summary dosage recommendations for CAZ in preterm infants for the first week of life should be based on GA and GFR, and in preterm infants who are prenatally exposed to indomethacin additional dosage adjustments are indicated.

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CHAPTER 6

AMOXICILLIN PHARMACOKINETICS IN PRETERM INFANTS WITH GESTATIONAL AGES OF LESS THAN 32 WEEKS

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CHAPTER 6

AMOXICILLIN PHARMACOKINETICS IN PRETERM INFANTS WITH GESTATIONAL AGES OF LESS THAN 32 WEEKS

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6.1 Abstract

The multiple-dose pharmacokinetics of amoxicillin (AM [administered twice daily in a 25 mg/kg of body weight intravenous dose]) in 17 preterm infants (11 males; gestational age, 29 ± 1.9 weeks; birth weight, 1175 ± 278 g) were evaluated on day 3 of life. Blood samples were collected from an arterial catheter at 0, 0.5, 1, 2, 4, 8 and 12 h after the intravenous dose. A high-performance liquid chromatography method was used to determine AM concentrations in serum. AM pharmacokinetics followed a one-compartment open model. The glomerular filtration rates (GFRs) of all patients were simultaneously studied by means of the 24 h continuous inulin infusion technique. The serum half-life, apparent volume of distribution, and total body clearance of AM (mean ± SD) were 6.7 ± 1.7 h, 584 ± 173 mL, and 62.4 ± 23.3 mL/h, respectively. The (mean ± SD) AM peak and trough levels were 53.6 ± 9.1 and 16.0 ± 4.9 mg/L, respectively. All infants had a serum trough level above 5 mg/L. The total body clearance and apparent volume of distribution of AM and the clearance of inulin increased significantly with increasing gestational age (GA). The total body clearance of AM (1.0 ± 0.4 mL/min) and the clearance of inulin (1.0 ± 0.3 mL/min) were similar. The total body clearance of AM increased significantly with increasing clearance of inulin. We conclude that an AM dose of 25 mg/kg given twice daily to preterm infants in the first week of life with GAs of

less than 32 weeks results in serum levels well above the MIC of major micro-organisms involved in neonatal infections.

6.2 Introduction

AM, a penicillin derivative, is an antibiotic frequently used for the treatment of infectious diseases in newborn infants. It is active against common gram-positive neonatal pathogens such as *Listeria monocytogenes, Streptococcus_agalactiae* and *Streptococcus faecalis* and against gram-negative bacilli, including non-ß-lactamase producing *Haemophilus influenzae* and *Escherichia coli.* The combination of AM with a broad-spectrum cephalosporin or an aminoglycoside is an effective empiric treatment of suspected neonatal septicemia[1]. Despite the widespread use of AM in neonatal intensive care units, the pharmacokinetics of AM in preterm infants have not been studied.

The currently recommended dosage for ampicillin in preterm infants less than 4 weeks of life with a birth weight below 1200 g is 25-50 mg/kg of body weight every 12 h[2,3,4]. Dosage recommendations for AM are extrapolated from studies of ampicillin which did not stratify patients according to GA or postnatal age [5,6,7,8,9,10]. However, the GFR of preterm infants increases significantly with advancing GA and postnatal age[11,12]. This has a major effect on the pharmacokinetics of antibiotics which are mainly excreted by glomerular filtration, as has been demonstrated for the pharmacokinetics of ceftazidime[13]. AM has a low level of serum protein binding (±17%) and is excreted primarily by glomerular filtration[14]. We hypothesized that the pharmacokinetic behaviour of AM in preterm infants in the first week of life would be influenced by GA-dependent differences in GFR. We therefore investigated the pharmacokinetics of AM (25 mg/kg twice daily) during the first week of life in 17 infants with a GA below 32 weeks and studied the effect of GA-dependent differences in GFR on the kinetic parameters.

6.3 Methods

Patients and study design

Seventeen preterm infants with GAs of less than 32 weeks, admitted to the neonatal intensive care unit with suspected or documented septicemia or invasive infection, were eligible for study. Subjects were recruited by informed parental consent. The inclusion criteria were postnatal age of 3 days, stability of hemodynamic function (diuresis >1 mL/kg of body weight per h; systolic and diastolic blood pressure above the third percentile adjusted for GA), normal liver function, and no concurrent administration of nephrotoxic or inotropic drugs. All patients had an indwelling arterial catheter. The partial pressure of oxygen in arterial blood was kept at greater than 50 mmHg or oxygen saturation greater than 92%.

Neonates assigned to receive therapy were given AM (25 mg/kg intravenously) every 12 h and ceftazidime (25 mg/kg intravenously) every 12 h. Patients with documented invasive bacterial infections received at least 10 days of intravenous therapy. Patients with sterile cultures and without a focus of infection received a total of 72 h of therapy. From each patient, the following laboratory parameters were obtained: complete blood count with differential and platelet count, blood and urine cultures, and arterial blood-gas analysis.

Pharmacokinetic study

The pharmacokinetics of AM were studied on day 3 after birth. Blood samples were taken from indwelling arterial lines before administration of an intravenous bolus injection (t=0) and at 0.5, 1, 2, 4, 8, and 12 h after the intravenous dose. Serum samples obtained after centrifugation in a microcentrifuge (Merck-type Eppendorf 5414; 3000 x g for 1 minute) were stored at -70°C.

Measurement of the glomerular filtration rate

The GFR was measured by the continuous inulin infusion technique on day 3 after birth[12]. A 10% glucose-inulin solution containing 25 g of inulin per liter was infused at a rate of 0.6 mL/kg/h, beginning at time (t) zero of the pharmacokinetic study. After 24 h the inulin clearance (CL_{in}) was calculated from the infusion rate (R), the inulin concentration in the infusate (I) and the serum inulin concentration (P_{in}) by the equation: $CL_{in} = I.R/P_{in}$.

Amoxicillin assay

Analysis of AM serum concentrations was performed according to the method described by Haginaka and Wakai[15] with minor modifications. HPLC-grade acetonitrile was purchased from Rathburn (Walkerburn, Scotland). The other chemicals were purchased from Aldrich-Chemie (Steinheim, Germany). All chemicals applied were of the highest grade commercially available.

Chromatographic analysis was performed with a glass-prepacked column (100 by 3 mm) containing ODS-2 Chromospher Spherisorb beads (5-μm-diameter particle size; Chrompack, Middelburg, The Netherlands) combined with a guard column. A Bio LC pump (model 410, Perkin-Elmer, Norwalk, Conn.) was used to deliver the eluent: 15% (vol/vol) acetonitrile, 50 mM sodium phosphate buffer, and 10 mM thiosulfate buffer (pH 4.6) at a flow rate of 0.8 mL/min. The separations were carried out at room temperature. The eluate was monitored with a Perkin-Elmer LC-95 UV/visible spectrophotometer detector at a wavelength of 328 nm.

To a 100-μl aliquot of the serum sample, 100 μl of 10 M urea solution was added. Subsequently the mixture was ultrafiltrated with an Amicon MPS-1 micropartition system with Amicon YMT membranes (Amicon Corp., Lexington, Mass.) by centrifugation at 1500 x g for 30 minutes at room temperature. To an 80-μl aliquot of the ultrafiltrate, 80 μl of 0.1 M borate buffer (pH 9.0) and 8 μl of 0.2 M acetic anhydrate solution were added, and the mixture was allowed to stand at room temperature for 3 minutes. Subsequently, 160 μl of 2 M triazole reagent (pH 9.0) containing 1 mM mercury (II) chloride was added. The solution was sealed in a screw-top vial and heated at 60°C for 10 minutes. Subsequently, 20 μl was transferred by an automatic sample injector (Perkin Elmer) to the column.

A calibration curve was made by dissolving 4, 12, 25, 50, and 100 mg of AM per liter in serum. These spiked standard samples were processed according to the procedure mentioned above. A standard line of peak areas versus spiked AM concentrations was determined. A linear calibration curve was obtained over a range of 4 to 100 mg of AM per liter. Because the spiked samples of the calibration curve underwent the same processing procedure as the clinical samples, the clinical samples were directly converted by linear regression from the calibration curve to actual AM concentrations per liter of serum. The lower limit of detection of AM in serum was 1 mg/L. The coefficients of interassay variation determined at concen-

trations of 8.6 and 86 mg/L were 7.9 and 3.4%, respectively. The intraassay values were 2.1 and 4.7%, respectively. Recovery of 95% of the derivatized AM, which had been incubated for 24 h at room temperature, was established.

Pharmacokinetic analysis

Kinetic studies were performed on the third day after birth. Visual inspection of individual model fits gave no indication that a more complex (e.g., two-compartment) pharmacokinetic model was required. Pharmacokinetic parameters were calculated with the multiple-dose equations described by Rowland and Tozer[16]. The basic equation used was C_t = dose/V x $(1-r^N)/(1-r)$ x e^{-kt}. In this equation, C_t is the plasma concentration of AM at times t after each dose, V is the apparent volume of distibution, N is the dose number, and $r = e^{-k\tau}$, in which k is the elimination rate constant and τ is the dosing interval. Because doses were given twice daily, the AM concentration-versus-time curve was assumed attributable to the 7th dose (and the trough level at t=0 was assumed to be attributable to the 6th dose). The data were weighted by $1/(Ycal)^2$. All calculations were carried out with the non-linear regression module of SPSS/PC+ V 4.0.1 (SPSS, Inc., Chicago, Ill.), which uses a Levenberg-Marquardt algorithm.

6.4 Results

Seventeen neonates, including 11 male and 6 female infants, were enrolled in the study. The demographic and laboratory parameters for these patients are shown in Table 1. The pharmacokinetic parameters of AM and the inulin clearances are indicated in Table 2. Figure 1 demonstrates the serum AM concentration-(mean ± SD)-versus-time curve. The mean peak and trough levels (± SD) were 53.6 ± 9.1 mg/L and 16.0 ± 4.9 mg/L, respectively. All neonates had serum trough levels above 5 mg/L.

We examined the relationship between GA and inulin clearance (as a parameter of the GFR) in our patients. We demonstrated that the inulin clearance increased significantly with in-creasing GA ($r=0.84$, $p<0.001$). With increasing GA, the total body clearance of AM increased significantly ($r=0.75$, $p<0.001$) (Figure 2).

Table 1. Demographic and laboratory parameters of 17 patients studied on day 3 after birth[a]

Parameter	
Gestational age (weeks)	29 ± 1.9
Sex (M/F)	11 / 6
Weight (g)	1,175 ± 278
AGA/SGA	15 / 2
Culture positive	0
Hematocrit (%)	44 ± 7
Leukocytes (10^3/mm^3)	15.6 ± 12.6
Platelets (10^3/mm^3)	215 ± 112
Artificial ventilation (+/-)	10 / 7

[a] Values are mean ± SD or numbers of patients
Abbreviations: AGA, appropriate for gestational age; SGA, small for gestational age; M, male; F, female

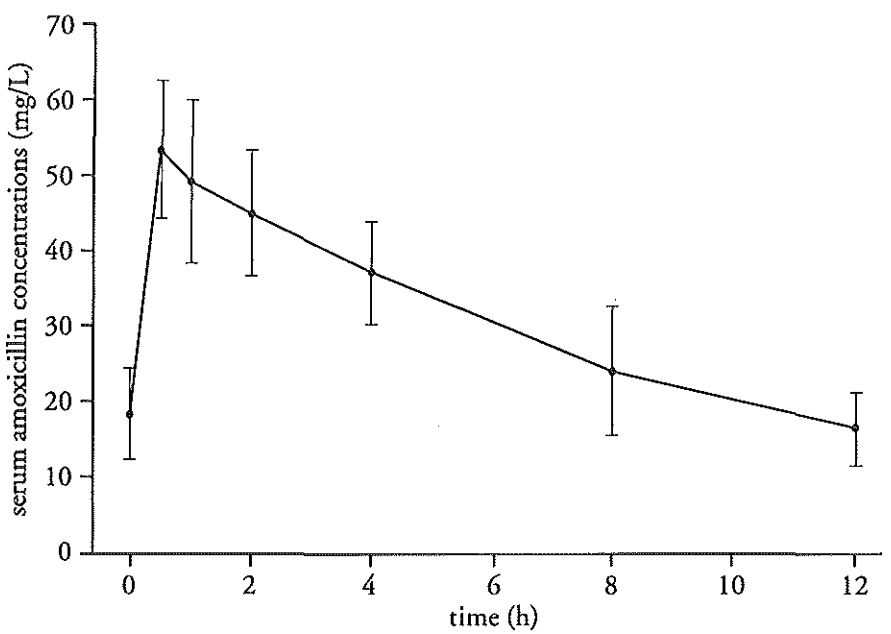

Figure 1. Serum drug concentration-versus-time profiles of amoxicillin (25 mg/kg of body weight) in 17 preterm infants on day 3 after birth Bars indicate standard deviations

Table 2. Pharmacokinetic parameters of amoxicillin and inulin clearances of 17 infants studied on day 3 after birth[a]

Parameter	
$t_{1/2}$ (h)	6.7 ± 1.7
CL (mL/min)	1.0 ± 0.4
CL (mL/min/kg)	1.1 ± 0.2
V (mL)	584 ± 173
V (mL/kg)	671 ± 117
CL_{in} (mL/min)	1.0 ± 0.3
Trough level (mg/L)	16.0 ± 4.9

[a]Values are mean ± SD
Abbreviations: $t_{1/2}$, serum half-life; CL, total body clearance; V, apparent volume of distribution; CL_{in}, inulin clearance

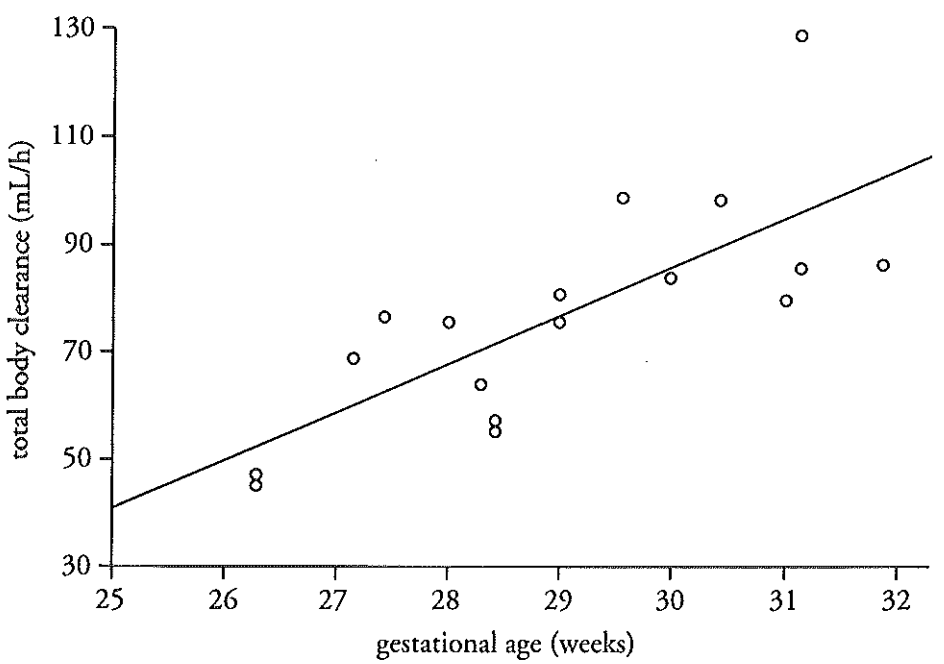

Figure 2. Linear regression analysis of total body clearance of amoxicillin (mL/h) versus gestational age (weeks) in 17 preterm infants on day 3 after birth ($r=0.75$, $p<0.001$, $y=8.88x-181.2$)

