Ceftriaxone Use in Neonates

Nawal Merjaneh, MD[1]
Mobeen H. Rathore, MD[1,2,3]
[1]Department of Pediatrics
[2]University of Florida Center for HIV/AIDS Research Education and Service (UF CARES)
[3]Wolfson Children's Hospital
Jacksonville, Florida

Corresponding Author:
Mobeen H. Rathore, MD
900 N Jefferson Street
Jacksonville, FL 32209
Tel: 904-798-4179
Fax: 904-798-4568
email: mobere.rathore@jax.ifl.edu

Both Ceftriaxone and Cefotaxime have been used to treat infections in children since the 1980s. These two antibiotics have been the mainstay for the management of sepsis in children. However, most experts recommend that only cefotaxime should be used in the neonatal age group. This is in large part because of concerns about the risk of hyperbilirubinemia associated with ceftriaxone use in neonates. Despite this concern some centers used ceftriaxone for treatment of neonatal sepsis in those neonates in whom hyperbilirubinemia was not a concern.

With the recent shortage of cefotaxime there has been a renewed interest in the possible ceftriaxone use in the neonates. More recently, an additional serious adverse effect of the use of ceftriaxone with calcium has raised concerns.

In this review, we discuss the potential risks of ceftriaxone use in neonates and offer suggestions when ceftriaxone may be considered for use in neonates, especially when cefotaxime is not available.

Ceftriaxone safety in newborns:

Ceftriaxone is an attractive medication to use in children given its long half-life, excellent CSF penetration, wide spectrum of activity against microorganisms, and good safety profile. Ceftriaxone has been used in the neonates since its approval in 1984, however, the limitation to use was in premature neonates with hyperbilirubinemia.

In neonates, ceftriaxone given at a dose of 50 mg/kg intravenously or intramuscularly reaches a similar maximum plasma concentration level[1]. A loading dose of 100 mg/kg/day and subsequent doses of 80 mg/kg/day to treat meningitis has been suggested by some[2]. However, a dose of 50 mg/kg/day is sufficient to reach bactericidal levels in CSF[2,3]. Almost 60% of

ceftriaxone is eliminated in the urine and the rest in the gastrointestinal tract through the hepatobiliary system. Ceftriaxone clearance increases with the increase of postnatal age and decreases with worsening kidney function.

Cardiorespiratory adverse events:

In 2006 a fatal neonatal case associated with ceftriaxone use was reported to the French regulatory agency. This resulted in ultimately updating the ceftriaxone label in 2007[4]. After the initial French report, an additional nine cases of cardiorespiratory arrest in neonates were also reported to the FDA. These cases were associated with the concurrent use of ceftriaxone with calcium containing fluids. Bradly et al [4] reviewed eight of these nine cases. Seven of the eight infants died. A dose of 200 mg/kg either once daily or divided every 12 hours was used in two neonates. This dose was much higher than the recommended dose of ceftriaxone. In addition, ceftriaxone was administered as a fast push over 2-4 minutes instead of the recommended 30 minutes infusion in two other cases. In four neonates who had autopsies done, arterial crystalline thrombi were found in all of them.

A follow-up study showed that, *in vitro,* the presence of calcium and ceftriaxone together can result in precipitations in both neonatal and adult plasma. For unknown reasons, the affinity of ceftriaxone to make insoluble calcium ceftriaxone salts was significantly higher in neonates. This study added to the concerns about ceftriaxone use in neonates [5].

Indirect hyperbilirubinemia:

Hyperbilirubinemia associated with ceftriaxone use has been a concern since the approval of this drug. The major risk of hyperbilirubinemia is kernicterus. Kapitulnik at el found that the

bilirubin-binding affinity to albumin in full term infants increases as early as the third day of life and gradually reaches the adult level by 5 months of ages[6,7]. However, a prolonged bilirubin binding defect in sick premature infants is seen[8]. That could be explained by a significant albumin decrease in sick infants after birth[9]. Consequently, the effect of ceftriaxone-albumin affinity would be less hazardous if the drug is used after 5 days of age in full term babies since their bilirubin binding capacity recovers as early as 5 days of life[9]. Ceftriaxone competes with bilirubin on the albumin binding sites. *In vitro,* ceftriaxone at a dose of 50 mg/kg over 30 minutes has a maximal displacement factor (MDF) of 2. The MDF defines a numeric estimate of the effect of the drug in displacing bilirubin from albumin binding sites and MDF of $\geq$1.2 is considered a potential risk for all jaundice infants[9,10]. In neonatal studies, the MDF dropped with a prolonged infusion of ceftriaxone over a 60-minute period[11].

