REVIEW

Pharmacokinetics of cephalosporins in the neonate: a review

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The aim of this work was to review the published data on the pharmacokinetics of cephalosporins in neonates to provide a critical analysis of the literature as a useful tool for physicians.   The bibliographic search was performed for articles published up to December 3, 2010, using PubMed. In addition, the book *Neofax: A Manual of Drugs Used in Neonatal Care* by Young and Mangum was consulted.   The cephalosporins are mainly eliminated by the kidneys, and their elimination rates are reduced at birth. As a consequence, clearance is reduced and $t_{1/2}$ is more prolonged in the neonate than in more mature infants. The neonate's substantial body water content creates a large volume of distribution (Vd) of cephalosporins, as these drugs are fairly water soluble. Postnatal development is an important factor in the maturation of the neonate, and as postnatal age proceeds, the clearance of cephalosporins increases. The maturation of the kidney governs the pharmacokinetics of cephalosporins in the infant. Clearance and $t_{1/2}$ are influenced by development, and this must be taken into consideration when planning a cephalosporin dosage regimen for the neonate.

INTRODUCTION

Cephalosporins are the most common class of antibiotics used to treat bacterial infection. These drugs have proven to be safe, clinically effective, and easy to use.[1,2] The expanded-spectrum cephalosporins (e.g., cefotaxime, ceftriaxone, and ceftazidime), either alone or in combination with other antibiotics, are the most common antibiotics used as initial empiric therapy for treating serious infections.[3]

The first generation of cephalosporins has good activity against Gram-positive bacteria and relatively modest activity against Gram-negative bacteria. The second generation of cephalosporins has increased activity against Gram-negative microorganisms but tends to be much less active than the third-generation agents. The fourth generation of cephalosporins is particularly useful for the empirical treatment of serious infections in hospitalized patients when Enterobacteriaceae and pseudomonas are potential etiologies.[4] Cephalosporins are minimally toxic, with the exception of ceftriaxone, which displaces bilirubin from albumin[5,6] and precipitates calcium, resulting in serious adverse effects.[7,8] The aim of this paper was to review the literature on the kinetics of cephalosporins in the neonate and provide a critical analysis of the literature as a useful tool for physicians.

Bibliographic search

The bibliographic search was performed electronically, using PubMed to find articles published up to December 3, 2010. First, a Medline search was performed with the key words ''pharmacokinetics of cephalosporins in neonates," with the limit of ''human''. Other Medline searches were performed with the key words ''pharmacokinetics of ……… in neonates,'' followed by the names of single cephalosporins. In addition, the book *Neofax: A Manual of Drugs Used in Neonatal Care* by Young and Mangum[9] was consulted. The bibliographic search produced 37 original articles, four review articles and two book chapters. The publication years of this material ranged from 1977 to 2010.

RESULTS

The demographic data for the neonates and the pharmacokinetic parameters of different cephalosporins are presented in four tables. Information relative to the first-generation cephalosporin, cefazolin, and the second-generation cephalosporins, cefoxitin, and cefuroxime, is provided in Table 1. Table 2 summarizes the results relative to the third-generation cephalosporins. Table 3 shows the results relative to cefepime, a fourth-generation cephalosporin, and Table 4 shows the concentrations of various cephalosporins in the cerebrospinal fluid (CSF) and serum.

Clearance (Cl) is expressed in different units by different authors. This makes comparisons between studies difficult. To overcome this difficulty, Cl was converted into ml/min/kg. SD cannot be converted; therefore, Cl values are reported without SDs.

Table 1 - Demographic data of the studied neonates and pharmacokinetic parameters of first- and second-generation cephalosporins. Figures are the mean ± SD.

Cefazolin – First-generation cephalosporins										
Gestational age (wk)	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	Cl (ml/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	Peak conc. (µg/ml)	Trough conc. (µg/ml)	Reference
35 ± 3	9.4 ± 7.4	2,326 ± 943	11	30	0.80	0.28 ± 0.05	na	na	na	10

Cefoxitin and cefuroxime – Second-generation cephalosporins										
Drug	Gestational age (wk)	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	Cl (ml/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	Peak conc. (µg/ml)	Trough conc. (µg/ml)	Reference
Cefoxitin	36 ± 4	<2 months	2,404 ± 599	15	30×3	4.5	0.50 ± 0.21	1.43 ± 0.53	69.8 ± 31.9	na	11
Cefuroxime	na	<3 weeks	<1,000 >4,000	104	10×3	na	na	4.6 ± 0.7[a]	24.2 ± 8.2 [b]	6.4 ± 5.6 [b]	12

na = not available.
[a] Data obtained in 10 neonates.
[b] Data obtained in 5 neonates.