Table 3. Correlation coefficients of amoxicillin pharmacokinetic parameters with gestational age and inulin clearance[a]

Parameter	Gestational age	Inulin clearance
$t_{1/2}$ (h)	-0.20	-0.09
CL (mL/min)	0.75***	0.72***
V (mL)	0.58*	0.62**
Trough levels (mg/L)	-0.36	-0.21

Abbreviations: $t_{1/2}$, serum half-life; CL, total body clearance; V, apparent volume of distribution
[a] Statistical significance: *, $p \leq 0.05$ **, $p \leq 0.01$ ***, $p \leq 0.001$

A similar increase was detected for volume of distribution ($r=0.58$, $p<0.05$). AM clearance also increased significantly with weight ($r=0.66$, $p<0.005$). A similar increase was seen for volume of distribution ($r=0.78$, $p<0.001$). After we normalized the parameters volume of distribution and clearance of AM for weight, the previously significant correlations between GA and volume of distribution and between GA and clearance disappeared ($p=0.735$ and $p=0.283$, respectively). clearance of AM (1.0 ± 0.4 mL/min) and inulin clearance (1.0 ± 0.3 mL/min) were equal. We determined the presence of a regression between inulin clearance and AM clearance. We found that AM clearance was equal to (47.1 x inulin clearance) + 28. Calculations showed no significant relationships between GA and inulin clearance versus the serum half-life of AM (Table 3). In addition the elimination rate constant and inulin clearance were fitted and no relationship was detected.

6.5 Discussion

During the previous decade, it became apparent that the pharmacokinetics of a large variety of drugs in preterm infants are significantly different from those in term children. Clearance rates are usually much lower in the preterm infant, mainly because of immaturity of renal function or hepatic drug metabolism. Dosage recommendations for the use of AM in preterm infants have been extrapolated from data

about ampicillin obtained for older infants and adults[17,18]. We questioned the validity of these recommendations and studied the pharmacokinetics of AM in preterm infants with GAs of less than 32 weeks on day 3 of life by using the lowest recommended dose (25 mg/kg intravenously twice daily).

Our results indicate that administration of this dose results in high serum drug levels during the complete dosing interval. The MIC of AM for AM-susceptible microorganisms, including non-ß-lactamase-producing *Haemophilus influenzae* and *Escherichia coli*, does not exceed 5 mg/L[19]. Taking this level as a reference, serum AM levels are sufficiently high. The prolonged serum half-life of AM (6.70 ± 1.67 h) and the high serum drug trough levels (16.0 ± 4.9 mg/L) suggest that the dosing interval may even be extended to ± 18 h. A study of 10 infants with a mean age of 10 months showed a substantially lower serum half-life (mean 1.22 h)[18]. A serum half-life of 1.1 to 1.3 h after administration of different intravenous doses of AM was also found in seven healthy adults[17]. AM is predominantly excreted in the urine in unaltered form. It has been shown that clearance of penicillin in the newborn is not significantly greater than the creatinine clearance[20]. These findings suggest that glomerular filtration, rather than tubular secretion, is primarily responsible for most of the renal elimination of penicillin in neonates. clearance increases with age and surpasses creatinine clearance, which probably reflects the development of renal function (both filtration and secretion) throughout the neonatal period. Our results showed that the GFR (1.0 ± 0.3 mL/min) and the clearance (1.0 ± 0.4 mL/min) of AM were equal. We therefore assume that AM, like penicillin, is almost completely cleared by glomerular filtration in preterm infants with GAs of less than 32 weeks during the first days of life. This is also in agreement with previous studies of penicillins in older neonates and infants[14,15]. The GFR increased in our patients with advancing GA. These data are in agreement with those from other studies in which a positive relationship between the GA and the GFR was detected[11,12]. We also found a positive correlation between the GA and the clearance of AM ($r=0.75$, $p<0.001$). This was not surprising in view of the relationship between GA and GFR and GFR and AM clearance. The volume of distriburion of many drugs is altered in infants during the first month of life because of the difference in body composition. Approximately 75% of total body weight in the newborn is water. Hence, drugs that are water soluble and that are distributed

in extracellular water (e.g., aminoglycosides or penicillins) have an increased volume of distribution per kilogram of body weight[21]. Our data show that the volume of distribution of AM, as expected, increased with body weight ($r=0.78$, $p<0.001$).
A significant relationship between the serum half-life and the GA could not be demonstrated in our patients. One must take into account that not only the clearance but also the volume of distribution affects the serum half-life of AM. With increasing GA, clearance increased, which would be expected to lead to a decrease in serum half-life. The volume of distribution also increased, which would be expected to result in an increase in serum half-life. The interaction between these two developmental mechanisms may explain the absence of a significant relationship between the GA and the serum half-life of AM.
The present data indicate that preterm infants in the first week of life with GAs of less than 32 weeks should receive a maximum AM dosage of 25 mg/kg twice daily. This is only one-half or less of the dosage given to more mature infants but will result in serum drug levels well above the MIC for the major microorganisms involved in neonatal infections. Further studies are necessary to elucidate if higher dosage recommendations are necessary in preterm infants with postnatal ages of between 1 and 4 weeks.

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CHAPTER 7

ONCE-DAILY VERSUS TWICE-DAILY ADMINISTRATION OF CEFTAZIDIME IN THE PRETERM INFANT

Antimicrobial Agents and Chemotherapy, in press

CHAPTER 7

ONCE-DAILY VERSUS TWICE-DAILY ADMINISTRATION OF CEFTAZIDIME IN THE PRETERM INFANT

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7.1 Abstract

Ceftazidime (CAZ) pharmacokinetics in 28 preterm infants (gestational ages, 25.6 to 31.9 weeks) were studied on day 3 of life. Patients with suspected septicemia were randomized on day 1 of life in two groups. One group (n=13) was administered 25 mg of CAZ per kg of body weight once daily, and the other (n=15) was given 25 mg of CAZ per kg twice daily. Both groups also received 25 mg of amoxicillin per kg twice daily. Blood samples were collected on day 3 of life with an arterial catheter at 0, 0.5, 1, 2, 4, 8, and 12 h after an intravenous bolus injection. An additional blood sample was taken at 24 h from the group dosed once a day. High-performance liquid chromatography was used to determine serum CAZ concentrations. The pharmacokinetics of CAZ were best described by using a one-compartment model. The half-life for the elimination of the drug from serum, apparent volume of distribution, total body clearance of CAZ, and inulin clearance were not significantly different for both groups. The CAZ/inulin clearance ratio was 0.72 for both groups. However, trough concentrations in serum for the twice-daily group were significantly ($p<0.001$) higher (42.0 ± 13.4 mg/L) than those for the once-daily group (13.1 ± 4.7 mg/L). The latter concentrations were all still substantially higher than the MIC of CAZ for major neonatal pathogens. We conclude that the currently recommended dosage of 25 mg of CAZ per kg twice daily for preterm infants with

gestational ages (GAs) of less than 32 weeks may be adjusted during the first days of life to one daily dose at 25 mg/kg, provided that for the empirical treatment of septicemia, amoxicillin at 25 mg/kg is also given twice daily.

7.2 Introduction

CAZ, an expanded-spectrum cephalosporin, is commonly used in the treatment of bacterial infections in the newborn[1]. The currently recommended dosage regimen of CAZ for preterm infants less than 4 weeks old and whose birth weights are below 1200 g is 25 to 50 mg/kg of body weight given intravenously twice daily[2]. However, these dosage recommendations are based upon few pharmacokinetic data. Previous studies also did not stratify preterm infants according to GA or postnatal age, which has resulted in a substantial variability in pharmacokinetic parameters[3,4,5,6,7]. We have previously demonstrated that the pharmacokinetic behaviour of CAZ in preterm infants is strongly dependent on GA and postnatal age. At a dosage of 25 mg of CAZ per kg given intravenously twice daily, high trough levels were observed, especially in infants with GAs of less than 32 weeks[8]. High concentrations of beta-lactam antibiotics in serum and tissues do not result in a more rapid killing of bacteria[9], but they may lead to neutropenia and impairment of cellular and humoral immune responses[10]. We therefore designed a prospective randomized study to evaluate the pharmacokinetic effects of reducing the dosage of CAZ from 25 mg/kg twice daily to 25 mg/kg once daily for preterm infants with GAs of less than 32 weeks.

7.3 Methods

Patients

Preterm infants (n=28) admitted to the neonatal intensive care unit of the Sophia Children's Hospital between October 1991 and January 1992 with suspected or documented septicemia were enrolled in this study. The inclusion criteria were stability of hemodynamic function (a diuresis rate of >1 mL/kg/h and systolic and

diastolic blood pressure above the third percentile adjusted for GA) and normal liver function. Infants receiving nephrotoxic or inotropic drugs were excluded. All infants had an indwelling arterial catheter. The GAs of the newborns were determined on the basis of the mother's menstrual history and were confirmed by early ultrasound examinations and by physical examination based on the criteria of Dubowitz et al.[11]. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. Patients were enrolled only after informed consent was obtained from the parents. Eligible neonates were randomized at day 1 of life for 25 mg of CAZ per kg given intravenously once or twice daily in combination with 25 mg of amoxicillin per kg given intravenously twice daily. Patients with sterile cultures and without a focus of infection received a total of 72 h of antibiotic therapy. Patients with documented septicemia received at least 10 days of antibacterial treatment.

Pharmacokinetic study

The pharmacokinetics of CAZ were studied on day 3 after birth. Blood samples were taken from the indwelling arterial lines before the administration of an intravenous bolus injection of CAZ (time zero) and at 0.5, 1, 2, 4, 8, and 12 h afterwards. An additional blood sample was taken at 24 h for the once-daily group. Serum samples obtained after centrifugation (Merck type Eppendorf 5414; 3000 x g for 1 minute) were stored at -70°C.

Measurement of the glomerular filtration rate

The GFR was measured on day 3 after birth by means of the continuous inulin infusion technique[12,13].

Ceftazidime assay

Analysis of serum CAZ concentrations was performed by a modification of the high-performance liquid chromatography assay described by Ayrton[14].

Concentrations of CAZ in serum were calculated from peak areas by comparison with those of standards in water containing 200, 100, 20 and 10 mg of CAZ per liter. Calibration curves were found to be linear over the range of 10 to 200 mg of CAZ per liter. The lower limit of detection of CAZ in serum was 0.5 mg/L. The

coefficients of interassay variation at different concentrations were less than 7%. The intraassay values were less than 5%. Recovery of 95% of CAZ, which had been incubated for 24 h at room temperature, was established.

Pharmacokinetic analysis

Kinetic studies were performed on the third day of life. Visual inspection of individual model fits gave no indication that a more complex (e.g., two-compartment) pharmacokinetic model was required. Pharmacokinetic parameters were calculated with the multiple-dose equations described by Rowland and Tozer[15]. The basic equation used was C_t = dose/V x $(1-r^N)/(1-r)$ x e^{-kt}. In this equation C_t is the plasma concentration of CAZ at times t after each dose, V is the apparent volume of distribution, N is the dose number, r is $e^{-k\tau}$, in which k is the elimination rate constant and τ the dosing interval. For the twice-daily group, the CAZ concentration-versus-time curve was assumed attributable to the 7th dose (and the trough level at time zero was assumed to be attributable to the 6th dose). For the once-daily group, the CAZ concentration-versus-time curve was assumed to be attributable to the 3rd dose (and the trough level at time zero was assumed to be attributable to the 2nd dose). The data were weighted by calculating $1/(Ycal)^2$. All calculations were carried out with the non-linear regression module of SPSS/PC+ V 4.0.1 (SPSS, Inc., Chicago, Ill.), which uses a Levenberg-Marquardt algorithm.

Statistical analysis

Data given are mean ± SD unless indicated otherwise. The comparison of mean values was done by the unpaired Student t test. P values ≤ 0.05 (two tailed) were considered significant.

7.4 Results

Preterm infants (n=28) were enrolled in this study. After randomization, 13 infants received 25 mg of CAZ per kg once daily and 15 were treated with 25 mg of CAZ per kg twice daily. All infants were also treated with 25 mg of amoxicillin per kg twice daily. Both groups appeared to be well matched on the basis of the demographic and clinical parameters of the patients (Table 1).

Table 1. **Demographic and clinical parameters of the infants in the once- and twice-daily treatment groups**[a]

	Once daily (n=13)	Twice daily (n=15)
Gestational age (weeks)	29.1 ± 2.0	29.6 ± 2.1
Birth weight (grams)	1168 ± 309	1141 ± 400
AGA/SGA	12/1	12/3
Artificial ventilation (+/-)	7/6	8/7

[a]Values are mean ± SD or numbers of patients
Abbreviations: AGA, appropriate for gestational age; SGA, small for gestational age

All infants survived without any short- or long-term sequelae. Data for the pharmacokinetic parameters of CAZ and inulin clearances are given in Table 2. No significant differences between the predose blood sample and the poststudy dose trough concentration were found for the once-daily (p=0.92) and twice-daily (p=0.89) groups. Therefore, steady-state conditions were achieved. The CAZ/inulin clearance ratio was 0.72 for both groups. GFRs, as measured by inulin clearances, were similar in both groups and were all within the same range as reported by us previously[12]. Values for total body clearance, apparent volume of distribution, serum half-life, and inulin clearance were not significantly different for both groups. Serum trough levels for the twice-daily group (42.0 ± 13.4 mg/L) were significantly ($p<0.001$) higher than those for the once-daily group (13.1 ± 4.7 mg/L). The serum CAZ concentrations over time for both groups are depicted in Figure 1.