Biliary Sludge:

Ceftriaxone calcium salt was identified as a major component of the biliary sludge associated with ceftriaxone use [12]. Transient and asymptomatic pseudolithiasis with ceftriaxone use has been seen in infants up to 24 months of age [13,14]. Biliary sludge has been reported more frequently in children older than 24 months of age in whom ceftriaxone was dosed more than 2 grams. Other risk factors of biliary sludge with ceftriaxone use include, a course longer than 4 days, decreased biliary flow and increased ceftriaxone excretion though the biliary tract[15]. A recent study has suggested that a possible genetic predisposition to developing pseudolithiasis[16]. It appears that infants as opposed to older children tend to develop pseudolithiasis after 2-4 days of use [14,17]. Like older children, neonates rarely have clinical or laboratory evidence of cholelithiasis.

Nephrolithiasis:

The association between ceftriaxone use and obstructive kidney stones was first reported in 1988[18]. Similar to biliary pseudolithiasis, small, asymptomatic and transit urinary stones can be formed in the first 10 days of treatment[19,20]. There are conflicting reports about hypercalciuria associated with ceftriaxone use [19,20 21,22] . The incidence of ceftriaxone induced nephrolithiasis in children is reported to be 1.4% and is less than biliary pseudolithiasis[19]. Risk factors that can result in large obstructing stones include dehydration, fluid restriction and nephrotoxic medication[20,23]. To the best of our knowledge there are no reports of nephrolithiasis in the neonatal period.

Allergic reactions:

Anaphylactic reactions with cephalosporin use are rare with frequency of 0.0001 to 0.1%[24]. There are two reports of anaphylactic reactions in neonates with ceftriaxone use. A 3-day old newborn experienced classical symptom including skin manifestations with the very first dose of ceftriaxone. A repeated dose in controlled environment revealed the same presentation which was immediately reversed with epinephren[25]. The second case is of a 10-day old male who had a sudden cardiorespiratory collapse immediately after the fifth dose of ceftriaxone[26]. Anaphylactic reactions with ceftriaxone use have also been reported in older children[27].

Type 3 immune complex hypersensitivity linked to ceftriaxone has also been reported in the pediatric population. A total of 23 cases of acute intravascular hemolytic anemia have been reported in children ≥ 2 years old[28]. Almost all the cases had either a hematological disorder or

chronic or recurrent infections. To our knowledge there are no similar adverse events reported in neonates.

Other adverse events:

Ceftriaxone induced hepatitis is observed rarely. Two cases in adolescents have been reported in the literature. Elevated hepatic enzymes with direct hyperbilirubinemia has also been seen. Hepatitis was the result of either a delayed ceftriaxone hypersensitivity[29] or a severe immune complex hypersensitivity reaction with acute hemolytic disease[30]. Other possible causes of ceftriaxone induced hepatitis could be cholestatic reaction, direct toxicity or idiosyncratic drug injury[29]. Ceftriaxone induced reversible pancreatitis has been reported in a two-year-old child[31].

Conclusion:

Although ceftriaxone has not commonly been used in neonates, the recent shortage of cefotaxime has allowed an opportunity to re-evaluate this practice. There may be a place for use of ceftriaxone as an alternative in a selected group of neonates who are not premature and do not have hyperbilirubinemia or a risk for developing hyperbilirubinemia. In addition, ceftriaxone should not be used in neonates receiving calcium containing fluids. Ceftriaxone use should be considered in term, previously healthy neonates as a definitive antimicrobial therapy for neonatal sepsis if cefotaxime is not available.

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