First generation cephalosporin

Cefazolin. The pharmacokinetics of cefazolin (Table 1) in 11 neonates were studied by Deguchi et al.[10] There was marked interindividual variability in the distribution volume (Vd). This parameter ranged from 0.21 to 0.37 L/kg. The unbound fraction of cefazolin in neonatal plasma ranged from 0.22 to 0.83. The Vd of cefazolin highly correlated (r = 0.936; $p<0.001$) with the unbound fraction of this drug.

Young and Mangum[9] suggested administering 25 mg/kg cefazolin every 8 to 12 h according to the neonate's postmenstrual age and postnatal age. When the postmenstrual age is >45 weeks, the interval between doses should be six hours.

Second-generation cephalosporins

Cefoxitin. Regazzi et al[11] studied the pharmacokinetics of cefoxitin in 15 neonates. Their reported kinetic parameters are summarized in Table 1. The half-life ($t_{1/2}$) negatively correlated with postnatal age (r = -0.58; $p<0.05$). Young and Mangum[9] suggested administering 25 to 33 mg/kg cefoxitin every 8 to 12 h according to the neonate's postmenstrual age and postnatal age. When the postmenstrual age is >45 weeks, the interval between doses should be six hours.

Cefuroxime. Renlund and Pettay[12] studied the pharmacokinetics of cefuroxime in 104 neonates, and their reported kinetic parameters are summarized in Table 1. The serum concentration of cefuroxime decreased with body weight from 25.6 ± 9.9 µg/ml (<1 kg body weight) to 19.5 ± 6.8 µg/ml (>4 kg body weight) because of the increase in GFR with neonatal maturation. $t_{1/2}$ showed similar behavior, decreasing from 5.6 h (2.83 kg body weight) to 4.0 h (3.83 kg body weight). Cefuroxime did not accumulate over a period of 8 days and was excreted in the urine by more than 70%.

Third-generation cephalosporins

Cefotaxime. The kinetic parameters of cefotaxime are summarized in Table 2. Kafetzis et al[13] described treating infections with cefotaxime in 32 neonates. The pathogens that sustained the infection were Escherichia coli, Klebsiella species, Pseudomonas aeruginosa, Serratia marcescens Staphylococcus aureus, Staphylococcus epidermidis, and β-hemolytic streptococcus. All of the isolated pathogens were susceptible to cefotaxime. These authors clustered the pharmacokinetic parameters of cefotaxime into four groups according to the neonates' gestational age and postnatal age. With neonatal maturation, $t_{1/2}$ decreased and Cl increased. For brevity, Table 2 shows the two extremes of the cohort. In five patients with meningitis who received 50 mg/kg cefotaxime twice daily, the concentration of the drug was simultaneously measured in the CSF and serum 1 to 2 h after cefotaxime administration. The CSF and serum concentrations (mean ± SD) were 18.2 ± 7.4 and 38.6 ± 10.3 µg/ml, respectively. The CSF-to-serum ratio was 45 ± 0.12%.

McCracken et al[14] compared the kinetic parameters of cefotaxime in two groups of neonates; the first had an average body weight of 1,103 g, and the second had an average body weight of 2,561 g ($p<0.0001$). Vd and $t_{1/2}$ were greater in the former than the latter group, whereas Cl was greater in the latter group and AUC was not different in the two groups.

Cefotaxime is converted into desacetyl cefotaxime in the neonate, and the peak concentration of desacetyl cefotaxime is about one-tenth of that of cefotaxime.[15-17] The $t_{1/2}$ of desacetyl cefotaxime is 9.4 h in very low-body-weight neonates.[18] After 50 mg/kg cefotaxime, 50 to 60% of the dose is excreted unchanged in the urine, and approximately 20% is excreted as desacetyl cefotaxime.[18] The renal Cl of cefotaxime is quantitatively more important than its metabolic Cl. Gouyon et al[15] observed that the $t_{1/2}$ of cefotaxime was negatively correlated with gestational age (r = -0.8954; $p<0.01$) and body weight (r = -0.8500; $p<0.01$). In contrast, Cl was positively correlated with gestational age (r = 0.7280; $p<0.02$) and body weight (r = 0.8667; $p<0.02$). The AUC of cefotaxime was negatively correlated with gestational age (r = -0.7950; $p<0.01$), but it did not correlate with body weight.

One recent study examined cefotaxime in neonates undergoing extracorporeal membrane oxygenation (ECMO).[19] Doses of 50 mg/kg of body weight twice a day (postnatal age <1 week), 50 mg/kg three times a day (postnatal age 1 to 4 weeks) or 37.5 mg/kg four times a day (postnatal age >4 weeks) were found to provide sufficient periods of supra-MIC concentrations to give adequate treatment of infants on ECMO.