Table 2. Pharmacokinetic parameters of ceftazidime and inulin clearances of the infants in the once- and twice-daily treatment groups[a]

	Once daily (n = 13)	Twice daily (n = 15)
CL (mL/h)	32.4 ± 10.9	35.7 ± 16.8
CL (mL/h/kg)	27.8 ± 5.8	30.8 ± 7.5
V (mL)	376 ± 120	350 ± 138
V (mL/kg)	323 ± 62	305 ± 57
$t_{1/2}$ (h)	8.15 ± 1.18	7.09 ± 1.66
CL_{in} (mL/h)	45.0 ± 7.2	49.8 ± 16.2
CL_{in} (mL/h/kg)	38.6 ± 3.8	43.0 ± 7.2

[a]Values are mean ± SD
Abbreviations: CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life; CL_{in}, inulin clearance

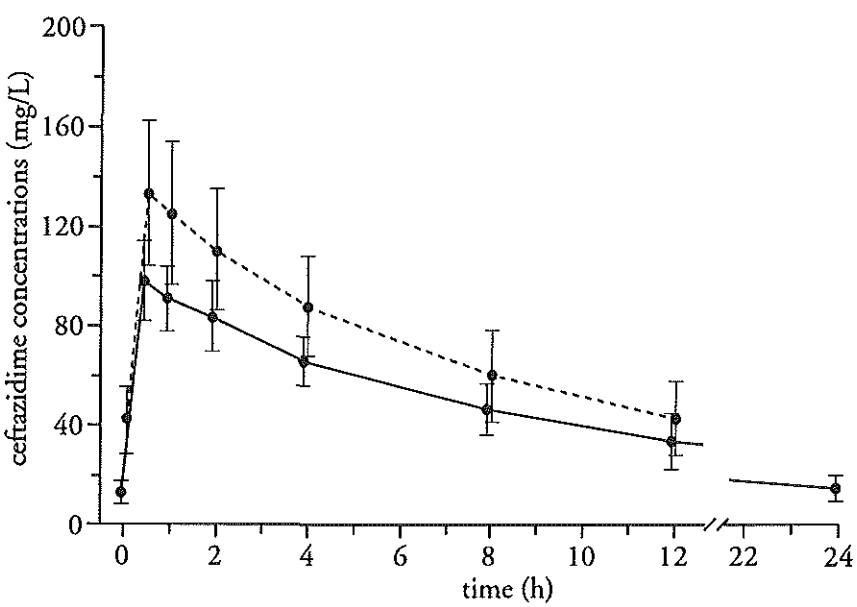

Figure 1. Serum ceftazidime concentrations-(mean ± SD)-versus-time curve of once-daily (continuous line) or twice-daily (dotted line) treatment groups

7.5 Discussion

The clearance rates for many compounds, including antibiotics, are much lower for preterm infants than for term infants. This can be attributed to the immaturity of renal function or the hepatic drug metabolism[16,17]. Pharmacokinetic studies are therefore necessary to improve dosing regimens. We have previously demonstrated that the use of the lowest recommended dose for preterm infants, i.e., 25 mg of CAZ per kg given intravenously twice daily, resulted in high concentrations of CAZ in serum throughout the entire dosing interval[8]. However, serious side effects were not seen. Nevertheless, high concentrations of CAZ may result in inhibition of cell proliferation in cultured human myeloid precursor and lymphoid cells[10]. This might lead to neutropenia and impairment of cellular and humoral immune responses. In addition, a dose-dependent suppressive effect of beta-lactam antibiotics on the differentiation and proliferation of oligodendrocytes has been demonstrated in the rat model[18]. We questioned the validity of the current dosage recommendations, and in a prospective, randomized way, we studied the pharmacokinetic effects of a dosage reduction from 25 mg of CAZ per kg twice-daily to 25 mg/kg once-daily for preterm infants with GAs of less than 32 weeks.

The data presented in this paper indicate that twice-daily dosing with CAZ leads to high serum trough concentrations (42.0 ± 13.4 mg/L). Dosage reduction from twice-daily to once-daily results in a significant ($p<0.001$) reduction in mean serum trough concentrations. However, the individual values (8.1-25.6 mg/L) are still well above the MIC of CAZ for such major neonatal pathogens as *Streptococcus agalactiae* and *Escherichia coli*[19,20]. The therapeutic efficacy in animal models and for immunocompromised patients may be improved by the presence of concentrations of beta-lactam antibiotics in serum which continuously exceed the MIC[21,22]. This effect is achieved in adults by the continuous infusion of CAZ or by intermittent administration of high doses of CAZ two or three times daily. We show here that CAZ has such a prolonged half-life in preterm infants that once-daily administration of a low dose results in concentrations (8.1-25.6 mg/L) that are above the MICs for major neonatal pathogens during the complete 24 h dosing interval.

Our data also indicate that the mean CAZ/inulin clearance ratios for both groups are similar (0.72). This is in agreement with the results of previous studies showing

ratios of between 0.65 and 0.97[23]. The combination of a CAZ/inulin clearance ratio of 0.72 and the previously reported low (17%) protein binding suggest that renal elimination of CAZ is almost completely mediated by glomerular filtration[24]. A recent study in adults indicated that in addition to glomerular filtration some tubular excretion of CAZ occurs, which is probably triggered by passive reabsorption[25]. At this moment, data on tubular excretion of CAZ in the preterm infant are not available. In our study, the co-administration of amoxicillin might have led to the inhibition of tubular transport of CAZ by competition.

We conclude that the recommended twice-daily administration of CAZ in preterm infants with GAs of less than 32 weeks may be adjusted to once-daily dosing in the first days of life. Alternatively, twice-daily dosing with doses lower than 25 mg/kg might even lead to an increased therapeutic effect compared with that of once-daily dosing at 25 mg/kg[20,24]. However, for the empirical treatment of neonatal septicemia, amoxicillin (at 25 mg/kg twice daily) should be added to the antibiotic treatment protocol. These dosage recommendations cannot yet be applied to infants with suspected or documented meningitis, since data on the penetration of cerebrospinal fluid in infants with once-daily dosing are missing.

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CHAPTER 8

CEFTAZIDIME PHARMACOKINETICS IN PRETERM INFANTS: EFFECT OF POSTNATAL AGE AND POSTNATAL EXPOSURE TO INDOMETHACIN

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CHAPTER 8

CEFTAZIDIME PHARMACOKINETICS IN PRETERM INFANTS: EFFECT OF POSTNATAL AGE AND POSTNATAL EXPOSURE TO INDOMETHACIN

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8.1 Abstract

1. The effects of postnatal age and postnatal exposure to indomethacin on the pharmacokinetic parameters of ceftazidime (CAZ) were investigated in 23 preterm infants (gestational age 28.7 ± 1.7 weeks; weight 1086 ± 311 g) on day 3 and day 10 after birth.
2. CAZ (25 mg/kg) was administered by intravenous bolus injection. Blood samples were drawn from an arterial catheter at 0, 0.5, 1, 2, 4, 8, and 12 h after the dose and CAZ concentrations in serum were determined by HPLC-assay. CAZ pharmacokinetics followed a one-compartment open model.
3. The glomerular filtration rate (GFR) of all infants was studied by means of the 24 h continuous inulin infusion technique.
4. The total body clearance of CAZ (34.7 ± 9.2 vs 50.6 ± 19.6 mL/h, $p<0.05$; 30.7 ± 5.9 vs 41.6 ± 9.0 mL/h/kg, $p<0.05$) and the GFR (0.72 ± 0.11 vs 0.91 ± 0.15 mL/min, $p<0.05$) increased, whereas the apparent volume of distribution (425 ± 147 vs 352 ± 108 mL, $p<0.05$; 363 ± 59 vs 292 ± 44 mL/kg, $p<0.005$) and the serum half-life (8.7 ± 2.8 vs 5.0 ± 0.9 h, $p<0.005$) decreased significantly

between day 3 and day 10 after birth. Clearance of CAZ increased with increasing GFR ($r=0.81$, $p<0.001$).

5. In infants with postnatal exposure to indomethacin the changes in CAZ pharmacokinetics were markedly reduced.
6. These results indicate that the dosage regimen of CAZ should be adjusted after the first week of life except in infants who were postnatally exposed to indomethacin.

8.2 Introduction

CAZ is frequently used for the treatment of infectious diseases in newborn infants. The currently recommended dosage in preterm infants less than 4 weeks of life with a birth weight of less than 1200 g is 25-50 mg/kg of body weight every 12 h [1,2,3,4,5,6]. Despite the fact that these dosage recommendations are derived from studies that did not stratify patients according to postnatal age, Prober et al.[6] recommend not to reduce dosage intervals for CAZ in preterm infants until after the fourth week of life. This recommendation was made on the assumption that no significant postnatal increment in GFR has been documented in these preterm infants. Previous studies on the postnatal development of GFR in preterm infants indeed show conflicting data[7,8,9,10,11,12,13]. However, several investigators report the presence of a significant increase in the GFR in the first 10 days after birth[8,11,13,14]. This postnatal age dependent increase would be predicted to exert a major effect on the pharmacokinetics of drugs such as CAZ which are mainly eliminated by glomerular filtration.

Animal and human studies have indicated that the use of indomethacin results in an impaired blood flow and a concomitant reduction in the GFR[15]. Postnatal exposure to indomethacin which is administered to preterm infants in order to close a patent ductus arteriosus was therefore also thought to influence the developmental pharmacokinetics of CAZ between day 3 and day 10 after birth.

The purpose of the present study was to determine the effects of postnatal age, changes in GFR, and postnatal exposure to indomethacin on the pharmacokinetics of CAZ between day 3 and day 10 after birth in preterm infants with gestational

ages (GAs) of less than 32 weeks and to investigate if dosage adjustments are indicated additional to those suggested by Prober et al.[6,16].

8.3 Methods

Patients

Twenty-three preterm infants with GAs of less than 32 weeks, admitted to the neonatal intensive care unit with suspected or documented septicemia or invasive infection, were eligible for study. The inclusion criteria on day 3 after birth were stability of hemodynamic function (diuresis >1 mL/kg of body weight per h; systolic and diastolic blood pressure above the third percentile adjusted for GA), a normal liver function, and no history of prenatal exposure to indomethacin or beta-methasone. Infants who received inotropic or nephrotoxic drugs were excluded. All patients had an indwelling arterial catheter. The partial pressure of oxygen in arterial blood was kept at greater than 50 mmHg or oxygen saturation greater than 92%.

The GA of the 23 enrolled infants were estimated from the mother's menstrual history, early ultrasound if available and from physical examination using the criteria of Dubowitz et al.[17]. Study infants were given CAZ (25 mg/kg intravenously) every 12 h and amoxicillin (25 mg/kg intravenously) every 12 h. Patients with sterile blood cultures and without a focus of infection received a total of 72 h of therapy.

These 23 infants were also studied on day 10 after birth. The inclusion criteria on day 10 after birth were stability of hemodynamic function, and a normal liver function. Infants with suspected or documented septicemia or invasive infection were excluded. All infants had an indwelling arterial catheter on day 10 and received a single dose of CAZ (25 mg/kg intravenously). Twelve of the 23 infants had postnatally (days 4 or 5) been exposed to indomethacin. Eleven infants were not postnatally exposed to indomethacin (controls).

The study protocol was approved by the Medical Ethics Committee of the University Hospital Rotterdam. Patients were only enrolled after informed consent was obtained from the parents.

Pharmacokinetic study

The multiple-dose pharmacokinetics of CAZ were determined on day 3 after birth. Single-dose pharmacokinetics of CAZ were studied on day 10 after birth. Blood samples were taken from indwelling arterial lines before administration of an intravenous bolus injection (t=0) and at 0.5, 1, 2, 4, 8, and 12 h after the administration. These sampling times were selected based on the known disposition profile for CAZ. Serum samples obtained after centrifugation (Merck type Eppendorf 5414, 3000 x g for 1 minute) were stored at -70°C.

Measurement of the glomerular filtration rate

The GFR was measured by the continuous inulin infusion technique on day 3 and day 10 after birth[13,14]. A 10% glucose-inulin solution containing 25 g of inulin per liter was infused at a rate of 0.6 mL/kg/h, beginning at time (t) zero of the pharmacokinetic study. After 24 h, the inulin clearance (CL_{in}) was calculated from the infusion rate (R), the inulin concentration in the infusate (I), and the serum inulin concentration (P_{in}) by the equation $CL_{in} = I \cdot R/P_{in}$. The determination of the inulin in serum was performed after acid hydrolysis in 0.3 mmol/L perchloric acid for 15 minutes at 70°C. The fructose thus formed was measured enzymatically.

Ceftazidime assay

Analysis of serum CAZ concentrations was performed according to the method described by Ayrton[18] with minor modifications. To a 50-µL aliquot of the serum sample, an equal volume of 6% (vol/vol) perchloric acid containing 50 mg/L cephaloridine as an internal standard was added. Samples were centrifuged at 1500 g for 5 minutes. Subsequently 25 µL was transferred by an automatic sample injector to the column.

A calibration curve was made by dissolving 4, 12, 25, 50, 100, and 200 mg CAZ per liter in serum. These spiked standard samples were processed according to the procedure mentioned above. A linear calibration curve was obtained over a range of 4 to 400 mg of CAZ per liter. Spiked samples of the calibration curve underwent the same processing procedure as clinical samples. Hence, clinical samples were directly converted from the calibration curve to actual CAZ concentrations per liter of serum. The lower limit of detection of CAZ in serum was 0.5 mg/L.

The coefficients of interassay variation at different concentrations were less than 7%. The intraassay values were less than 5%. Recovery of 95% of CAZ, which had been incubated for 24 h at room temperature, was established.

Pharmacokinetic analysis

Kinetic data were described using a one-compartment open model. Visual inspection of individual model fits gave no indication that a model more complex than a one-compartment open model was required. Pharmacokinetic parameters were calculated with the multiple-dose equations described by Rowland and Tozer[19]. The basic equation used was C_t = dose/V x $(1-r^N)/(1-r)$ x e^{-kt}. In this formula, C_t is the plasma concentration of CAZ at times t after each dose, V is the apparent volume of distribution, N is the dose number, $r = e^{-k\tau}$, in which k is the elimination rate constant and τ the dosing interval. The conversion factor for CAZ to SI units is: 1 mg/L = 1.83 nmol/L. Because doses were given twice daily, the CAZ concentration-versus-time curve on day 3 after birth was assumed attributable to the 7th dose (and the trough level at t=0 was assumed to be attributable to the 6th dose). Total body clearance (CL) was calculated with the following equation: CL=k.V.
Concentration time plots showed linear decrease over time and no indication of levelling off. Scatter was evenly distributed on log-scale indicating the need for $1/(Ycal)^2$ weighting. The CAZ concentration-versus-time curve on day 10 after birth was attributable to the 1st dose. All calculations were carried out using the non-linear regression module of SPSS/PC+ V 4.0.1 (SPSS, Inc., Chicago, Ill.), which uses a Levenberg-Marquardt algorithm.

