Pediatric Pharmacotherapy

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Ceftriaxone Use in Pediatrics

Ceftriaxone, a parenteral third generation cephalosporin, was introduced in the United States in 1984. Since that time, it has gained considerable popularity with clinicians providing pediatric health care. With its favorable spectrum of activity, long half-life, ease of administration, and relatively few adverse effects, ceftriaxone has become a frequent choice for empiric antimicrobial therapy in hospitals, emergency departments, and in ambulatory care settings.[1]

Spectrum of Activity

Ceftriaxone has bactericidal activity against many common pediatric pathogens, including: Acinetobacter and Enterobacter species, *Haemophilus influenzae* (including beta-lactamase producing strains), *Klebsiella pneumoniae*, Morganella, Neisseria and Proteus species, and *Serratia marcescens*. It possesses activity against most strains of *Staphylococcus aureus* and *Streptococcus pneumoniae*, but *Staphylococcus epidermidis*, methicillin-resistant strains of staphylococcus, and *Enterococcus faecalis* (Group D streptococci) are typically resistant. Ceftriaxone has poor activity against anaerobes.[2,3]

Indications

Ceftriaxone is indicated for the prevention or treatment of a variety of infections, including meningitis and bacterial sepsis, lower respiratory tract infections, skin, bone, and soft tissue infections, urinary tract infections, intra-abdominal infections, gonorrhea, and pelvic inflammatory disease. It is also indicated for surgical prophylaxis, except for surgeries involving the central nervous system.[3]

Clinical Trials in Pediatric Patients

In children, many clinical trials have been conducted which support the efficacy and safety of ceftriaxone use. While earlier trials focused on its use in the inpatient treatment of meningitis[4,5], more recent studies have documented its role in a number of different patient populations.

Several publications have explored the use of intramuscular ceftriaxone in the ambulatory and emergency room settings.[6-8] For example, Mustafa and colleagues[6] conducted a pilot study of the outpatient use of ceftriaxone for the management of febrile, neutropenic cancer patients. In their preliminary report of 19 children, only one child required hospitalization for a full course of intravenous antibiotics. In studies such as these, ceftriaxone use has been shown to both reduce hospitalization rates and decrease the overall cost of patient care.

Perhaps one of the most controversial uses of ceftriaxone has been in the treatment of otitis media. The rationale for this use is based on the convenience and lack of compliance concerns with a single injection versus a standard five to ten day treatment course with an oral antibiotic. In 1993, Green and Rothrock[9] compared ceftriaxone to a standard regimen of oral amoxicillin in a blinded, randomized study of 233 children. They found no statistically significant differences between the groups in rates of improvement, failure, relapse, or reinfection. A year later, Chamberlain and colleagues[10] produced similar results in an unblinded trial of 54 children comparing single-dose ceftriaxone to a 10 day course of cefaclor.

These papers have generated a great deal of controversy. Although they clearly demonstrate that ceftriaxone is equivalent to amoxicillin in otitis media, there are other factors that must be considered. For example, the costs involved in the acquisition and administration of ceftriaxone must be weighed against its convenience in the out-patient setting. Single-dose therapy is still significantly more expensive than oral antibiotics in most areas. In addition, concern exists with the potential for the development of bacterial resistance with overuse of this agent in children. Issues such as these must be more fully evaluated before clinicians adopt the wide-spread use of ceftriaxone for relatively self-limiting conditions such as otitis media.

Pharmacokinetics

Ceftriaxone is poorly absorbed from the gastrointestinal tract and must be given parenterally. Like other cephalosporins, it is widely distributed throughout the body. It reaches the cerebrospinal fluid in adequate concentrations through inflamed meninges to effectively treat meningitis.[2,3]

Unlike most other cephalosporins, ceftriaxone is highly protein-bound. Controversy remains over the significance of ceftriaxone's displacement of bilirubin from protein binding sites in neonates.[2,3] Although several clinical trials have documented the safety of ceftriaxone in the neonatal population, many clinicians continue to avoid its use in this population, particularly in premature neonates or those with hyperbilirubinemia.