Young and Mangum[9] suggested intravenously administering 25 to 33 mg/kg of cefotaxime every 8 or 12 h

Table 2 - Demographic data of the studied neonates and pharmacokinetic parameters of the third-generation cephalosporins. Figures are the mean$\pm$SD unless otherwise stated.

Cefotaxime – Third-generation cephalosporins												
Comment	Gestational age (wk)	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	AUC (µg.h/ml)	Cl (ml/min/kg)	Vd (L/kg)	t$_{1/2}$ (h)	Peak conc. (µg/ml)	Trough conc. (µg/ml)	Reference
Preterm	Preterm	<7	na	18	Note A	na	1.37 (ml/min)	0.61±0.05	5.7±0.8	na	na	13
Term	Term	7-28[b]	na	14		na	4.45 (ml/min)	0.69±0.08	2.0±0.5	na	na	
p	___	___	___	___	___	___	<0.05	NS	<0.05	___	___	
1.1±0.22 kg body weight	na	4.0±1.6	1,103±216	14	50	400±56	23.0 (ml/min/1.73 m²)	0.51±0.06	4.6±1.1	115.9±38.1	34.4±12.1	24
2.6±0.6 kg body weight	na	3.5±1.7	2,561±607	15	50	392±77	43.9 (ml/min/1.73 m²)	0.44±0.07	3.4±0.9	132.7±37.7	38.1±6.9	
p	___	NS	<0.0001	___	___	NS	<0.001	<0.01	<0.01	na	na	
Term	37±3	4.1±1.7	1,836±723	10	25x2	373±206	1.57	0.43±0.15	3.7±1.5	171[a]	5[a]	15
Preterm	28±2	4.0±1.6	1,016±350	18	50	na	1.23	0.46±0.03	4.4 [a]	159.0±11.6	na	18
Preterm	<32	<7	na	3	25	262±46	1.08	0.34±0.07	3.5±0.4	73.8±9.6	11.1[a]	17
Term	>37	≥7	na	5	25	177±25	2.33	0.36±0.08	2.0±0.5	68.2±9.6	22±1.3	
p	___	___	___	___	___		<0.001	<0.005	NS	<0.001	NS	<0.05

Ceftazidime – Third-generation cephalosporins												
Comment	Gestational age (wk)	Postnatal age (days)	Body weight (g)	No. of Cases	Daily dose (mg/kg)	AUC (µg.h/ml)	Cl (ml/min/kg)	Vd (L/kg)	t$_{1/2}$ (h)	Peak conc. (µg/ml)	Trough conc. (µg/ml)	Reference
Intravenous	35[a]	6[a]	2,470[a]	7	50	na	na	na	4.7±1.5	109±19.9	11.8±4.1	20
Intramuscular	37[a]	8[a]	2,860[a]	9	50 IM	na	na	na	3.8±1.1	53.0±22.4	8.9±5.6	
p	___	___			___	___			<0.05	<0.001	<0.05	
Preterm	≤32	1-22 [b]	805-4170 [b]	7	Note B	912±203	0.98	0.53±0.12	6.7±2.6	111±15	41±8	21
Preterm	33-37			14		691±156	1.25	0.51±0.12	4.9±1.6	118±28	31±9	
Controls	31±3	3	1,579±597	84	50×2		0.68	0.36±0.09	6.3±1.7	115±39	34±18	23
Term	≥38			8		619±151	1.42	0.48±0.09	4.2±1.2	102±18	29±8	
Indomethacin	29±2	3	1,133±334	23	50×2		0.46	0.36±0.2	9.4±3.1	na	na	
3 days old	29±1	3	1,154±201	23	25×2		0.51	0.36±0.06	8.7±2.8	na	na	24
10 days old	29±1	10	Weight at birth				0.69	0.29±0.04	5.0±0.9	na	na	
p	___	___					<0.05	<0.005	<0.005	___	___	
Once daily	29±2	3	1,168±309	13	25		0.46	0.32±0.06	8.15±1.2	na	13.1±4.7	25
Twice daily	29±2	3	1,141±400	15	25×2		0.41	0.30±0.06	7.09±1.7	na	42.0±13.4	
p	___	___	NS	___	___		NS	NS	NS	___	p<0.001	