Statistical analysis

Data given are mean ± SD unless indicated otherwise. Correlation coefficients given are Pearson's. Comparison of outcomes on day 3 and day 10 was performed using the paired t-test. P-values ≤ 0.05 (two-tailed) were considered significant.

8.4 Results

The demographic and clinical parameters of indomethacin-treated and control infants on day 3 of life are shown in Table 1. None of the infants had a positive

Table 1. **Demographic and clinical parameters of study infants**[a]

	Indomethacin-exposed (n=12)	Controls (n=11)
Gestational age (weeks)	28.4 ± 1.7	29.1 ± 1.1
Weight (g)	1024 ± 319	1154 ± 301
Appropriate for gestational age	10 (83%)	9 (82%)
Artificial ventilation	10 (83%)	8 (73%)
Respiratory distress syndrome	4 (33%)	3 (27%)

[a]Values are mean ± SD or numbers (%) of patients

Table 2. **Pharmacokinetic parameters of ceftazidime and inulin clearances on day 3 and day 10 after birth of eleven infants without postnatal exposure to indomethacin**[a]

	Day 3	Day 10	p-value	mean difference (95% CI)
CL (mL/h)	34.7 ± 9.2	50.6 ± 19.6	< 0.05	15.8 (3.5, 28.1)
CL (mL/h/kg)	30.7 ± 5.9	41.6 ± 9.0	< 0.05	10.9 (2.4, 19.5)
V (mL)	425 ± 147	352 ± 108	< 0.05	-74 (-37, -111)
V (mL/kg)	363 ± 59	292 ± 44	< 0.005	-71 (-42, -101)
$t_{1/2}$ (h)	8.7 ± 2.8	5.0 ± 0.9	< 0.005	-3.7 (-1.8, -5.5)
CL_{in} (mL/h)	43.2 ± 6.6	54.6 ± 9.0	< 0.05	12.4 (4.6, 20.3)

[a]Values are mean ± SD with 95% confidence interval between parentheses
Abbreviations: CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life; CL_{in}, inulin clearance; CI, confidence interval

blood culture or another invasive infection. All neonates had serum trough concentrations above 5 mg/L. In control infants inulin clearance (as a parameter of the GFR) increased significantly between day 3 and day 10 of life (0.72 ± 0.11 mL/min vs 0.91 ± 0.15 mL/min, $p<0.05$). In these infants a positive linear relationship ($r=0.81$, $p<0.001$) was demonstrated between the clearance of CAZ and the GFR. The clearance of CAZ (34.7 ± 9.2 vs 50.6 ± 19.6 mL/h, $p<0.05$), and clearance of CAZ per kg (30.7 ± 5.9 vs 41.6 ± 9.0 mL/h/kg, $p<0.05$) increased significantly. The apparent volume of distribution (425 ± 147 vs 352 ± 108 mL, $p<0.05$), volume of distribution per kg (363 ± 59 vs 292 ± 44 mL/kg, $p<0.005$), and the serum half-life decreased significantly (8.7 ± 2.8 vs 5.0 ± 0.9 h, $p<0.005$) between day 3 and day 10 (Table 2). In the indomethacin-exposed infants inulin clearance did not change significantly between day 3 and day 10 of life (0.67 ± 0.13 mL/min vs 0.80 ± 0.14 mL/min, $p=0.066$). Clearance of CAZ increased significantly (32.7 ± 14.5 vs 39.9 ± 20.4 mL/h, $p=0.049$) between day 3 and day 10 after birth, whereas clearance of CAZ per kg, volume of distribution and volume of distribution per kg, and serum half-life did not change in this 7-day period (Table 3).

Table 3. **Pharmacokinetic parameters of ceftazidime and inulin clearances on day 3 and day 10 after birth of twelve infants with postnatal exposure to indomethacin**[a]

	Day 3	Day 10	p-value	mean difference (95% CI)
CL (mL/h)	32.7 ± 14.5	39.9 ± 20.4	< 0.05	7.2 (0.3, 14.1)
CL (mL/h/kg)	31.1 ± 6.0	34.3 ± 10.3	0.31	3.3 (-2.9, 9.5)
V (mL)	337 ± 132	354 ± 106	0.39	17 (-27, 61)
V (mL/kg)	327 ± 71	317 ± 37	0.70	-11 (-61, 40)
$t_{1/2}$ (h)	7.4 ± 1.3	6.8 ± 1.8	0.43	-0.5 (-2.0, 0.9)
CL_{in} (mL/h)	42.0 ± 7.8	48.0 ± 8.4	0.07	7.0 (-1.7, 15.7)

[a]Values are mean ± SD with 95% confidence interval between parentheses
Abbreviations: CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life; CL_{in}, inulin clearance; CI, confidence interval

8.5 Discussion

The data presented in this paper indicate that GFR values in preterm infants with GAs of less than 32 weeks, and without postnatal exposure to indomethacin increase significantly between days 3 and 10 of life. These findings are consistent with the results of several other studies[8,11,13,14], although some investigators could not find a postnatal age dependent increase of the GFR[7,8,9]. However, all these studies did not specify whether infants were postnatally exposed to indomethacin. GFR values in infants who are not exposed postnatally to indomethacin increase by a mean of 0.19 mL/min during the 7-day period between days 3 and 10 after birth. Recently we reported that the GFR undergoes a weekly intrauterine increase of 0.035 mL/min[14]. This indicates that the postnatal increase of the GFR in the first days of life is 5.4 times higher in comparison with the intrauterine increase. Therefore postnatal age seems to be associated with an acceleration of the development of the GFR. However, the possible impact of invasive bacterial infection on these postnatal age induced changes in the GFR could not be investigated, because none of the infants enrolled in this study had a proven bacterial infection.

The positive relationship ($r=0.81$, $p<0.001$) between the GFR and the clearance of CAZ indicates the important role of the GFR in the clearance of CAZ. The increase in the GFR results in a significant increase in the clearance of CAZ. These findings are consistent with the results of some investigators[3,20], whereas other studies could not find any relation with postnatal age[21,22]. Kenyon et al.[22] have previously reported that postnatal renal function maturation exerts a significant influence on the developmental pharmacokinetics of amikacin. These authors speculate however that the rapid maturation of the renal function in the first week of life is not present in the extremely preterm population. Our data show that the rapid postnatal change in the GFR is equally present in very young preterm infants and is primarily responsible for the increase in the clearance of CAZ.

The volume of distribution of CAZ decreased significantly between day 3 and day 10 of life in control infants. During the first week of life a significant decrease of the extracellular water volume has been observed[23]. This may have caused the decrease of the volume of distribution of CAZ in this 7-day period because CAZ is mainly distributed into the extracellular water compartment. Both the postnatal

age dependent increase in the clearance of CAZ and the decrease of the volume of distribution contribute to the decrease in serum half-life between days 3 and 10 as was shown in this study.

In infants with postnatal exposure to indomethacin the increase in the GFR between days 3 and 10 of life was not seen. Consequently, the increase of the clearance of CAZ was markedly less (clearance in ml/h) or absent (clearance per kg) in infants with postnatal exposure to indomethacin compared with the controls. After normalization for weight the previously significant (p=0.049) increase in clearance between days 3 and 10 was not present anymore. This was probably caused by the increase in the mean body weight from 1052 to 1163 g. The decrease of volume of distribution of CAZ during this 7-day period was also not seen in the indomethacin-exposed infants. This may be explained by the dependence of postnatal changes in extracellular water on renal function[24], and the impairment of the GFR with the use of indomethacin. Serum half-life of CAZ, influenced by both clearance and volume of distribution, did not show any change between days 3 and 10 in infants with postnatal exposure to indomethacin.

The differences observed between indomethacin-exposed and control infants are probably not only caused by the postnatal use of indomethacin alone. The question remains whether the persistence of a patent ductus arteriosus, which may lead to congestive heart failure, can be held partially responsible.

Once-daily dosing of 25 mg/kg CAZ or twice-daily administration of 10-15 mg/kg seems appropriate in the first week of life[25,26]. In the second week of life the dosage of CAZ should be adapted to twice daily 25 mg/kg because of the rapidly improving neonatal renal capacity. We conclude that dosage recommendations in the first four weeks of life should be based on postnatal age induced changes in the GFR. However, both the existence of a patent ductus arteriosus and postnatal exposure to indomethacin may alter this developmental process. This probably will delay the need for dosage adjustment of CAZ during the first two postnatal weeks in these preterm infants. Finally further studies will be necessary to determine if these dosage recommendations can also be applied to infants with invasive bacterial infections.

8.6 References

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CHAPTER 9

THE EFFECT OF ASPHYXIA ON THE PHARMACOKINETICS OF CEFTAZIDIME IN THE TERM NEWBORN

Pediatric Research, in press

CHAPTER 9

THE EFFECT OF ASPHYXIA ON THE PHARMACOKINETICS OF CEFTAZIDIME IN THE TERM NEWBORN

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9.1 Abstract

The multiple-dose pharmacokinetics of ceftazidime (CAZ) [administered twice daily in a 50 mg/kg of body weight intravenous dose] were studied in ten severely asphyxiated term infants with suspected septicemia on day 3 of life. Nine term infants with suspected septicemia but without asphyxia served as controls. Blood samples were collected from an arterial catheter at 0, 0.5, 1, 2, 4, 8 and 12 h after an intravenous bolus injection. A high performance liquid chromatography method was used to determine CAZ concentrations from serum. CAZ pharmacokinetics followed a one-compartment open model. The glomerular filtration rates (GFRs) of all infants were simultaneously studied by means of the 24 h continuous inulin infusion technique. Serum half-life (5.86 ± 1.13 h vs 3.85 ± 0.40 h) and serum trough concentrations (46 ± 14 mg/L vs 23 ± 7 mg/L) of CAZ were significantly ($p<0.001$) increased in the asphyxiated newborn, whereas total body clearance of CAZ (128.4 ± 25.1 mL/h vs 205.7 ± 55.4 mL/h), CAZ clearance per kg (40.9 ± 6.1 mL/h/kg vs 60.8 ± 8.3 mL/h/kg), and the GFR expressed in mL/min (3.14 ± 0.43 vs 4.73 ± 0.89) were significantly ($p<0.001$) decreased in the asphyxiated newborn. We conclude that twice daily administration of 50 mg/kg of body weight

CAZ given to asphyxiated term newborns in the first days of life results in significantly higher serum trough levels in comparison with control infants. The impaired CAZ clearance is a result of a significantly decreased GFR.

9.2 Introduction

Perinatal asphyxia is a result of complicated or traumatic deliveries and may exert profound effects on renal and liver function. McCance and Widdowson[1] reported as early as 1954 a reduction in the GFR, a poor urea clearance and a low urine output in fullterm and postmature infants after prolonged and difficult labour. A redistribution of the fetal circulation leading to an increased blood flow to the brain, heart and adrenals and a concomitantly decreased blood flow to the lungs, intestines and kidneys is responsible for this asphyxia-induced renal impairment[2]. Several drugs such as the beta-lactam antibiotic CAZ are primarily excreted by the kidneys. CAZ, a broad spectrum cephalosporin, is an antibiotic frequently used for the treatment of infectious diseases in newborn infants. The currently recommended dosage for CAZ in term infants is 50-150 mg/kg of body weight per day in two or three daily doses[3,4]. The dosage and dosing interval of CAZ will be influenced by changes in GFR such as those caused by asphyxia. However, pharmacokinetic studies in asphyxiated newborns have not been performed. Hence, recommendations to adjust drug dosages of CAZ are not available.
We therefore examined the impact of asphyxia on the disposition characteristics of CAZ in the term newborn.

9.3 Methods

Patients
Ten term infants with severe asphyxia were included in this study. All infants met the criteria as recently defined by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics Committees on Maternal-Fetal Medicine and Fetus and Newborn[5]. All of the following were present: profound umbilical artery acidemia (pH <7.00), persistence of an Apgar score of 0 to 3

longer than 5 minutes, neonatal neurologic sequelae (e.g., seizures, coma, hypotonia), and multiorgan system dysfunction (e.g., cardiovascular, gastrointestinal, hematologic, pulmonary or renal). Nine term infants without asphyxia served as controls. Five of these infants had meconium aspiration syndrome but normal Apgar scores and an umbilical arterial pH above 7.15, and four had transient tachypnea of the newborn. Infants receiving nephrotoxic or inotropic drugs were excluded. All infants had an indwelling radial artery catheter. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. Patients were only enrolled after informed consent was obtained from the parents. All infants received because of suspected septicemia directly from birth 50 mg/kg of body weight CAZ and 50 mg/kg of body weight amoxicillin intravenously every 12 h as a bolus injection. In patients with sterile blood cultures and without a focus of infection the therapy was discontinued after 72 h.

Pharmacokinetic study

The multiple-dose pharmacokinetics of CAZ were studied on day 3 after birth because antibiotic treatment was stopped after 72 h in infants with sterile blood cultures. Blood samples were taken from indwelling arterial lines before an intravenous bolus injection of CAZ (t=0) and at 0.5, 1, 2, 4, 8, and 12 h after the administration. These sampling times were selected based on the known disposition profile for CAZ. Serum samples obtained after centrifugation (Merck type Eppendorf 5414, 3000 x g for 1 minute) were stored at -70°C.

Measurement of the glomerular filtration rate

The GFR was measured on day 3 after birth by means of the continuous inulin infusion technique[6,7]. A 10% glucose-inulin solution containing 25 g of inulin per liter was infused at a rate of 0.6 mL/kg/h, beginning at time (t) zero of the pharmacokinetic study. After 24 h, the inulin clearance (CL_{in}) was calculated from the infusion rate (R), the inulin concentration in the infusate (I), and the serum inulin concentration (P_{in}) by the equation $CL_{in} = I.R/P_{in}$. The determination of inulin in serum was performed after acid hydrolysis in 0.3 mmol/L perchloric acid for 15 minutes at 70°C. The fructose thus formed was measured enzymatically according to Beutler[8].

Ceftazidime assay

Analysis of serum CAZ concentrations was performed according to the method described by Ayrton[9] with minor modifications. HPLC-grade acetonitrile was purchased from Rathburn (Walkerburn, Scotland). The other chemicals were purchased from Aldrich-Chemie (Steinheim, Germany). All chemicals applied were of the highest grade commercially available. Chromatographic analysis was performed with a glass-prepacked C_{18} column (100 by 8 mm, Resolve Radial Pak, Waters, USA) combined with a guard column. A Waters Chromatography pump (model 6000 A, Waters, USA) was used to deliver the eluent: 4.8% (vol/vol) acetonitrile, 13.5% methanol in 20 mM sodium acetate buffer (pH 3.6) at a flow rate of 2 mL/min. The separations were carried out at room temperature. The eluate was monitored with two Waters Absorbance Detectors (Model 440/wavelength of 254 nm and Model 484/wavelength 265 nm, Waters, USA).