Ceftriaxone is 60 to 70% eliminated as unchanged drug by renal excretion. The remainder is secreted unchanged in the bile. The long elimination half-life of ceftriaxone, approximately 6 to 9 hours in adults and 5 to 18 hours in infants and children, allows for once or twice daily dosing.[3,11,12]

Dosing and Dose Preparation

The recommended dosage of ceftriaxone for the treatment of meningitis in children is 100 mg/kg/day in one daily dose or divided into two doses and given every 12 hours, up to a total daily dose of 2 grams. For other infections, the recommended dosage is 50 to 75 mg/kg/day. The usual dose in adults is 1 to 2 grams given once daily.[2,3]

Ceftriaxone may be administered either intravenously or intramuscularly. For intravenous use, ceftriaxone should be diluted to a concentration of 10 to 40 mcg/ml and infused over 30 minutes. For intramuscular use, the manufacturer recommends that ceftriaxone be diluted to a concentration of 250 mg/ml or 350 mg/ml with sterile water, 5% dextrose solution, normal saline, or 1% lidocaine.[2] The use of lidocaine as a diluent has been shown to reduce the pain associated with injection in children.[13]

In an effort to reduce the volume of fluid injected in children and minimize the number of intramuscular injection sites, Bradley and colleagues[11] have documented the stability of more concentrated ceftriaxone solutions. These authors found that ceftriaxone concentrations of up to 450 mg/ml, prepared with lidocaine, were stable and resulted in an appropriate serum concentrations and clinical response.[14]

Adverse Effects

Ceftriaxone is well tolerated by most patients. As with other cephalosporins, the most common adverse effects associated with ceftriaxone are: hypersensitivity reactions (in approximately 2% of patients), diarrhea (2%), eosinophilia (6%), thrombocytosis (5%), leukopenia (2%), transient elevations of hepatic function tests (4%), and renal dysfunction. This latter effect can range in severity from a transient, asymptomatic increase in blood urea nitrogen (BUN) values in 1 to 2% of patients to rare cases of acute renal failure. The development of severe renal failure may be accompanied by seizures. Although not well documented, the concomitant use of other nephrotoxic agents, such as aminoglycosides, may predispose patients to adverse renal effects.

As with nearly all antibiotics, ceftriaxone use has been associated with the development of pseudomembranous colitis. Symptoms may appear during or after discontinuation of therapy. Mild cases may respond to discontinuing the antibiotic, while more severe cases may result in life-threatening illness requiring full medical support.

In addition to the general adverse effects listed above, the intramuscular administration of ceftriaxone is associated with pain, swelling, and tenderness at the site of injection in approximately 5 to 17% of patients.[1-3]

Some adverse effects, such as biliary sludging and pseudolithiasis, may be more prevalent in younger patients.[15] This reaction is the result of the formation of a ceftriaxone-calcium complex. It is believed to occur in a dose-dependent manner, and may be more common in children who, by weight, receive proportionately higher doses than adults. Biliary sludging may be more likely to occur in fluid-restricted patients or those predisposed to biliary stasis, such as children who have recently received a liver transplant.

Of even greater concern, three recent cases of fatal ceftriaxone-induced hemolysis have been reported in children within the last two years.[16-18] This reaction occurs suddenly, with patients developing symptoms within 10 to 45 minutes after ceftriaxone administration and progressing to cardiopulmonary arrest within a period of a few hours. The patients in all of the cases

reported to date had received ceftriaxone previously without incident.

The mechanism for this reaction appears to be immune-mediated. It is thought to result from the activation of an IgM antibody directed against ceftriaxone. When bound to ceftriaxone, the antibody creates an immune complex which interacts with the erythrocyte membrane, activating complement and causing hemolysis.[15] It has been suggested that since all reports to date have involved immunocompromised patients that this group may be more susceptible, but further investigation in this area is needed.[17]

Cost

One of the primary disadvantages of ceftriaxone use is its cost relative to other antibiotic regimens. Current average wholesale price (AWP) for ceftriaxone is approximately $34.00 for a 1 gram vial. In comparison, the cost for a 1 gram vial of cefotaxime is approximately $11.00 and a 2 gram vial is $21.00.