Ceftriaxone – Third-generation cephalosporins											
Comment	Gestational age (wk)	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	Cl (ml/min/kg)	Vd (L/kg)	t$_{1/2}$ (h)	Peak conc. (µg/ml)	Trough conc. (µg/ml)	Reference
50 mg/kg	5 term neonates and 25 infants 6 weeks to 2 years old	na	na	15	50	0.85	0.38±0.13	5.8±2.6	230±64	na	29
75 mg/kg		na	na	15	75	0.93	0.39±0.06	5.4±2.1	295±75	na	
Intravenous	32±4	1-60 [b]	1880±860	12	50	0.28	0.33±0.07	15.4±5.6	153±39	54±22	30
Intramuscular	These values refer to the entire population of 18 cases.			6	50 IM	0.28	0.32±0.04	15.8±5.8	120±37	54±19	
Preterm	na	3.2[a]	1164[a]	10	50	1.0 (ml/min)	0.61±0.02	7.7±0.6	145±18	66±3.3	31
Preterm	na	6.7[a]	1176[a]	3	50	0.73 (ml/min)	0.53±0.03	8.4±1.6	136±8.9	71±4.4	
Term	na	2.8[a]	2670[a]	9	50	1.8 (mL/min)	0.52±0.04	7.4±0.5	159±9.1	74±5.4	
Preterm	na	22.5[a]	2112[a]	4	50	1.6 (ml/min)	0.50±0.05	5.2±0.6	173±23	67±12	

Table 2 - Cont.

Cefoperazone – Third-generation cephalosporins											
Comment	Gestational age (wk)	Postnatal age (days)	Body Weight (g)	No Cases	Daily dose (mg/kg)	Cl (ml/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	Peak conc. (µg/ml)	Trough conc. (µg/ml)	Reference
50 mg/kg	32-36[b]	1.6	1,420-2,810[b]	12	50	0.60	0.12 ± 0.01	5.5 ± 1.7	136 ± 28	na	32
250 mg/kg	These values refer to the entire population of 15 cases.			3	250	0.58	0.11 ± 0.01	2.8 ± 1.7	720 ± 264	na	
Preterm and term	28-42[b]	2-6[b]	1,300-3,700[b]	10	100×2	0.78	0.41 ± 0.04	6.5 ± 0.9	352 ± 75	60 ± 10	33
Preterm	27-32[b]	1-2[b]	1,220[a]	5	50	na	0.44 ± 0.04	8.9 ± 2.1	159 ± 22	17 ± 11	34
Preterm	33-36[b]	1-2[b]	1,896[a]	9	50	na	0.48 ± 0.14	7.6 ± 3.1	110 ± 41	14 ± 17	
Term	≥37	1-2[b]	3,068[a]	11	50	na	0.45 ± 0.01	7.2 ± 2.0	109 ± 29	13 ± 9	
Ceftizoxime – Third-generation cephalosporins											
Comment	Gestational age (wk)	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	Cl (ml/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	Peak conc. (µg/ml)	Trough conc. (µg/ml)	Reference
See Note A	36 ± 3	0.6 ± 0.4	2600 ± 1000	19	Note C	0.68 ± 0.3	0.37 ± 0.1	7.2 ± 3.6	na	na	36
	38 ± 3	3.4 ± 1.6	2800 ± 1000	15		0.94 ± 0.3	0.46 ± 0.1	6.3 ± 2.3	na	na	
	37 ± 4	16.0 ± 1.0	2600 ± 1000	6		1.5 ± 0.5	0.57 ± 0.1	4.7 ± 1.6	na	na	
	na	116 ± 52	4600 ± 1100	12		2.4 ± 1.1	0.44 ± 0.1	2.4 ± 0.9	na	na	

na = not available. NS = not significant. IM = intramuscular.
[a]Mean; the SD was not available;
[b]range. Note A: The cefotaxime dose was 25 mg/kg and 50 mg/kg in patients with meningitis. Doses were administered every 12 h in neonates younger than one week of age and every 8 h in patients 1 to 4 weeks of postnatal age. Note B: The ceftazidime dose was 50 mg/kg every 12 h for neonates in the first week of life and every 8 h for older infants. Note C: Twenty-five patients received 25 mg/kg, and 27 patients received 50 mg/kg.

according to the postmenstrual age. When the postmenstrual age is >45 weeks, the interval between doses should be six hours.

Ceftazidime. The pharmacokinetic parameters of ceftazidime are summarized in Table 2. The ceftazidime concentration was measured after intravenous administration to seven neonates and after intramuscular administration to 9 infants.[20] Ceftazidime concentrations after intravenous injection declined biexponentially, and the postdistributive phase occurred 30 to 60 min after administration. The peak ceftazidime concentration was 109 ± 19.9 (intravenously) and 53.0 ± 22.4 (intramuscularly; $p < 0.05$). The $t_{1/2}$ of ceftazidime was 4.7 ± 1.5 (intravenously) and 3.8 ± 1.1 (intramuscularly; NS).