To a 50-µL aliquot of the serum sample, an equal volume of 6% (vol/vol) perchloric acid containing 50 mg/L cephaloridine as an internal standard was added. Samples were centrifuged at 1500 g for 5 minutes (Eppendorf Centrifuge 5412). Subsequently 25 µL was transferred by an automatic sample injector (WISP 710 B, Waters, USA) to the column.

A calibration curve was made by dissolving 4, 12, 25, 50, 100, 200, and 400 mg CAZ per liter in serum. These spiked standard samples were processed according to the procedure mentioned above. A linear calibration curve was obtained over a range of 4 to 400 mg of CAZ per liter. Spiked samples of the calibration curve underwent the same processing procedure as the clinical samples. Hence, clinical samples were directly converted from the calibration curve to actual CAZ concentrations per liter of serum. The lower limit of detection of CAZ in serum was 0.5 mg/L. The coefficients of interassay variation at different concentrations were less than 7%. The intraassay values were less than 5%. Recovery of 95% of CAZ, which had been incubated for 24 h at room temperature, was established.

Pharmacokinetic analysis

Kinetic studies were performed on the third day of life. Kinetic data were described using a one-compartment open model. Visual inspection of individual model fits gave no indication that a model more complex than a one-compartment open

model was required. Pharmacokinetic parameters were calculated using the multiple dose equations described by Rowland and Tozer[10]. The basic equation used was C_t = dose/V x $(1-r^N)/(1-r)$ x e^{-kt}. In this equation C_t is the plasma concentration of CAZ at times t after each dose, V the apparent volume of distribution, N the dose number, $r = e^{-k\tau}$, in which k is the elimination rate constant and τ the dosing interval. Because doses were given twice daily, the CAZ concentration-versus-time curve was assumed attributable to the 7th dose (and the trough level at t=0 to the 6th dose). Total body clearance (CL) was calculated with the following equation: CL=k.V. Concentration time plots showed linear decrease over time and no indication of levelling off. Scatter was evenly distributed on log-scale indicating the need for $1/(Ycal)^2$ weighting. All calculations were carried out using the non linear regression module of SPSS/PC+ V 4.0.1 (SPSS, Inc., Chicago, Ill.), which uses a Levenberg-Marquardt algorithm.

In order to examine different dosing strategies, based on the assumption that serum concentrations should never drop below 5 mg/L, dosage recommendations for CAZ were calculated using the following equation:

$$5 < C_\tau = \frac{D \times wt}{V} \times e^{-k\tau}$$

In this formula C_τ is the serum trough concentration, D the prescribed dose in mg/kg, wt the weight in kg, k the elimination rate constant, τ the dosing interval in h, and V the apparent volume of distribution of CAZ.

Statistical analysis

Data given are mean ± SD unless indicated otherwise. Correlation coefficients are Pearson's. Continuous data were compared using the Mann-Whitney test. P-values ≤0.05 (two-tailed) were considered significant. With the numbers studied, differences between groups can be demonstrated (alpha=0.05, beta=0.20) if these exceed 1.2 standard deviation.

9.4 Results

The demographic and clinical parameters of all infants (asphyxiated versus non-asphyxiated) on day 3 of life are shown in Table 1.

Table 1. Demographic and clinical parameters of study infants[a]

	Asphyxiated (n=10)	Controls (n=9)
Gestational age (weeks)	39.3 ± 1.6	35.7 ± 1.3
Weight (g)	3057 ± 371	3367 ± 531
Artificial ventilation	5 (50%)	4 (44%)
Apgar score 5 minutes	2 ± 1[b]	8 ± 1
Convulsions	10 (100%)[b]	0 (0%)
Umbilical pH	6.7 ± 0.1[b]	7.3 ± 0.1

[a]Values are mean (± SD) or numbers (%) of patients
[b]Significantly different ($p<0.01$) from controls

Table 2. Pharmacokinetic parameters of ceftazidime and inulin clearances of infants with severe asphyxia and in control infants without asphyxia[a]

	Asphyxiated (n=10)	Controls (n=9)	P-value
CL (mL/h)	128.4 ± 25.1	205.7 ± 55.4	<0.001
CL (mL/h/kg)	40.9 ± 6.1	60.8 ± 8.3	<0.001
V (mL)	1090 ± 304	1132 ± 258	NS
V (mL/kg)	344 ± 79	336 ± 46	NS
$t_{1/2}$ (h)	5.86 ± 1.13	3.85 ± 0.40	<0.001
CL_{in} (mL/h)	188.4 ± 25.5	284.2 ± 53.1	<0.001
CL_{in} (mL/min)	3.14 ± 0.43	4.73 ± 0.89	<0.001

[a]Values are mean ± SD
Abbreviations: CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life, CL_{in}, inulin clearance; NS, not significant

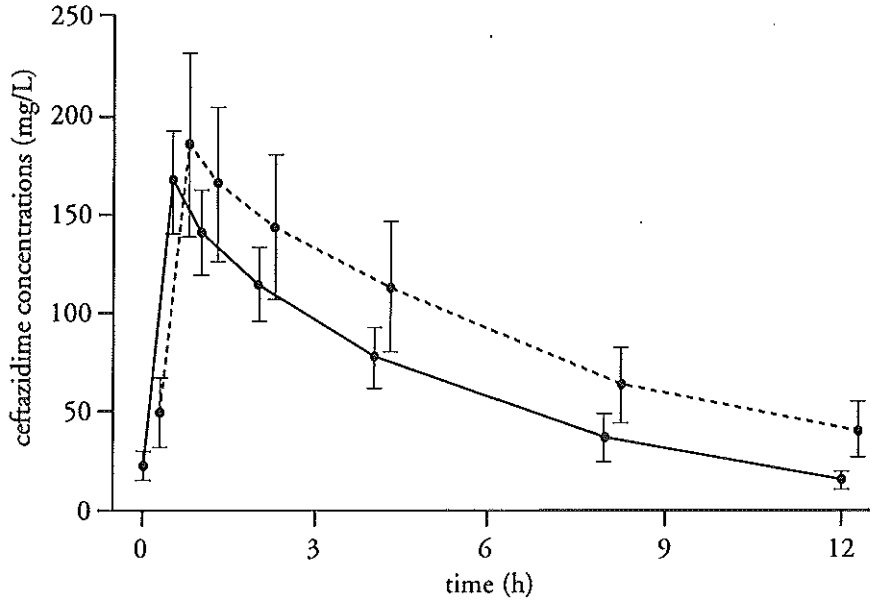

Figure 1. Serum ceftazidime concentrations-(mean ± SD)-versus-time curve of asphyxiated (dotted line) and control (continuous line) groups

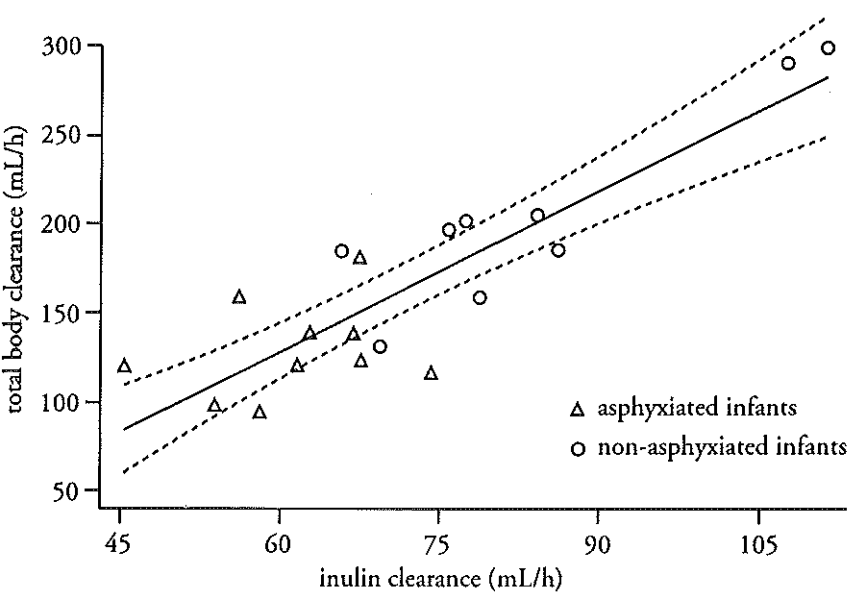

Figure 2. Total body clearance of ceftazidime versus inulin clearance expressed in mL/h. The curved lines indicate the 95% confidence limits The regression line equals: y = -50.2 + 3.0 x inulin clearance

None of the infants in both groups had a positive blood culture. The pharmacokinetics of CAZ and the inulin clearances are shown in Table 2.

Figure 1 demonstrates the serum CAZ concentration (mean ± SD)-versus-time curve of the asphyxiated and control infants. Inulin clearance was significantly lower in the asphyxiated newborn (3.14 ± 0.43 mL/min vs 4.73 ± 0.89 mL/min, $p<0.001$). A positive linear relationship ($r=0.87$, $p<0.001$) was demonstrated between CAZ clearance and the inulin clearance. In Figure 2 this relation is shown. As there was no significant difference between the separate regression lines of the two groups, the common regression line is depicted with 95% confidence limits. CAZ clearance was significantly lower in the asphyxiated newborns (128.4 ± 25.1 mL/h vs 205.7 ± 55.4 mL/h, $p<0.001$). After correction for body weight CAZ clearance was still significantly lower in the asphyxiated newborns (40.9 ± 6.1 mL/h/kg vs 60.8 ± 8.3 mL/h/kg, $p<0.001$). The apparent volume of distribution of CAZ did not differ significantly between the groups. After correction for body weight there still was no difference in the volume of distribution of CAZ between both groups. Consequently, the serum half-life of CAZ was significantly longer in the asphyxiated newborns (5.86 ± 1.13 h vs 3.85 ± 0.40 h, $p<0.001$). Serum peak levels of CAZ showed no significant difference between both groups. Serum trough levels of CAZ were significantly ($p<0.005$) higher in the asphyxiated group (46 ± 14 mg/L) in comparison with the control infants (23 ± 7 mg/L).

Based on the assumption that serum concentrations should never drop below 5 mg/L, using the equation given in the methods section, dosage recommendations for CAZ were calculated.

9.5 Discussion

The data presented in this paper indicate that asphyxia in term infants results in a significant decrease in the GFR as measured by the inulin clearance. The positive relationship ($r=0.87$, $p<0.001$) between the GFR and the CAZ clearance indicates the important role of the GFR in the clearance of CAZ. The decrease in the GFR results in a significant decrease in the CAZ clearance and a concomitant increase of the serum half-life of CAZ and serum trough levels (46 ± 14 mg/L) in the asphyxiated

infants. These results indicate that twice-daily administration of 50 mg/kg CAZ to term asphyxiated newborns results in high serum concentrations of CAZ during the entire dosing interval. An optimal dose regimen should result in a high clinical efficacy and a minimal chance on toxicity. To ensure clinical efficacy the serum concentrations of CAZ should be above the MIC of CAZ for major neonatal pathogens such as *Streptococcus agalactiae* (MIC_{90} <0.25 mg/L) and *Escherichia coli* (MIC_{90} <0.25 mg/L)[11,12]. The serum levels of CAZ in the current study were far above the MICs during the entire dosing interval. Therefore, modification of the CAZ dose in the asphyxiated newborn is not indicated to improve clinical efficacy. However, beta-lactam antibiotics are all neurotoxic to some extent[13,14]. Several factors have been identified or suggested to contribute to the neurotoxicity of the beta-lactam antibiotics: excessive dosage, renal insufficiency, disruption of the blood-brain barrier, pre-existing central nervous system diseases, and competitive inhibition of the transport system that exports beta-lactam antibiotics out of the central nervous system. In adults CAZ has been reported to cause encephalopathy, hallucinations, confusion, and neuromuscular excitability[15,16,17,18,19]. In the rat model, a dose dependent suppressive effect of beta-lactam antibiotics has been demonstrated on the differentiation and proliferation of oligodendrocytes[20].

Asphyxia neonatorum is associated with an impaired renal function, which will result in high serum levels of CAZ. Cerebrospinal fluid acidosis and increased cerebrospinal fluid lactate levels may lead to an impaired capacity to export beta-lactam antibiotics out of the central nervous system, resulting in accumulation of the drug inside the cerebrospinal fluid. Finally cerebral edema, hypoxia and ischemia will make the brain more vulnerable for neurotoxicity. In our study we could not detect CAZ-related neurotoxicity, because asphyxia in itself was responsible for clinical neurologic sequelae in the immediate neonatal period including seizures, hypotonia, coma or hypoxic-ischemic encephalopathy. Although no CAZ-related side effects could be demonstrated in this study, the data described above indicate that modifications of the dose of CAZ in the asphyxiated newborn should be performed to prevent potential drug-induced neurotoxicity.

We decided to use a model in which a trough level of 5 mg/L was chosen as the minimum level desired for appropriate bacterial killing of the most important neonatal microorganisms. Two different strategies were used for the calculations.

Dosage recommendations were calculated using a fixed dosing interval of 12 h, which resulted in a CAZ dose of 25 mg/kg every 12 h. Alternatively appropriate dosing could also be achieved by extending the dosing interval to 18 h using a CAZ dose of 50 mg/kg. We conclude that asphyxia has a significant impact on the disposition characteristics of CAZ in the term newborn and that dosage adjustments of CAZ are indicated in term asphyxiated infants with a decreased GFR. Further studies are needed to examine the impact of asphyxia on the disposition of drugs with extensive renal clearance like CAZ. In addition the impact of asphyxia on the disposition of drugs with extensive non-renal clearance like theophylline needs to be investigated.

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CHAPTER 10

PENETRATION OF CEFTAZIDIME INTO THE CEREBROSPINAL FLUID OF PRETERM INFANTS

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CHAPTER 10

PENETRATION OF CEFTAZIDIME INTO THE CEREBROSPINAL FLUID OF PRETERM INFANTS

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10.1 Abstract

Cerebrospinal fluid (CSF) levels of ceftazidime (CAZ) were measured in 14 preterm infants who were suspected of meningitis. Serum and CSF samples were simultaneously collected in 8 infants to calculate the percentage penetration of CAZ into the CSF. CSF cultures were all negative and CSF showed no signs of inflammation. CAZ administered intravenously in a dose of 25 mg/kg every 12 h resulted in CSF levels well above the MIC of the major neonatal pathogens, also in the absence of meningeal inflammation.