Several investigators have attempted to compare the cost:benefit ratios of the third generation cephalosporins in order to choose a single agent to be purchased in large quantities.[1] In a study of pediatric patients at Johns Hopkins Hospital, an evaluation comparing ceftriaxone with cefotaxime led to the selection of cefotaxime as the preferred agent.[19] From this change alone, the authors predicted an annual cost savings of more than $18,000.

The results of studies such as these, however, are difficult to apply to other institutions because of differences in hospital drug acquisition costs and estimates of nursing and pharmacy time expended in drug preparation and administration.

In summary, ceftriaxone offers several advantages for pediatric use. It has activity against most common pathogens seen in children, requires only once or twice daily dosing, can be given intravenously or intramuscularly, and has relatively few adverse effects. Routine use of this agent, however, should not be considered without weighing its disadvantages, primarily the cost of therapy and the risk of developing bacterial resistance.

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Pharmacology Literature Review

Acellular Pertussis Vaccines

An evaluation of the frequency of common adverse effects associated with the acellular pertussis vaccines is presented in this review.

Five key adverse effects are used to evaluate trials comparing acellular and whole cell vaccines: fever, moderate or severe fussiness, erythema at the injection site, swelling at the injection site, and pain upon injection. With all of the acellular products studied to date, there have been fewer reports of these five adverse effects than in the groups receiving whole cell vaccine. The differences among the acellular products has not been found to be clinically significant. The author suggests that the occurrence of severe adverse effects may be reduced as well with the use of acellular pertussis vaccines, based on preliminary data from Japan. Pichichero ME. Acellular pertussis vaccines: Towards an improved safety profile. **Drug Safety 1996;15:311-24.**

Bayesian Pharmacokinetics in Children

The Bayesian method, developed by Sheiner and colleagues in the 1970's, provides a means of predicting pharmacokinetic parameters from limited population data. This paper addresses the benefits and potential problems of applying Bayesian techniques in the pediatric population. A discussion of currently available computer programs and their applicability for pediatric patients is also included. de Gatta M, Garcia MJ, Lanao JM et al. Bayesian forecasting in p(a)ediatric populations. **Clin Pharmacokinet 1996;31:325-30.**

Cefepime Review

Cefepime is an extended-spectrum cephalosporin recently added to our formulary. This paper provides a complete review of the antibacterial spectrum, pharmacokinetics, adverse effects, drug interactions, and dosing recommendations for cefepime. Although studied primarily in adults, cefepime doses of 50 mg/kg (to a maximum of 2 grams) given every 8 hours have been found to be effective in infants and children. Wynd MA, Paladino JA. Cefepime: A fourth-generation parenteral cephalosporin. **Ann Pharmacother 1996;30:1414-24.**

Effects of Antineoplastics on Endocrine Function

This review focuses on the data collected regarding outcomes after childhood acute lymphoblastic leukemia (ALL) and Hodgkin's disease. The authors discuss the development of testicular and ovarian dysfunction, thyroid dysfunction, and growth retardation following chemotherapy. While little evidence exists for long-term endocrine dysfunction, the influence of treatment on overall growth is not as clear. In addition to reviewing the available longitudinal studies of current regimens, the authors identify those chemotherapeutic agents and treatments most likely to be associated with adverse outcomes. Wallace WHB, Kelnar CJH. Late effects of antineoplastic therapy in childhood on growth an endocrine function. **Drug Safety 1996;15:325-32.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/24/97:

1. Simvastatin (Zocor®) was added to the formulary. This agent is another HMG-CoA reductase inhibitor used in the management of patients with Type II diabetes mellitus.

2. Dicyclomine (Bentyl®), an antispasmodic for the treatment of irritable bowel syndrome, was also added to the formulary.

3. Olanzapine (Zyprexa®), an antipsychotic, was added to the formulary.

4. Terbinafine (Lamisil®), an antifungal agent available in both topical and oral dosage forms, was added to the formulary for the treatment of fungal infections of the skin or nails.

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