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Cefotaxime Pharmacokinetics and Treatment of Meningitis in Neonates

**Summary:** Pharmacokinetic studies on cefotaxime/desacetylcefotaxime were carried out in very low birth weight newborns (n = 18; 500–1500 g; 28.4 ± 2.4 weeks gestational age) during the first week of life. We have previously reported that the elimination t 1/2 of cefotaxime (3.4–6.4 h) and desacetylcefotaxime (9.4 h) was longer than previously described in term infants and children. In very low birth weight neonates, a single 50 mg/kg daily dose of cefotaxime may produce accumulation of the metabolite desacetylcefotaxime in serum. In a non-comparative prospective clinical trial, 22 infants (one week–three months) were treated for gram-negative enteric bacillary meningitis with cefotaxime at a dosage of 50 mg/kg/day. The predominant pathogen was *Escherichia coli* in 14 cases and *Enterobacter cloacae* in four cases. Cultures of the cerebrospinal fluid obtained 24–48 h after the initiation of treatment were sterile in all subjects. Survival and complication rates of 95% and 19%, respectively, were observed. This compared favorably to previously published experiences with alternative treatment regimens for neonatal gram-negative enteric meningitis. In both the pharmacokinetic and meningitis studies, the safety profile for cefotaxime was excellent with no adverse reactions.

**Zusammenfassung:** Cefotaxim-Pharmakokinetik und Behandlung der Meningitis bei Neugeboren. Studien zur Pharmacokinetik von Cefotaxim/Desacetylcefotaxim wurden bei Neugeborenen mit sehr niedrigem Geburtsgewicht (n = 18; 500–1500 g; Gestationsalter 28,4 ± 2,4 Wochen) während der ersten Lebenswoche durchgeführt. Wie wir bereits berichtet haben, ist die Eliminations-Halbwertzeit von Cefotaxim (3,4–6,4 h) und Desacetylcefotaxim (9,4 h) bei diesen Kindern länger als bei reifen Neugeborenen und Kindern beschrieben wurde. Bei Neugeborenen mit sehr niedrigem Geburtsgewicht kann es nach Gabe von Cefotaxim in einer Dosis von einmal 50 mg/kg täglich möglicherweise zur Akkumulation des Metaboliten Desacetylcefotaxim im Serum kommen. In einer prospektiven, nicht vergleichenden klinischen Studie wurde Cefotaxim in einer Dosis von 50 mg/kg/Tag bei 22 Säuglingen im Alter von einer Woche bis drei Monaten zur Behandlung einer Meningitis durch gramnegative Enterobakterien eingesetzt. Als häufigster Erreger wurde *Escherichia coli* bei 14 Fällen isoliert, in vier Fällen *Enterobacter cloacae*. Bei allen Kindern waren die Liquorkulturen 24–48 h nach Therapiebeginn negativ. 95% der Kinder überlebten, bei 19% traten Komplikationen auf. Diese Ergebnisse stimmen gut mit früheren Erfahrungen mit Alternativtherapien bei der Meningitis durch grammnegative Enterobakterien überein. Das Sicherheitsprofil war sowohl in der Pharmakokinetik- wie in der Meningitis-Therapie studie ausgezeichnet, unerwünschte Reaktionen traten in keinem Fall auf.

**Introduction**

Cefotaxime has been studied and used extensively since 1981 for the treatment of bacterial meningitis in children [1–5]. With its broad spectrum of antimicrobial activity against gram-negative *Enterobacteriaceae* [6], it has also been considered an excellent antimicrobial for treating gram-negative enteric meningitis in neonates and infants [2, 4]. More recently, the major metabolite, desacetylcefotaxime, has been shown to possess antimicrobial activity against a number of significant pathogens [6]. With the new information on desacetylcefotaxime there has been interest in clinical investigations of cefotaxime treatment of meningitis in newborns and infants. Cefotaxime and desacetylcefotaxime have excellent cerebrospinal fluid penetration and have been shown to obtain significant concentrations in cerebrospinal fluid [7–9]. The spectrum of activity, production of high levels of both cefotaxime and desacetylcefotaxime in serum and CSF, resistance to hydrolysis by beta-lactamases, and an excellent safety profile have proved to be major reasons for consideration of the use of cefotaxime in serious infections in newborns, infants and children. With concern over displacement of bilirubin from albumin binding sites, hyperbilirubinemia and gall bladder precipitates with other cephalosporins [10–12], the demonstrated efficacy and safety profile of cefotaxime/desacetylcefotaxime in the neonate and infant continue to make it an attractive choice. At present, the Task Force from the American Academy of Pediatrics considers cefotaxime as the alternative drug of choice for use in neonates when aminoglycoside serum concentration monitoring is not available [13]. Part of the consideration for the use of cefotaxime in the neonate was the extensive pharmacokinetic data and clinical experience available for the drug, as well as its favorable safety profile [13]. Although no prospective comparative trial has demonstrated superior efficacy for third generation cepha-