10.2 Introduction

In the last decade important changes were made in the initial empiric antibiotic regimens for treatment of bacterial meningitis in the newborn period[1]. In the 1970s and early 1980s ampicillin and an aminoglycoside were used in most North American and European neonatal intensive care units. Because of the emergence of aminoglycoside-resistant gram-negative enteric bacilli, the concern about ototoxicity and the poor penetration of aminoglycosides into the central nervous system, many centers changed their empiric therapy to ampicillin and a third generation cephalosporin. CAZ is a third generation cephalosporin with a high activity against most

bacteria involved in neonatal meningitis[2]. Previous studies in adults and children have shown that CAZ penetrates inflamed meninges much better than noninflamed meninges[3,4]. However, despite the introduction and use of CAZ in suspected or documented bacterial meningitis little is known about the penetration of the CSF by CAZ in preterm infants with or without meningeal inflammation. We therefore measured the concentration of CAZ in CSF and serum in preterm infants who needed a second septic work-up and calculated the percentage penetration of CAZ into the CSF.

10.3 Methods

Patients and study design

Fourteen preterm infants with a gestational age (GA) of less than 34 weeks, admitted to the neonatal intensive care unit with suspected or documented septicemia/ meningitis, were eligible for study. Infants were only enrolled after informed consent was obtained from a parent or a guardian. At the time of inclusion all infants were already treated during at least 48 h for suspected septicemia with CAZ (25 mg/kg intravenously) every 12 h and amoxicillin (25 mg/kg intravenously) every 12 h. A second septic work-up (blood, CSF and urine cultures) was performed in these infants because they remained ill despite maximal supportive therapy. CSF and serum samples were obtained simultaneously in 8 infants. In another 6 infants only CSF samples were collected. CSF and serum samples were collected at different time intervals after administration of an intravenous bolus injection of CAZ.

Ceftazidime assay

Analysis of CSF and serum CAZ concentrations was performed according to the method described by Ayrton[5] with minor modifications. HPLC-grade acetonitrile was purchased from Rathburn (Walkerburn, Scotland). The other chemicals were purchased from Aldrich-Chemie (Steinheim, Germany). All chemicals applied were of the highest grade commercially available. Chromatographic analysis was performed with a glass-prepacked C_{18} column (100 by 8 mm, Resolve Radial Pak, Waters, USA) combined with a guard column. A Waters Chromatography pump

(model 6000 A, Waters, USA) was used to deliver the eluent: 4.8% (vol/vol) acetonitrile, 13.5% methanol in 20 mM sodium acetate buffer (pH 3.6) at a flow rate of 2 mL/min. The separations were carried out at room temperature. The eluate was monitored with two Waters Absorbance Detectors (Model 440/wavelength of 254 nm and Model 484/wavelength 265 nm, Waters, USA). To a 50-µL aliquot of the serum or CSF sample, an equal volume of 6% (vol/vol) perchloric acid containing 50 mg/L cephaloridine as an internal standard was added. Samples were centrifuged at 1500 g for 5 minutes (Eppendorf Centrifuge 5412).
Subsequently 25 µL was transferred by an automatic sample injector (WISP 710 B, Waters, USA) to the column. A calibration curve was made by dissolving 4, 12, 25, 50, 100, and 200 mg CAZ per liter of serum. These spiked standard samples were processed according to the procedure mentioned above. A linear calibration curve was obtained over a range of 4 to 200 mg of CAZ per liter. Spiked samples of the calibration curve underwent the same processing procedure as clinical samples. Hence, clinical samples were directly converted from the calibration curve to actual CAZ concentrations per liter of serum. The lower limit of detection of CAZ in serum and CSF was 0.5 mg/L. The coefficients of interassay variation at different concentrations were less than 7%. The intraassay values were less than 5%. Recovery of 95% of CAZ, which had been incubated for 24 h at room temperature, was established.

Percentage penetration

The percentage penetration of CAZ into the CSF was calculated using the following equation:

percentage penetration = CAZ CSF level/CAZ serum level x 100.

10.4 Results

In all 14 infants CSF cultures were negative and CSF analysis (cell count, protein and glucose content) gave no indication for the presence of meningeal inflammation. The demographic parameters and CSF concentrations of CAZ after administration of an intravenous bolus injection of 25 mg/kg CAZ are shown in Table 1.
The CSF concentrations varied between 4.3 and 23.4 mg/L. CSF concentrations,

Table 1. **Demographic parameters and cerebrospinal fluid concentrations of ceftazidime at various time intervals after administration of an intravenous bolus injection of 25 mg/kg ceftazidime**

Patient number	Gestational age (weeks)	Postnatal age (days)	Time interval (h)	CSF CAZ levels (mg/L)
1	26.4	3	3.75	6.2
2	31.0	3	2.75	10.9
3	29.4	2	8	16.6
4	31.1	3	3.5	19.2
5	28.1	3	4.75	8.3
6	28.4	2	4	12.6
7	28.4	2	7	8.7
8	27.3	2	12	5.2
9	32.9	2	7.75	9.4
10	31.9	3	10	7.4
11	33.9	2	0.5	23.4
12	29.3	3	7	8.1
13	30.0	3	12	4.3
14	31.9	3	6.75	17.8

serum concentrations and the percentage penetration of CAZ into the CSF at various time intervals after CAZ administration for 8 of these infants are shown in Table 2. Serum concentrations varied between 14.2 and 80.0 mg/L. CSF concentrations varied between 5.2 and 19.2 mg/L. The calculated percentage penetration of CAZ into the CSF varied between 11.3 and 39.7%. The percentage penetration

Table 2. Cerebrospinal fluid concentrations, serum concentrations and percentage penetration of ceftazidime into the cerebrospinal fluid at various time intervals after administration of an intravenous bolus injection of 25 mg/kg ceftazidime

Patient number	Time interval (h)	CSF CAZ levels (mg/L)	serum CAZ levels (mg/L)	penetration (%)
1	3.75	6.2	55.0	11.3
2	2.75	10.9	59.0	18.5
3	8	16.6	41.8	39.7
4	3.5	19.2	55.5	34.6
5	4.75	8.3	60.0	13.8
6	4	12.6	80.0	15.8
7	7	8.7	55.0	16.0
8	12	5.2	14.2	36.6

of CAZ into the CSF was not dependent on the serum level of CAZ, the time interval after CAZ administration nor the GA in this study.

10.5 Discussion

The data presented in this paper show that administration of CAZ twice daily intravenously in a dose of 25 mg/kg body weight results in CSF concentrations well above the MIC of major neonatal patho-gens, also in the absence of meningeal inflammation. Our results are in contrast with the very low CSF concentrations of CAZ in children and adults with non-inflamed meninges, which ranged from 0 to 1.8 mg/L[3,4]. Data on the penetration of CAZ into the CSF of newborns without evidence of meningeal inflammation are scarce. In one study two preterm infants without meningitis (27 and 35 weeks of gestation) had CSF levels of 9.0 mg/L and <1.0 mg/L, respectively[6]. In a recent study 16 newborns with a mean GA of 38 weeks, of which 15 had no meningitis, had CSF levels of CAZ between 2.5 and 17 mg/L with a median value of 7 mg/L[7].

The CSF levels (5.2-19.2 mg/L) measured in our study in the absence of meningeal inflammation are in the same range as described by Tessin et al.[7]. However, the mean GA of our infants was considerably lower (30 weeks). The difference in the CAZ dose between the study of Tessin et al.[7] and our study (50 mg/kg versus 25 mg/kg every 12 h) is probably responsible for the similar CSF levels in these significantly younger patients.

Our data support the concept of a gradual development of the blood-CSF barrier from high permeability in the early fetal and neonatal phase to the greatly restricted permeability by the end of the first year of life. Statz and Felgenhauer[8] demonstrated with the use of serum-CSF concentration ratios of albumin and alpha-2-macroglobulin, that the permeability of the blood-CSF barrier of a 25-week-old preterm infant is identical with that of a school-aged child suffering from purulent meningitis. We speculate that the permeability of the blood-CSF barrier is higher in infants with a mean GA of 30 weeks than in infant with a mean GA of 38 weeks. This will allow a reduction of the daily dose of CAZ in preterm infants with a GA of less than 34 weeks without jeopardizing the treatment of a possible meningitis.

Approximately one fourth of newborn infants with septicemia have accompanying meningitis[9]. Appropriate drug selection and dosing should therefore assure that adequate drug concentrations are present in the CSF. The excellent penetration of the CSF by CAZ even without meningeal inflammation allows early treatment of bacteria invading the central nervous system. We speculate that this may prevent or mitigate the natural course of neonatal meningitis by earlier sterilization of the CSF[10]. The common practice to use higher dosages of antibiotics in the case of meningitis may therefore not be necessary in these preterm infants.

We conclude that CAZ shows an excellent penetration into the CSF and therefore can be safely used in preterm infants with suspected meningitis.

10.6 References

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CHAPTER 11

TRANSPLACENTAL PASSAGE OF CEFTAZIDIME IN THE SECOND HALF OF PREGNANCY

Submitted

CHAPTER 11

TRANSPLACENTAL PASSAGE OF CEFTAZIDIME IN THE SECOND HALF OF PREGNANCY

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11.1 Abstract

Objective

The aim of the study was to determine if maternal administration of 1 g ceftazidime (CAZ) intravenously every 6 h in the second half of pregnancy results in therapeutic concentrations in the fetus.

Study design

Ten pregnant women with suspected intra-uterine infection (median gestational age [range] 30 [25.6-33.6 weeks]) were treated with CAZ 1 g intravenously every 6 h. Blood samples were drawn after delivery simultaneously from the umbilical vein and the mother's cubital vein. CAZ concentrations were measured by HPLC-assay.

Results

Umbilical vein concentrations of CAZ varied between 8.2 and 32.4 mg/L (median 15.2 mg/L). Maternal serum concentrations of CAZ varied between 5.0 and 43.9 mg/L (median 10.5 mg/L). The calculated ratio's of umbilical vein to maternal serum concentration varied between 0.74 and 2.21 (median 1.34). Three pregnant women had a culture proven bacterial intra-uterine infection (*Escherichia coli, Neisseria gonorrhoeae, Listeria monocytogenes*); their newborns had a positive blood culture with the same pathogen.

Conclusion

We conclude that administration of 1 g CAZ every 6 h to pregnant women results in fetal serum concentrations above the MIC of most perinatally important bacterial pathogens.

11.2 Introduction

Intra-uterine infection is diagnosed during the second half of pregnancy in approximately 1% of pregnancies and is responsible for considerable maternal morbidity and fetal as well as neonatal morbidity and mortality[1]. The diagnosis of intra-uterine infection is generally based on the presence of fever and signs and symptoms such as maternal or fetal tachycardia, uterine tenderness, foul odor of the amniotic fluid, and maternal leukocytosis[2]. Antimicrobial agents are routinely given to treat or prevent maternal and fetal complications of intra-uterine infection. The choice of a specific antibiotic is based on the susceptibility of bacterial pathogens that are most likely to cause these infections, and on the extent of transplacental passage of the drug. Because fetal toxicity must be avoided, amino-glycosides and tetracyclines are preferably not used during pregnancy[3]. Third generation cephalosporins are non-toxic compounds with a broad antibacterial spectrum that are increasingly used for the treatment of suspected or documented intra-uterine infections[4,5]. Previous studies have demonstrated good transfer of CAZ from the mother to the fetus during the first half of pregnancy[6,7], but data on transplacental passage of CAZ during the second half of pregnancy are not available. We therefore studied the transplacental passage of CAZ in the second half of pregnancy.

11.3 Methods

Ten pregnant women with a singleton pregnancy suspected of intra-uterine infection and admitted to the department of Obstetrics of the Academic Hospital Rotterdam were included in the study. Patients were enrolled after informed consent was obtained. The gestational age (GA) of the newborns was determined on the basis

of the mother's menstrual history, confirmed by early ultrasound examinations, and by physical examination with the use of the criteria of Dubowitz et al.[8]. At the time of inclusion the women were treated for suspected intra-uterine infection with CAZ (1 g intravenously every 6 h) and amoxicillin (1 g intravenously every 6 h). After delivery blood samples were obtained simultaneously from the umbilical vein and the mother's cubital vein at various time intervals (10-330 minutes) after the last intravenous bolus injection of CAZ. Additionally, samples for bacterial culture were taken from amniotic fluid and blood of the newborns. After birth infants were treated with CAZ (25 mg/kg intravenously every 12 h) and amoxicillin (25 mg/kg intravenously every 12 h) for a period of 7 days. When a positive culture in the newborn was found, antibiotics were adjusted according to susceptibility testing and continued for 10 days.

Serum samples were centrifuged (Merck type Eppendorf 5414, 3000 g for 1 minute) and stored at -70°C until assayed within 6 months. The concentration of CAZ in serum was determined by means of high-pressure liquid chromatography according to the method described by Ayrton[9] with minor modifications. HPLC-grade acetonitrile was purchased from Rathburn (Walkerburn, Scotland). The other chemicals were purchased from Aldrich-Chemie (Steinheim, Germany).

Chromatographic analysis was performed with a glass-prepacked C_{18} column (100 by 8 mm, Resolve Radial Pak, Waters, USA) combined with a guard column. A Waters Chromatography pump (model 6000 A, Waters, USA) was used to deliver the eluent: 4.8% (vol/vol) acetonitrile, 13.5% methanol in 20 mM sodium acetate buffer (pH 3.6) at a flow rate of 2 mL/min. The separations were carried out at room temperature. The eluate was monitored with two Waters Absorbance Detectors (Model 440/wavelength of 254 nm and Model 484/wavelength 265 nm, Waters, USA). To a 50-µL aliquot of the serum, an equal volume of 6% (vol/vol) perchloric acid containing 50 mg/L cephaloridine as an internal standard was added. Samples were centrifuged at 1500 g for 5 minutes (Eppendorf Centrifuge 5412). Subsequently 25 µL was transferred by an automatic sample injector (WISP 710 B, Waters, USA) to the column. A calibration curve was made by dissolving 4, 12, 25, 50, 100, and 200 mg CAZ per liter of serum. These spiked standard samples were processed according to the procedure mentioned above. A linear calibration curve was obtained over a range of 4 to 200 mg of CAZ per liter. Spiked samples of the

calibration curve underwent the same processing procedure as clinical samples. Hence, clinical samples were directly converted from the calibration curve to actual CAZ concentrations per liter of serum. The lower limit of detection of CAZ in serum was 0.5 mg/L. The coefficients of interassay variation at different concentrations were less than 7%. The intraassay values were less than 5%. Recovery of 95% of CAZ, which had been incubated for 24 h at room temperature, was established.

11.4 Results

Demographic and clinical parameters of the studied infants are shown in Table 1. The umbilical vein and maternal serum concentrations of CAZ are depicted in Figure 1.