McCracken et al[21] described the pharmacokinetics of ceftazidime in three groups of neonates with gestational ages of ≤32, 33-37, and ≥38 weeks. Cl increased with gestational age, whereas $t_{1/2}$, AUC and the trough concentrations decreased with gestational age.

Blumer et al[22] described ceftazidime's pharmacokinetics and penetration into CSF in ten children aged 12 to 540 days. Ceftazidime at 50 mg/kg was intravenously administered once per day. The $t_{1/2}$ of ceftazidime was 1.8 ± 0.8 h, which was 2- to 4-fold lower than that reported in neonates during the first week of life (see Table 2). The two youngest children, aged 12 and 23 days, had a $t_{1/2}$ of 3.6 and 2.18 h, respectively. The Cl of ceftazidime varied by more than 300%; such a large variation makes it inappropriate to report the average Cl, so the data from Blumer et al[22] are not shown in Table 2. In contrast, Vd showed little variation and ranged from 0.27 to 0.38 L/kg, with a mean ± SD of 0.34 ± 0.07 L/kg. The ceftazidime concentrations in the CSF and serum were 4.7 ± 2.5 and 145 ± 30.4 µg/ml, respectively. The CSF-to-serum concentration of ceftazidime was 3.5 ± 1.8%. The ratio

of CSF to serum ceftazidime concentration showed a time-dependent increase, suggesting that ceftazidime was eliminated more slowly from the CSF than from the vascular compartment. The MIC of the isolated pathogens ranged from 0.0156 µg/ml (Neisseria meningitidis) to 0.125 µg/ml (Haemophilus influenzae, Type B).

Prenatal exposure to indomethacin resulted in significantly lower GFR and ceftazidime Cl values.[23] The Cl of ceftazidime was 0.46 ml/min/kg (n = 23) in neonates who were prenatally exposed to indomethacin and 0.68 ml/min/mg (No = 84) in infants who were not exposed to indomethacin ($p < 0.05$). The Cl of ceftazidime increased with gestational age (r = 0.83; $p < 0.001$), whereas $t_{1/2}$ showed an opposite trend (r = -0.54; $p < 0.001$).[23] The positive relationship between the Cl of ceftazidime and the Cl of inulin (r = 0.73; $p < 0.001$) indicated that glomular filtration had an important effect on the Cl of ceftazidime. The Cl of ceftazidime correlated with the reciprocal of the serum concentration of creatinine (r = 0.72; $p < 0.001$), suggesting that this compound may interfere with the renal Cl of ceftazidime.

The ceftazidime Cl increased from days 3 to 10 of life[24] (Table 2). Such increases are due to an increase in GFR. The inulin Cl was 0.72 (day 3) and 0.91 ml/min (day 10; $p < 0.05$). The Cl of ceftazidime correlated with GFR (r = 0.81; $p < 0.001$). This correlation indicates the important role of GFR in the clearance of ceftazidime. The Vd of ceftazidime decreased between days 3 and 10 of life. During the first week of life, there was a significant decrease in extracellular water. Ceftazidime is mainly distributed in the extracellular water component, and a decrease of extracellular water may cause a decrease in the Vd during this period. Postnatal exposure to indomethacin prevented the pharmacokinetic

modification seen from days three to ten of life. This may be explained by renal function's dependence on postnatal changes in extracellular water[24] and the GFR impairment associated with indomethacin use.

Once-daily versus twice-daily administration of ceftazidime was studied by van den Anker et al.[25] After 25 mg/kg twice daily, the trough concentration of ceftazidime was 42.0 ± 13.4 µg/ml, which was higher than the target value of 10 µg/ml. After once-daily dosing, the trough concentration was 13.1 ± 4.7 µg/ml, higher than the target value of 10 µg/ml and higher than major neonatal pathogen MIC_{99} values such as those for Streptococcus agalactiae and Escherichia coli[26,27] (MIC_{99} <0.25 µg/ml). Therefore, these authors suggested that once-daily 25 mg/kg ceftazidime is the appropriate therapeutic schedule for ceftazidime in the neonate. This administration schedule conflicts with the one suggested by Young and Mangum.[9] They suggested administering 30 mg/kg of ceftazidime every 8 or 12 h according to the postmenstrual and postnatal age. When the postmenstrual age is ≥45 weeks, ceftazidime should be administered every eight hours.