*Addendum*
Cefotaxime and Desacetylcefotaxime Pharmacokinetics in Infants and Neonates

Cefotaxime possesses an aceto-methyl side chain at the 3-position of the cephalosporanic acid nucleus which undergoes hydrolysis by hepatic and plasma esterases to form the active metabolite, desacetylcefotaxime [18, 19]. In human neonates, the pathways responsible for the biotransformation of cefotaxime to desacetylcefotaxime have been shown to be active as early as 27 to 28 weeks of gestation [20, 21]. Once formed, desacetylcefotaxime is further metabolized in man to two microbiologically inactive lactones which are then excreted in the urine [18]. Over a 24 h post-dose period in adults, approximately 50 to 60% of a cefotaxime dose is excreted unchanged in the urine while 15 to 20% of the dose appears as desacetylcefotaxime [19, 22, 23].

Hepatic biotransformation, glomerular filtration and active tubular secretion are collectively responsible for the plasma clearance of cefotaxime [18, 24]. In adults, cefotaxime total plasma clearance ranges between 207 and 341 ml/min/1.73 m² (approximately 0.234 and 0.307 l/h/kg) and the renal clearance between 104 and 170 ml/min/1.73 m² (approximately 0.09 and 0.145 l/h/kg) [19, 25, 26]. We have previously demonstrated that the mean plasma (0.289 l/h/kg) and renal (0.174 l/h/kg) clearances of cefotaxime in infants and children with meningitis [7] were comparable to values previously reported for adults [19, 25, 26]. The similarity in the hepatic and renal clearance, as well as the apparent volume of distribution (i.e., 0.36 l/kg for children versus 0.21 to 0.45 l/kg for adults with normal renal function) for cefotaxime between adults and children [7, 23, 27–29] results in plasma elimination half life (t½) values ranging from 0.8 to 1.5 h for infants, children and adults [7, 24, 40]. Since cefotaxime is not appreciably bound (i.e., 30–40%) to plasma albumin [25, 26], one would not expect changes in protein binding to significantly alter either the plasma clearance or the apparent volume of distribution. Consequently, expected developmental differences in glomerular filtration, active tubular secretion and body water:mass relationships [31, 32], the disposition of both cefotaxime and desacetylcefotaxime is markedly different between neonates and older infants and children. In previous investigations of cefotaxime pharmacokinetics in both term and preterm neonates, average values for the apparent volume of distribution ranged from 0.3 to 0.6 l/kg while those for plasma clearance and t ½ from 1.1 to 1.7 ml/min/kg and 3.1 to 5.7 h, respectively [17, 33–37]. The similarity found between the plasma clearance for cefotaxime (0.074 ± 0.003 l/h/kg) and the expected normal glomerular filtration rate (i.e., 2 to 3 ml/min) for premature infants during the first week of life, as well as the correlation between cefotaxime t ½ and gestational age, support glomerular filtration as the predominant route for cefotaxime total plasma clearance in the very low birth weight neonate [17]. As such, the marked increase in cefotaxime t ½ in the neonate (e.g., 3.1 to 5.7 h) as compared to older children and adults (e.g., 0.8 to 1.5 h) reflects the dramatic differences in both glomerular and renal tubular function which characterize these respective developmental periods [31, 32].

In infants and children who received a single intravenous dose of cefotaxime the renal clearance of desacetylcefotaxime (0.363 l/h/kg) has been shown to be considerably higher than the expected glomerular filtration rate [7]. This finding was associated with a relatively short plasma elimination t ½ for desacetylcefotaxime (2.1 h) and supported previous work in adults which demonstrated that both glomerular filtration and active renal tubular secretion were quantitatively the most important pathways for desacetylcefotaxime plasma clearance [24]. Average peak serum desacetylcefotaxime concentrations of 12.5 to 18.0 mg/l occurring at approximately two to six h post-dose have been reported in very low birth weight premature neonates following a single 50.0 mg/kg intravenous dose of cefotaxime [17, 35, 36]. In a recent study, the elimination t ½ of desacetylcefotaxime in preterm neonates (9.4 h) was found to be significantly greater than previously reported for infants and children with meningitis (t ½ = 2.1 h) [7] and adults (0.83 ± 0.23 h) [24]. In view of the presence of active biotransformation pathways for cefotaxime by 27 to 28 weeks of gestational age [20, 21], the prolonged desacetylcefotaxime t ½ in premature neonates may be due to either developmental immaturity in glomerular filtration and/or active tubular secretion [31, 32], or to possible rate-limited formation as significant concentrations of cefotaxime do persist for 12 to 24 h after administration [17]. The inability to administer desacetylcefotaxime in previous investigations [7, 17, 34–36] has precluded the accu-