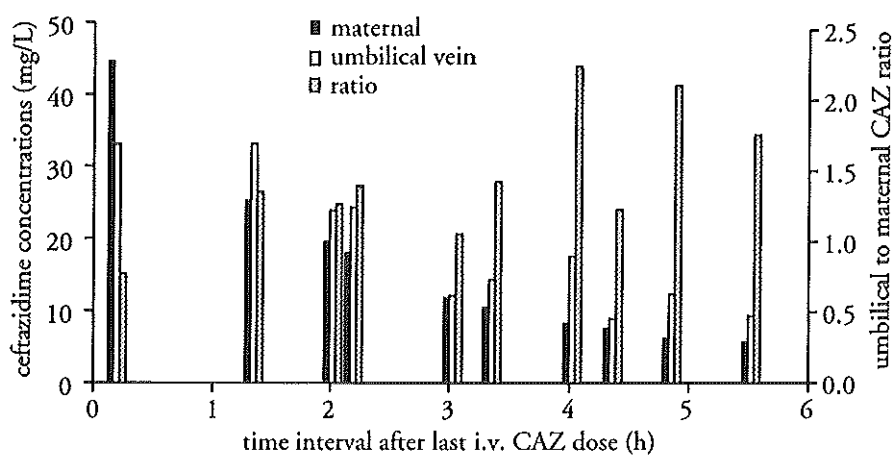

Figure 1. **Maternal and umbilical vein concentrations, and infant/maternal ratio of ceftazidime at various time intervals after the last intravenous dose of ceftazidime**

Maternal and fetal concentrations decreased with time after administration of CAZ. Umbilical vein levels decreased from 32.4 mg/L, 10 minutes after injection of CAZ, to 8.6 mg/L, 330 minutes after the last dose of CAZ. Maternal concentrations decreased from 43.9 mg/L, 10 minutes after injection of CAZ, to 5.0 mg/L, 330 minutes after the last dose of CAZ. The calculated umbilical to maternal CAZ

Table 1. Demographic and clinical parameters of studied infants

Number	Gestational age (weeks)	Birth weight (g)	Ventilation (+/–)	Intra-uterine infection
1	26.3	820	+	-
2	33.6	2190	–	-
3	30	1400	+	*Escherichia coli*
4	31	1680	+	-
5	30	1185	–	*Neisseria gonorrhoeae*
6	26.3	880	+	-
7	30	1400	+	-
8	27	1175	+	-
9	25.6	765	+	*Listeria monocytogenes*
10	30.7	1600	+	-

ratio's are also indicated in Figure 1 and varied between 0.74 and 2.21. All fetal concentrations were higher than those of the mother with the exception of one sample taken 10 minutes after maternal injection of CAZ. All women and their offspring survived without any short-term or long-term sequelae. Three of the ten women had a culture proven bacterial intra-uterine infection (*Escherichia coli, Neisseria gonorrhoeae, Listeria monocytogenes*). Their infants had a positive blood culture with the same pathogen and were subsequently treated with appropriate antibiotics (amoxicillin, penicillin and amoxicillin, respectively).

11.5 Discussion

Maternal serum drug concentrations are generally lower than those reported in non-pregnant women as a result of a larger volume of distribution and an increased renal plasma clearance during gestation[10,11]. In addition, maternal serum concentrations vary considerably because of differences in dosage, route of administration, and time interval from last dosage. Our results show that maternal serum concentrations varied between 43.9 mg/L shortly after injection and 5.0 mg/L

after approximately 6 hours. These values were all well above the MIC of the major perinatal pathogens, and far below the assumed toxic concentration of CAZ (trough concentration >40 mg/L).

The rate of transfer from mother to fetus is dependent on the free maternal drug concentration, and the size and physicochemical properties of the drug. Drugs with a molecular weight greater than 500 D cross the placenta incompletely[12]; water-soluble drugs cross the placenta more difficult than lipid-soluble compounds[13]. CAZ is a water-soluble substance with a molecular weight of 636 D, and 17% protein binding. Therefore one expects good, yet incomplete, diffusion across the placenta.

The umbilical vein levels of CAZ exceeded those in maternal serum in all infants, except the one sampled 10 minutes after maternal CAZ injection. Equilibration between the fetal and maternal compartments is apparently achieved between 10 and 80 minutes after maternal CAZ injection. It occurs most likely within 30 minutes after injection. After equilibration the mother can eliminate CAZ through the kidneys more rapidly than the fetus through the placenta. This results in a gradient between fetus and mother, favoring higher levels of CAZ in the fetus.

Maternal CAZ administration 1 g intravenously four times daily resulted in umbilical vein concentrations of at least 8.2 mg/L and maternal values of at least 5.0 mg/L, which are both well above the MIC for most major perinatal pathogens including *Streptococcus agalactiae* (MIC_{90} <0.25 mg/L) and *Escherichia coli* (MIC_{90} <0.25 mg/L)[4,5]. Assuming that a trough level of 5 mg/L is desired as a minimum for appropriate bacterial killing, the CAZ dosage of 1 g intravenously four times daily is appropriate for both the pregnant woman and her fetus. Despite adequate fetal CAZ levels, neonatal septicemia was present in 3 of the 10 patients. The 3 infants with positive blood cultures were born 2 to 5 hours after the first administration of CAZ and amoxicillin. In women with culture proven amnionitis 2 to 5 hours of CAZ therapy is apparently inadequate to effectively treat fetal septicemia.

We conclude that the administration of 1 g CAZ every 6 h to pregnant women results in maternal and fetal serum concentrations well above the MIC of most perinatally important bacterial pathogens.

11.6 References

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CHAPTER 12

SUMMARY

CHAPTER 12

SUMMARY

There is an increase in the survival rate of preterm infants due to rapid advances in medical knowledge and technology. However, the research and attention paid to the proper use of pharmacotherapy in these infants is still a relatively underdeveloped field. Effective and safe drug therapy requires a thorough understanding of human developmental biology and of the dynamic ontogeny of drug absorption, drug disposition, drug metabolism, and drug excretion. It is apparent that maturation of organ system function and changes in body composition during gestation and during the neonatal period exert a significant effect on the disposition of drugs. Hence, specific dosage recommendations are required for preterm infants. The various studies presented in this thesis were performed to investigate the impact of gestational age (GA), postnatal age and various pathophysiological conditions such as asphyxia or hyaline membrane disease, and the importance of in utero or postnatal exposure to drugs on these maturational processes.

Chapter 1 gives the general principles of clinical pharmacokinetics and a synopsis of the present knowledge on developmental physiology and drug disposition in newborn infants. The available data indicate that there are important differences in drug kinetics between preterm and fullterm infants. Parameters such as GA and postnatal age have to be considered in the institution of appropriate dosing regimens. The relative importance of other factors, such as drug exposure in utero, hemodynamic conditions, the presence of hypoxia, respiratory distress syndrome, cardiac, renal or gastrointestinal pathology has not yet been fully elucidated.

Chapter 2 reviews the clinical pharmacokinetics of antibacterial drugs in preterm infants. It is concluded that the currently available data on pharmacokinetics of antibiotics in preterm infants are insufficient, especially in those infants with GAs of less than 32 weeks. Despite these deficiencies new dosage recommendations are suggested that take into account the rapid GA and postnatal age dependent changes in renal function, hepatic function and body composition. Suggestions for future research are given.

Chapter 3 describes the effect of GA, body weight, and prenatal exposure to betamethasone and indomethacin on the glomerular filtration rate (GFR) on day 3 of life in 147 preterm infants. Mean GFR values increased significantly with GA ($r=0.60$, $p<0.001$) and with body weight ($r=0.44$, $p<0.001$). Multivariate analysis indicated that GA was the most important determinant for this increase. Prenatal exposure to indomethacin resulted in lower GFR values (-0.15 ± 0.03 mL/min, $p<0.001$) at day 3 of life. Prenatal administration of both betamethasone and indomethacin resulted in GFR values not different from those seen in preterm infants who were not prenatally exposed to betamethasone or indomethacin. This indicates that betamethasone increases GFR when co-administered prenatally with indomethacin. We hypothesize that an increase in renal plasma flow due to betamethasone may overcome intrarenal vasoconstriction secondary to the decreased synthesis of prostaglandins by indomethacin. It is concluded that in utero exposure to these drugs exerts significant effects on the renal function of preterm infants during the first days of life. These effects could no longer be detected at day 10 after birth.

Chapter 4 describes the results of a study that compared serum creatinine values, measured by an automated enzymatic method with special attention to bilirubin interference, with the inulin clearance, measured by the continuous inulin infusion technique in 144 preterm infants on day 3 of life. A positive relationship between the reciprocal of the serum creatinine values and the inulin clearance was found ($r=0.83$, $p<0.001$), indicating the practical usefulness of serum creatinine as a measure of the GFR on day 3 of life. To establish guidelines for clinical use reference values of serum creatinine measured with this method are presented.

Chapter 5 describes the effect of GA on ceftazidime (CAZ) pharmacokinetics in 136 preterm infants on day 3 of life. Clearance and volume of distribution of CAZ increased significantly with increasing GA, whereas serum trough levels and serum half-life of CAZ decreased significantly with increasing GA. These effects were related to changes in the GFR. It was shown that the clearance of CAZ increased significantly with increasing GFR. Dosage recommendations taking into account GA and GFR were calculated. In addition the effects of prenatal exposure to betamethasone and indomethacin on the pharmacokinetics of CAZ are described. The data indicate that the clearance of CAZ is significantly decreased after prenatal

exposure to indomethacin. Dosage adjustments for indomethacin-exposed preterm infants were calculated. It is concluded that dosage recommendations for administration of CAZ in preterm infants during the first week of life should be based on measurements of GA and GFR. Additional dosage adjustments during the first week of life are indicated in preterm infants who are prenatally exposed to indomethacin.

Chapter 6 describes the effect of GA on amoxicillin (AM) pharmacokinetics in 17 preterm infants with GAs of less than 32 weeks on day 3 of life. AM was administered twice daily intravenously in a 25 mg/kg body weight dose. Clearance and volume of distribution of AM increased significantly with increasing GA. These effects were related to changes in GFR. It was shown that clearance of AM increased significantly with increasing GFR. The clearance of AM (1.0 ± 0.4 mL/min) and the GFR (1.0 ± 0.3 mL/min) were similar, indicating that AM is almost completely cleared by glomerular filtration in these preterm infants during the first days of life. It is concluded that preterm infants with GAs of less than 32 weeks should receive a maximum AM dosage of 25 mg/kg twice daily.

Chapter 7 describes a study that compared once- versus twice-daily dosing of 25 mg/kg of CAZ in 28 preterm infants with GAs of less than 32 weeks on day 3 of life. This study was initiated to examine the effect of a prolongation of the dosing interval of CAZ to 24 h. CAZ 25 mg/kg once daily was administered in 13 infants and 25 mg/kg twice daily in 15 infants. Serum trough concentrations in the once-daily group (13.1 ± 4.7 mg/L) were significantly lower in comparison with the twice-daily group (42.0 ± 13.4 mg/L), but were still substantially above the MIC of major neonatal pathogens. It is concluded that the currently recommended twice daily 25 mg/kg administration of CAZ in preterm infants may be adjusted to once daily 25 mg/kg during the first days of life, provided that for the empirical treatment of septicemia, amoxicillin at 25 mg/kg is also given twice daily. Further studies are indicated to evaluate the clinical efficacy of the proposed dosage adjustment of CAZ.

Chapter 8 describes the effect of postnatal age and postnatal exposure to indomethacin on CAZ pharmacokinetics in 23 preterm infants. Twelve of these infants, with a patent ductus arteriosus, were postnatally treated with indomethacin. In the non-exposed infants the clearance of CAZ increased with increasing postnatal age,

whereas the volume of distribution and the serum half-life decreased with increasing postnatal age. These effects were related to changes in GFR. Mean GFR values increased by 0.19 mL/min between day 3 and day 10 after birth, indicating a postnatal acceleration (5.4 times faster than the in utero increase in GFR) of the development of the GFR. Furthermore it was shown that the clearance of CAZ increased significantly ($r=0.81$, $p<0.001$) with increasing GFR. The pharmacokinetic changes were markedly reduced in infants who were postnatally treated with indomethacin. These effects were also related to changes in GFR. In these infants a postnatal increase in GFR was not present. The data from this study indicate that the dosage regimen of CAZ should be adjusted after the first week of life except in infants who are postnatally exposed to indomethacin.

Chapter 9 describes the effect of asphyxia on the pharmacokinetics of CAZ in the term infant. Clearance of CAZ was significantly decreased in the asphyxiated newborn, whereas serum half-life and serum trough concentrations were significantly increased. These changes are related to changes in GFR, and it was shown that the impaired CAZ clearance is a result of a significantly decreased GFR. Dosage adjustments for asphyxiated term newborns are presented. The results of this study indicate that asphyxia has a significant impact on the disposition characteristics of CAZ in the term newborn.

Chapter 10 describes the extent of penetration of CAZ into the cerebrospinal fluid (CSF) of preterm infants who were suspected of meningitis. It is shown that intravenous administration of 25 mg/kg CAZ twice daily results in CSF concentrations well above the MIC of the major neonatal pathogens, also in the absence of meningeal inflammation. It is concluded that the penetration of CAZ into the CSF compartment is excellent (11.3-39.7%). These data suggest that the current guidelines to double the dosages of antibiotics in patients with neonatal meningitis need to be reconsidered.

Chapter 11 describes the transplacental transfer of CAZ in the second half of pregnancy. The data indicate that the intravenous administration of 1 g CAZ every 6 h to pregnant women results in fetal serum concentrations well above the MIC of most perinatally important bacterial pathogens. All fetal concentrations were higher than those of the mother with the exception of a sample taken as short as 10 minutes after maternal injection of CAZ. Equilibration between the fetal and

maternal compartments occurs most likely within 30 minutes after injection. After equilibration the mother can eliminate CAZ through the kidneys more rapidly than the fetus through the placenta. We conclude that the use of CAZ in pregnant women results in the rapid initiation of adequate antibacterial therapy in the unborn child.

This thesis illustrates that, in the preterm infant, most of the physiological variables important for drug disposition are different from those in children and adults and subject to rapid changes. For effective and safe drug therapy variables such as GA and postnatal age, drug exposure in utero, extrauterine drug administration, hemodynamic conditions, acid-base equilibrium, and developmental stage of excretory organs should be considered. The dependence of many drugs on renal elimination underscores the need to obtain specific data in preterm infants with a compromised renal function. CAZ served as an excellent model for the effects of GFR on clinical pharmacokinetics, because it is not metabolized and almost exclusively excreted by glomerular filtration. The effect of changes in the GFR on the pharmacokinetics of CAZ could therefore be thoroughly studied. The results of this thesis may thus be used as a guideline for other drugs that are primarily renally excreted and not extensively metabolized.