Ceftriaxone. Ceftriaxone is contraindicated in neonates because it displaces bilirubin from albumin binding sites, resulting in a higher free bilirubin serum concentration with subsequent accumulation of bilirubin in the tissues.[5,6] Even more dangerous is ceftriaxone's interaction with calcium. This interaction precipitates calcium, which results in serious adverse effects.[7,8]

Nonetheless, the literature on ceftriaxone was reviewed to provide a comprehensive study of cephalosporin use. The kinetic parameters of ceftriaxone are summarized in Table 2. The MIC_{90} of ceftriaxone ranged between 0.06 and 2 µg/ml for Escherichia coli, Klebsiella species, Proteus species, Enterobacter species, and Staphylococcus aureus, whereas Enterococci and Listeria monocytogenes are resistant.[28] Ceftriaxone reached CSF concentrations of 5.4 and 6.4 µg/ml after intravenous doses of 50 and 75 mg/kg, respectively, and the CSF-to-peak serum concentration was 2.2-2.3%.[29] Sixty percent of ceftriaxone is eliminated by the kidneys, and Mulhall et al[30] have described the pharmacokinetics of this drug in the neonate (Table 2).

McCracken et al[31] stratified the kinetic parameters of ceftriaxone based on neonatal body weight. The longest $t_{1/2}$, 7.7 to 8.4 h, was found in neonates weighing ≤1,500 g, compared with 5.2 to 7.4 h in those weighing >1,500 g. The shortest $t_{1/2}$ (3.5 and 4.8 h) was found in two neonates aged 45 to 33 days, respectively. Vd ranged between 0.50 and 0.61 l/kg; the smaller value was found in larger and older infants. Of nine neonates who received multiple ceftriaxone doses of 50 mg/kg every 12 h, five showed evidence of drug accumulation in the plasma. The concentrations of ceftriaxone increased from 20 to 208% (mean 82%) at 0.5 h and from 15 to 165% (mean 53%) at 6 h after dosing. The

ceftriaxone concentration in randomly collected urine ranged from 113 to 3,350 µg/ml (median 618 µg/ml).

Young and Mangum[9] suggested administering 50 mg/kg every 24 h. To treat meningitis, they suggested a 100-mg/kg loading dose and then 80 mg/kg once daily.

Cefoperazone. The kinetic parameters of cefoperazone are summarized in Table 2. Gestational age correlated with Cl (r = 0.67; p = 0.01) and with a constant rate of elimination[32] (Ke; r = 0.57; p = 0.05), while $t_{1/2}$ decreased with advancing gestational age[33] (r = -0.81; p<0.001). Rosenfeld et al[34] studied the pharmacokinetics of cefoperazone (50 mg/kg) in 25 infants with a postnatal age of 1 to 2 days. The neonates were divided into three groups according to their gestational age. These authors repeated the cefoperazone treatment in 14 neonates aged 5 to 7 days, and the kinetic parameters were similar to those obtained at a postnatal age of 1 to 2 days. The percentage of the cefoperazone dose excreted in the urine on days 1 and 2 after birth was highest in the most premature patients (55%) but was not statistically different from that of full-term infants (37%). In infants 5 to 7 days old, cefoperazone excretion decreased in the full-term neonates (27%) and was 55% in the most premature infants (p<0.03). These data suggest that cefoperazone is partially metabolized and that its rate of metabolism depends on neonatal maturation. In adults, 69% of cefoperazone administered orally is eliminated by hepatic routes.[35]

A study based on seven neonates with body weights ranging from 1,540 to 3,600 g determined that cefoperazone penetrates the CSF.[34] The cefoperazone concentration (µg/ml) in the CSF and serum was 5.3 ± 3.6 and 89 ± 58, respectively. The CSF-to-serum ratio was $10.9 \pm 9.6\%$ and ranged from 1.4 to 31.7%.

Ceftizoxime. The kinetic parameters of ceftizoxime are summarized in Table 2. The pharmacokinetics of ceftizoxime were studied in 52 infants whose postnatal age ranged from 0.1 to 189 days.[36] $t_{1/2}$ diminished steadily as the postnatal aged increased, whereas Cl showed the opposite trend. In this study, Vd remained relatively constant[37], and ceftizoxime was excreted essentially unchanged via the kidney.[36]

Fourth-generation cephalosporins

Cefepime. The kinetic parameters of cefepime are summarized in Table 3. The serum creatinine concentration was negatively correlated (r = -0.79) with cefepime Cl in neonates.[38] The serum concentration of creatinine was a strong predictor of cefepim Cl.[38] The relationship between cefepime Cl and gestational age was not significant. The maturation of the renal excretory function is an important dosing determinant for cephalosporins, including cefepime. In premature infants, renal function is impaired. Because cefepime is mainly excreted unchanged, the premature and

Table 3 - Demographic data of the neonates and pharmacokinetic parameters of the fourth-generation cephalosporin cefepime. Figures are the mean $\pm$ SD unless otherwise stated.