The pharmacokinetic behaviour of drugs depending on hepatic metabolism or elimination also needs to be studied carefully in these infants, since changes in liver function may also have important implications for dosage recommendations of drugs that are primarily dependent on hepatic biotransformation or elimination.

SAMENVATTING

Dankzij de snel voortschrijdende ontwikkelingen in de medische kennis en technologie nemen de levenskansen van preterme pasgeborenen toe. Het onderzoek en de aandacht die besteed worden aan het op de juiste wijze toepassen van farmacotherapie bij deze vroeggeborenen zijn hierbij echter relatief gezien achtergebleven. Het op een effectieve en veilige manier toedienen van geneesmiddelen vereist een grondige kennis van zowel de menselijke ontwikkelingsbiologie als van de veranderingen in absorptie, distributie, metabolisme en excretie van medicamenten. Het is evident dat rijping van verschillende organen en veranderingen in lichaamssamenstelling gedurende de zwangerschap en de neonatale periode een duidelijk effect zullen hebben op de farmacokinetiek van geneesmiddelen. Derhalve zijn specifieke doseringsvoorschriften noodzakelijk voor de preterme pasgeborene. De verschillende studies die in dit proefschrift worden beschreven hadden als doel het effect van zwangerschapsduur, postnatale leeftijd, pathologische omstandigheden zoals asphyxie of hyaliene membranen ziekte, en het effect van prenatale of postnatale blootstelling aan verschillende medicamenten op deze ontwikkelingsprocessen te bestuderen.

Hoofdstuk 1 geeft algemene principes van de klinische farmacokinetiek en een samenvatting van de stand van zaken met betrekking tot de huidige kennis omtrent de ontwikkelingsfysiologie en de farmacokinetiek bij pasgeborenen. De beschikbare gegevens duiden op aanzienlijke verschillen met betrekking tot de farmacokinetiek tussen het te vroeg geboren kind en het voldragen kind. Bij het vaststellen van het juiste doseringsschema van geneesmiddelen moet rekening gehouden worden met parameters als zwangerschapsduur en postnatale leeftijd. In hoeverre ook andere factoren van belang zijn, zoals in utero blootstelling aan geneesmiddelen, circulatoire omstandigheden, het voorkomen van hypoxie, hyaliene membranen ziekte, cardiale, renale of gastro-intestinale pathologie, is nog niet volledig opgehelderd.

Hoofdstuk 2 geeft een overzicht van de klinische farmacokinetiek van antimicrobiële middelen bij te vroeg geboren kinderen. De conclusie is dat de huidige beschikbare gegevens met betrekking tot de farmacokinetiek van antibiotica bij te vroeg geborenen onvoldoende zijn, met name bij pasgeborenen met een zwangerschapsduur

van 32 weken of korter. Ondanks deze onvolledige gegevens worden nieuwe doseringsvoorstellen gegeven. Hierbij is rekening gehouden met de effecten van de bekende, snelle veranderingen in de nierfunctie, leverfunctie en lichaamssamenstelling. Er worden tevens aanbevelingen gedaan voor toekomstig onderzoek.
Hoofdstuk 3 beschrijft het effect van de zwangerschapsduur, het lichaamsgewicht en de prenatale blootstelling aan betamethason en indometacine op de glomerulaire filtratiesnelheid (GFS), gemeten bij 147 preterme pasgeborenen op de derde levensdag. De gemiddelde GFS-waarden namen significant toe met de zwangerschapsduur ($r=0.60$, $p<0.001$) en met het lichaamsgewicht ($r=0.44$, $p<0.001$). Multivariate analyse wees uit dat de zwangerschapsduur de belangrijkste variabele in deze toename was. Prenatale blootstelling aan indometacine resulteerde in lagere GFS-waarden (-0.15 ± 0.03 ml/min, $p<0.001$) op de derde levensdag. De GFS-waarden bij prenataal gelijktijdige toediening van betamethason en indometacine waren gelijk aan de waarden gemeten bij preterme pasgeborenen die niet prenataal waren blootgesteld aan betamethason en indometacine. Dit wijst op een toename van de GFS door betamethason wanneer dit prenataal tegelijkertijd wordt toegediend met indometacine. Onze hypothese is dat een toename van de nierdoorstroming ten gevolge van betamethason de intrarenale vasoconstrictie tenietdoet, die is ontstaan als secundair gevolg van de verminderde prostaglandine-synthese door indometacine. De conclusie is dat in utero blootstelling aan deze middelen een significant effect heeft op de nierfunctie van preterme pasgeborenen in de eerste levensdagen. Deze effecten zijn op dag 10 na de geboorte niet meer aanwezig.
Hoofdstuk 4 geeft de resultaten weer van een onderzoek bij 144 preterme pasgeborenen op de derde levensdag. In dit onderzoek werden serum creatinine waarden, bepaald door middel van een geautomatiseerde enzymatische methode met speciale aandacht voor bilirubine interferentie, vergeleken met de inulineklaring, gemeten met behulp van de continue inuline infusie methode. Er werd een positieve relatie gevonden tussen de reciproke waarden van de serum creatinine waarden en de inuline klaring ($r=0.83$, $p<0.001$). Dit geeft aan dat de serum creatinine waarde in de praktijk bruikbaar is als maat voor de GFS op de derde levensdag. Om richtlijnen voor klinische gebruik vast te stellen, worden referentiewaarden van serum creatinine gegeven die zijn bepaald met behulp van deze methode.

Hoofdstuk 5 beschrijft de invloed van de zwangerschapsduur op de farmacokinetiek van ceftazidim (CAZ) bij 136 preterme pasgeborenen op de derde levensdag. De klaring en het verdeelvolume van CAZ namen significant toe met de zwangerschapsduur, terwijl de serumdalspiegels en serumhalfwaardetijd van CAZ significant afnamen met de zwangerschapsduur. Deze effecten werden gerelateerd aan veranderingen in de GFS. Aangetoond werd dat de CAZ-klaring significant toenam bij stijgende GFS. Er worden richtlijnen gegeven voor de juiste dosering van CAZ, gebaseerd op de zwangerschapsduur en de GFS. Ook worden de effecten beschreven van prenatale blootstelling aan betamethason en indometacine op de farmacokinetiek van CAZ. De gegevens wijzen op een significante afname van de CAZ-klaring na prenatale blootstelling aan indometacine. Voor aan indometacine blootgestelde preterme pasgeborenen worden doseringsaanpassingen gegeven. De conclusie is dat de aanbevolen doseringen voor toediening van CAZ bij preterme pasgeborenen tijdens de eerste levensweek gebaseerd zouden moeten zijn op zwangerschapsduur en GFS. Voor preterme pasgeborenen die prenataal zijn blootgesteld aan indometacine zijn gedurende de eerste levensweek extra doseringsaanpassingen geïndiceerd.

Hoofdstuk 6 beschrijft het effect van de zwangerschapsduur op de farmacokinetiek van amoxicilline (AM) op de derde levensdag bij 17 preterme pasgeborenen, geboren na een zwangerschapsduur van minder dan 32 weken. AM werd tweemaal daags intraveneus toegediend in een dosering van 25 mg/kg. De klaring en het verdeelvolume van AM namen significant toe met de zwangerschapsduur. Deze effecten werden gerelateerd aan veranderingen in de GFS. Aangetoond werd dat de AM-klaring significant toenam bij stijgende GFS. De AM-klaring (1.0 ± 0.4 mL/min) en de GFS (1.0 ± 0.3 mL/min) waren gelijk, wat aangeeft dat AM vrijwel volledig wordt geklaard door glomerulaire filtratie bij deze preterme pasgeborenen in hun eerste levensdagen. De conclusie is dat preterme pasgeborenen, geboren na een zwangerschapsduur van minder dan 32 weken, een maximale dosis amoxicilline van tweemaal daags 25 mg/kg toegediend zouden moeten krijgen.

Hoofstuk 7 beschrijft het onderzoek waarin op de derde levensdag bij 28 preterme pasgeborenen eenmaal daags toediening van 25 mg/kg CAZ werd vergeleken met tweemaal daags 25 mg/kg CAZ. Dit onderzoek werd opgezet om het effect te onderzoeken van een verlenging van het doseringsinterval naar 24 uur.

Aan 13 pasgeborenen werd eenmaal daags 25 mg/kg CAZ toegediend en aan 15 tweemaal daags 25 mg/kg. Serumdalspiegels in de groep van eenmaal daags (13.1 ±4.7 mg/L) waren significant lager in vergelijking tot de groep van tweemaal daags (42.0 ± 13.4 mg/L), maar waren nog steeds aanzienlijk hoger dan de minimale remmende concentratie voor de belangrijkste pathogenen. De conclusie is dat in de eerste levensdagen de huidige aanbevolen doseringsfrequentie van CAZ van tweemaal daags 25 mg/kg kan worden veranderd in eenmaal daags 25 mg/kg. Verder onderzoek is wenselijk om de klinische effectiviteit van de voorgestelde doseringsaanpassing van CAZ te beoordelen.

Hoofdstuk 8 beschrijft het effect van de postnatale leeftijd en postnatale blootstelling aan indometacine op de farmacokinetiek van CAZ bij 23 preterme pasgeborenen. Twaalf pasgeborenen, met een open ductus Botalli, werden postnataal behandeld met indometacine. Bij 11 pasgeborenen die niet aan indometacine waren blootgesteld, nam de CAZ-klaring toe met de postnatale leeftijd, terwijl het verdeelvolume en de serumhalfwaarde tijd afnam met de postnatale leeftijd. Deze effecten werden gerelateerd aan veranderingen in de GFS. De gemiddelde GFS-waarden namen toe met 0.19 mL/min tussen dag 3 en dag 10 na de geboorte, hetgeen duidt op een postnatale versnelling van de ontwikkeling van de GFS (5.4 maal sneller dan de in utero toename van de GFS). Bovendien werd aangetoond dat de CAZ-klaring significant toenam ($r=0.81$, $p<0.001$) bij stijgende GFS. De farmacokinetische veranderingen waren significant minder bij pasgeborenen die postnataal werden behandeld met indometacine. Ook deze effecten werden in verband gebracht met veranderingen in de GFS. Bij deze pasgeborenen werd geen postnatale toename in de GFS waargenomen. De gegevens uit dit onderzoek wijzen erop dat na de eerste levensweek het doseringsschema van CAZ moet worden aangepast, behalve bij pasgeborenen die postnataal worden behandeld met indometacine.

Hoofdstuk 9 beschrijft het effect van asfyxie op de farmacokinetiek van CAZ bij de voldragen pasgeborene. De CAZ-klaring was significant verlaagd bij de asfyctische pasgeborene, terwijl de serumhalfwaardetijd en serumdalspiegels significant waren verhoogd. Deze veranderingen werden gerelateerd aan veranderingen in de GFS en aangetoond werd dat de gestoorde CAZ-klaring een gevolg is van een significant verlaagde GFS. Er worden doseringsaanpassingen voor asfyctische, voldragen pasgeborenen gepresenteerd. De resultaten van dit onderzoek duiden erop dat asfyxie

een significante invloed heeft op de farmacokinetiek van CAZ bij de voldragen pasgeborene.
Hoofdstuk 10 beschrijft in welke mate CAZ in de liquor cerebrospinalis doordringt bij preterme pasgeborenen bij wie het vermoeden van meningitis bestaat.
Aangetoond wordt dat intraveneuze toediening van 25 mg/kg CAZ tweemaal daags resulteert in liquorconcentraties die ruim boven de minimaal remmende concentratie voor de belangrijkste neonatale pathogenen liggen, ook in de afwezigheid van meningitis. Geconcludeerd wordt dat CAZ uitstekend doordringt in het liquorcompartiment. Deze gegevens suggereren dat de huidige richtlijnen om bij de patiënten met neonatale meningitis de dosering van antibiotica te verdubbelen, heroverwogen moeten worden.
Hoofdstuk 11 beschrijft de passage van CAZ over de placenta in de tweede helft van de zwangerschap. De gegevens wijzen erop dat intraveneuze toediening van viermaal daags 1 gram CAZ aan zwangere vrouwen resulteert in foetale serum concentraties die de minimaal remmende concentratie voor de meeste perinataal belangrijke bacteriële pathogenen ver overtreffen. Alle foetale concentraties waren hoger dan die van de moeder, met uitzondering van een monster dat al 10 minuten na de injectie van CAZ bij de moeder werd verkregen. Evenwicht tussen de foetale en maternale compartimenten treedt hoogstwaarschijnlijk op binnen 30 minuten na de injectie. Na bereiken van de evenwichtstoestand kan de moeder CAZ sneller uitscheiden via de nieren dan de foetus dit kan via de placenta. Wij concluderen dat binnen 1 uur na toediening van CAZ aan zwangere vrouwen adequate serumspiegels bij het ongeboren kind gemeten kunnen worden.

Uit het onderzoek zoals beschreven in dit proefschrift blijkt dat bij de preterme pasgeborene het merendeel van de fysiologische variabelen, die van belang zijn voor de farmacokinetiek van een geneesmiddel, verschillen van die bij kinderen en volwassenen en tevens onderhevig zijn aan snelle veranderingen.
Voor een effectieve en veilige therapie moet bij elke pasgeborene afzonderlijk rekening worden gehouden met parameters zoals de zwangerschapsduur en postnatale leeftijd, blootstelling aan geneesmiddelen in utero, extra-uterine toediening van geneesmiddelen, circulatoire omstandigheden, zuur-base evenwicht en het ontwikkelingsstadium van de uitscheidingsorganen.

Het feit dat veel geneesmiddelen voornamelijk via de nieren worden uitgescheiden onderstreept de noodzaak om specifieke gegevens te verzamelen bij de te vroeg geborenen bij wie een verminderde nierfunctie kan worden verwacht. Ceftazidim diende als een uitstekend model om nierfunctie-ontwikkeling te bestuderen, omdat dit geneesmiddel niet door het lichaam wordt gemetaboliseerd en vrijwel volledig door glomerulaire filtratie wordt uitgescheiden. De resultaten zoals beschreven in dit proefschrift kunnen derhalve worden gebruikt als richtlijn voor andere geneesmiddelen die primair via de nieren worden uitgescheiden en niet volledig worden afgebroken.

Het farmacokinetische gedrag van geneesmiddelen die door de lever worden gemetaboliseerd en/of worden uitgescheiden, dient in de toekomst ook zorgvuldig te worden onderzocht bij deze pasgeborenen, omdat veranderingen in de leverfunctie ook belangrijke consequenties kunnen hebben voor de aanbevolen dosering van geneesmiddelen die primair afhankelijk zijn van biotransformatie en/of eliminatie door de lever.

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