Gestational age (wk)	Postnatal age (days)	Body Weight (g)	No. of cases	Daily dose (mg/kg)	Cl (ml/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	Peak conc. (µg/ml)	Trough conc. (µg/ml)	Reference
30 ± 5.3	14.7 ± 14.5	$1,910 \pm 1,040$	54	50×2	1.1	0.43 ± 0.13	4.9 ± 2.1	89 ± 27	18 ± 10	38
na	2 to 6 months	na	8	50×3	2.7	0.43 ± 0.1	1.9 ± 0.5	184 ± 38	6 ± 7	39
31 ± 3	21.8 ± 14	$1,400 \pm 400$	31	50×2	1.2	0.41 ± 0.12	4.3 ± 1.8	120 ± 38	18 ± 13	40

na = not available.

Table 4 - Cephalosporin concentration in the cerebrospinal fluid (CSF) and serum in neonates. Figures are the mean $\pm$ SD, unless otherwise stated.

Drug	Daily dose (mg/kg)	Drug concentration in CSF (µg/ml)	Drug concentration in serum (µg/ml)	% CSF-to-serum ratio	Reference
Cefotaxime*	50×2	18.2 $\pm$ 7.4	38.6 $\pm$ 10.3	45 $\pm$ 12	13
Ceftazidime * [a]	50	4.7 $\pm$ 2.5	145 $\pm$ 30.4	3.5 $\pm$ 1.8	22
Ceftriaxone*	75	6.5 [b]	295 $\pm$ 64	2.2 [b]	29
Ceftriaxone*	50	5.4 [b]	230 $\pm$ 64	2.3 [b]	
Cefoperazone *	50	5.3 $\pm$ 3.6	89 $\pm$ 58	10.9 $\pm$ 9.6 [c]	34
Cefepime *	50×2	4.7 $\pm$ 5.3	32.7 $\pm$ 23.1	25.8 $\pm$ 29.8	43

*Infants with meningitis.
[a]The infants' ages ranged from 12 to 540 days.
[b]Mean; SD was not available. Plasma.
[c]The CSF-to-serum ratio ranged from 1.4 to 31.7%.

term neonates clear cefepime more slowly than more mature infants. In neonates, the cefepime Cl value was approximately 40% of that of more mature infants, which results in a longer $t_{1/2}$ and a higher trough concentration. Vd was greater in infants with less than 30 weeks of postconceptional life.[38] This is consistent with the greater total body water content in the extremely premature neonate.

Reed et al[39] described the pharmacokinetics of cefepime in 37 infants and children aged between 2 months and 16 years. The data were grouped by age; the youngest patients ranged between two and six months of age, and the pharmacokinetic parameters of cefepime in these patients are reported in Table 3. Ninety percent of cefepime was recovered in the urine during 24-h urine collection; thus, the elimination of cefepime is in large part via the kidneys. The data for cefepime reveal disposition parameters similar to those of third-generation cephalosporins, including linearity over a broad dose range (250-2,000 mg), limited disposition and Cl mainly by the kidneys.

Lima-Rogel et al[40] compared their own results on the pharmacokinetics of cefepime in neonates with those of Capparelli et al[38] and Reed et al.[39] The kinetic parameters of cefepime measured by Lima-Rogel et al[40] and those of Capparelli et al[38] were obtained in infants with similar demographic data, and $t_{1/2}$ and Cl were comparable in these two studies. Reed et al[39] described the pharmacokinetics of cefepime in older infants and children. In this last study, $t_{1/2}$ was one-half and Cl was double the values in the neonates.

Information on the penetration of cephalosporins in the CSF is limited. Table 4 summarizes the concentrations of cefotaxime, ceftazidime, ceftriaxone, cefoperazone, and cefepime in the CSF and serum and the CSF-to-serum ratio. Information on the penetration in the CSF is available only for these cephalosporins. A relevant CSF-to-serum ratio was observed for cefotaxime[13] and it was 45 $\pm$ 12%. Another relevant penetration rate in the CSF was observed for cefoperazone,[34] which was 10.9 $\pm$ 9.6%. This figure seems to be overestimated, as it ranged from 1.4% to 37.1%. The rate of penetration of cefepime in the CSF was variable. In two preterm infants, the CSF-to-serum ratio was 30% and 87%, whereas in 7 term infants, it ranged from 3.6% to 59%, with a mean $\pm$ SD of 16.7 $\pm$ 21.4%. Table 4 shows the data for all nine neonates.

DISCUSSION

A common feature in the reviewed literature is the remarkable interindividual variability of the kinetic parameters of cephalosporins in the neonate. Such variability is due to renal maturation, as cephalosporins are fairly water soluble and are mainly eliminated with the urine.

The pharmacokinetic parameters of cephalosporins are development dependent; the $t_{1/2}$ of cefotaxime,[13,14] ceftazidime[24-26] and ceftizoxime[37] decrease with increasing gestational and postnatal age, whereas Cl shows an opposite trend. With prenatal and postnatal maturation, GFR increases, and consequently, the Cl of drugs that are mainly eliminated by kidneys increases.[41,42] Vd is only slightly influenced by neonatal maturation, although it tends to decrease with the maturation of the neonate. This has been observed for cefotaxime.[20,24] Preterm infants have a higher water content than term infants,[40] and because cephalosporins are fairly water soluble, they are distributed at a larger volume in preterm infants than in term infants.

The hypersensitivity, resistance and toxicology of cephalosporins have been studied in adults, but little is known about these characteristics in the neonate. Cephalosporin resistance may be related to the drug's inability to reach its sites of action, alterations in the penicillin-binding proteins that are the targets of cephalosporins or hydrolysis of the β-lactam ring by β-lactamase.[4] The most common side effects of cephalosporins are hypersensitivity reactions. The reactions appear to be identical to those caused by penicillins and may be related to the shared β-lactam structure of both groups of antibiotics. Immediate reactions, such as anaphylaxis, bronchospasm, and urticaria, are typically observed.[4] The cephalosporins have been implicated as potentially nephrotoxic agents, although they are not nearly as toxic to the kidneys as the aminoglycosides or polymyxins. In adults, renal tubular necrosis has followed the administration of cephaloridine in doses greater than 4 g/day.[4]

With the exception of cefotaxime[15,16] and cefoperazone,[34] which are partially metabolized, cephalosporins are mostly eliminated by the renal route, and maturation of the excretory renal function increases with development. Cl correlates with gestational age for cefotaxime,[15] cefoperazone,[32] and ceftazidime.[23] The Cl of cefotaxime is 2- to 3-fold higher in term than preterm infants.[13,14] With increasing Cl, $t_{1/2}$ clearly decreases. The Cl of ceftazidime negatively correlates with the reciprocal of serum concentration of creatinine; thus, the serum creatinine concentration negatively influences the Cl of ceftazidime.[23]

Little is known about the AUC, although this parameter for cefotaxime is similar in preterm and term infants.[14] In contrast, the AUC for ceftazidime is greater in neonates with a gestational age ≤32 weeks than in term infants.[21] This

finding is due to the reduced renal excretory function in preterm infants compared with term infants. In premature subjects, the Cl of ceftazidime is reduced; therefore, the ceftazidime serum concentration slowly decreases, and AUC tends to increase.

Most of the available information about the kinetics of cephalosporins deals with the third generation of these antibiotics. A considerable body of information is available on cefotaxime, ceftazidime, and ceftriaxone.

The Cl of ceftazidime increases between days 3 and 10 of life.[24] This increase is due to the increase in GFR. The Cl of ceftazidime is also correlated with GFR (r = 0.81; $p<0.001$). This correlation indicates the important effect of GFR on ceftazidime Cl. Intravenous administration of ceftazidime yields double the peak concentration of intramuscular administration.[20]

Ceftriaxone is active against Escherichia coli, Klebsiella species, Proteus species, Enterobacter species, and Staphylococcus aureus.[28] Cefepime is a fourth-generation cephalosporin and little is known about this drug, as it is the latest cephalosporin to enter clinical use. Creatinine negatively influences the Cl of cefepime.[39] Cefepime is primarily excreted unchanged. Preterm infants clear cefepime more slowly than full-term infants, as the renal excretory function rate is reduced in preterm subjects. Consequently, cefepime has a longer $t_{1/2}$ and a higher trough concentration in the preterm infant than the term infant.[38]

Meningitis can be treated with cephalosporins, so the penetration of these drugs in the CSF is important. Information on the concentration of cephalosporins in CSF is available for cefotaxime, ceftazidime, ceftriaxone, cefoperazone, and cefepime. Cefotaxime reaches a considerable CSF concentration, and the CSF-to-serum concentration ratio is relevant.[13] Only one study is available on the penetration of cefepime in CSF.[43] The concentration of this drug varies considerably in serum and CSF, and consequently, the CSF-to-serum ratio ranges widely.

The penetration of other cephalosporins into the CSF should be studied, and we feel that further research is required to ensure that the doses recommended for treating sepsis in neonates are entirely evidence-based.

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