Pediatric Pharmacotherapy

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Cefipime

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Literature Reviews:

Formulary Update

Cephalosporins, either alone or in combination with other agents, remain one of the most common classes of antibiotics used as initial empiric therapy for the treatment of serious infections in the pediatric patient. Cefepime is considered the first "fourth generation" cephalosporin by many clinicians because it is active against a broader spectrum of bacteria than the third-generation cephalosporins.[1-5] It has recently been approved by the Food and Drug Administration (FDA) for use in infants and children > 2 months of age.

Spectrum of Activity

Cefepime, like other new 7-methoxyimino "fourth-generation" cephalosporins, has demon- strated *in vitro* antibacterial activity against most gram-positive and gram-negative bacteria. Gram-positive coverage includes most Streptococci and Staphylococci species including *Staphylococcus aureus* and *Streptococcus pyogenes* and *pneumoniae*. However, it is not active against methicillin-resistant strains of *Staphylococcus aureus*. Cefepime is active against many gram-negative organisms including *E. coli, Haemophilus influenzae*, *Pseudomonas aeruginosa, Moraxella catarrhalis*, *Morganella morganii, Proteus mirabilis*, and strains of Acinetobacter, Citrobacter, Enterobacter, Klebsiella, Providencia, and Serratia.[1,3-8]

Indications

Cefepime has been approved by the FDA for treatment of urinary tract infections including pyelonephritis, uncomplicated skin and soft tissue infections, pneumonia, and as empiric therapy for febrile neutropenic patients. Initially released for adult patients, cefepime recently was approved for use in children between the ages of 2 months and 16 years. Safety and effectiveness in pediatric patients below the age of 2 months have not been established. Product labeling stipulates that there are insufficient clinical data to support the use of cefepime in the treatment of serious infections in the pediatric population where the suspected or proven pathogen is *Haemophilus influenzae* type b. In patients with suspected or documented meningitis, an alternative agent with demonstrated clinical efficacy should be used.

Experience in Children

The clinical efficacy and safety of cefepime and ceftazidime were compared in the treatment of pyelonephritis in 299 children, ages 1 month to 12 years.[9] This was a randomized, open label, multicenter trial conducted in Europe. Cefepime and ceftazidime were administered intravenously (IV) every 8 hours at a dose of 50 mg/kg. Patients received the assigned study drug until at least 48 hours after becoming afebrile. IV therapy could then be continued or replaced by oral trimethoprim/sulfamethoxazole for a maximum of 12 to 14 days.
The predominant causative pathogen was *E. coli* (88%); however, other pathogens included Proteus spp, Klebsiella spp, *Citrobacter diversus*, *P. aeruginosa*, and *S. epidermidis*. Bacteriologic and clinical responses were evaluated in 235 patients (115 in the cefepime group and 120 in the ceftazidime group), while safety was evaluated in all 299 patients. Bacterial eradication rates at the end of IV therapy were comparable in the cefepime and ceftazidime groups (96% and 94%, respectively). Eradication rates were also comparable between the two study drugs at the end of the IV plus oral period, at early follow-up (5 to 9 days after eradication) and at late follow-up (4 to 6 weeks after eradication). New infections occurred in eight cefepime patients (7%) and seven ceftazidime patients (6%). A satisfactory clinical response at the end of the IV

period occurred in 98% and 96% of cefepime and ceftazidime patients, respectively. At the end of treatment, and at the follow-up examinations, there were no significant differences between the two groups.

In a randomized double-blind study cefepime has been compared to ceftazidime as monotherapy for empiric treatment of pediatric cancer patients with febrile neutropenia.[10] The dosing regimen was not specified by the author. Of the 149 enrolled patients, 131 were considered evaluable. The clinical characteristics of the treatment groups were comparable. Two-thirds of the patients in each group had hematological malignancies and one-third had solid tumors. The extent and duration of neutropenia were comparable in both groups.

Documented infections occurred in 27% of cefepime-treated and 31% of ceftazidime-treated patients. Approximately 70% of patients in both groups had fever of unknown origin (FUO). A reduction in fever within 72 hours occurred in 71% of patients in each group. At the end of therapy, cefepime and ceftazidime treated patients demonstrated clinical cure rates of 90% and 93% respectively. Cefepime-treated patients with documented infections demonstrated a 67% response rate compared with 55% for ceftazidime-treated patients at 72 hours (not statistically significant). At the end of therapy, response rates for patients with documented infections were 94% for cefepime-treated and 70% for ceftazidime-treated groups.

In 1995, Saez-Llorens, et al.[11] compared the use of cefepime to cefotaxime for treatment of bacterial meningitis in children. Ninety pediatric patients, ages 2 months to 15 years, were randomized to receive cefepime 50 mg/kg every 8 hours or cefotaxime 50 mg/kg every 6 hours. Clinical response, cerebrospinal fluid sterilization, development of complications, and hospital stay were similar for the two treatment regimens. Concentrations of cefepime in cerebrospinal fluid varied from 55 to 95 times greater than the maximal MIC required by the causative pathogens. The authors concluded that cefepime is safe and therapeutically equivalent to cefotaxime for management of bacterial meningitis in children; however, it should be noted that cefepime DOES NOT have FDA approval for treatment of meningitis.

Pharmacokinetics

The pharmacokinetics of cefepime have been well described in adults with normal and impaired renal function.[1] After intravenous or intramuscular (IM) administration, cefepime is widely distributed throughout the body. It is 16 to 19% protein-bound and is primarily renally eliminated. In adult patients with normal renal function, the elimination half-life of cefepime ranges from 2 to 2.3 hours, and at least 85% of the drug is eliminated as unchanged drug in urine. Approximately 68% of the drug is removed by hemodialysis; a repeat dose, equivalent to the initial dose, should be given at the completion of each dialysis session. In patients undergoing peritoneal dialysis, cefepime may be administered at normally recommended doses given every 48 hours.[3]

In 1997, Reed and colleagues[12] studied the pharmacokinetic characteristics of cefepime after first dose and at steady state in a group of 37 infants and children (2 months to 16 years of age). Pharmacokinetics of a dose administered intramuscularly were also studied in eight of the children. Elimination half-life, steady-state volume of distribution and renal clearance after first dose administration averaged 1.7 hr, 0.35 L/kg, and 1.9 ml/min/kg, respectively. Half-life was slightly longer for patients less than six months of age than for older patients. There were no differences in cefepime disposition characteristics between first dose and steady-state. The half-life of cefepime was slightly longer (1.8 versus 1.9 hour) with IM administration than IV at steady-state, while bioavailability was unchanged.

Dosing

The recommended dosage in pediatric patients up to 40 kg for urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia is 50 mg/kg/dose administered IV or IM every 12 hours for 7 to 10 days. The length of therapy should be determined by indication and severity of infection. The dosage for empiric therapy in febrile neutropenic patients is 50 mg/kg/dose administered every 8 hours. The maximum dose should not exceed the recommended adult dose of 2 grams every 8 hours.[3]
Data in pediatric patients with impaired renal function are not available; however, since cefepime pharmacokinetics are comparable in adult and pediatric patients, changes in dosing regimens similar to those in adults are recommended for pediatric patients. Product labeling states that the dose of cefepime should be adjusted to compensate for the slower rate of renal elimination in patients with a creatinine clearance <60 ml/min. The dose and dosing interval should be adjusted depending of the severity of the renal dysfunction.[13]

Adverse Effects

The most commonly reported adverse effects in pediatric cefepime trials have been local reaction (3%), including phlebitis (1.3%), and rash (1.1%). Other adverse reactions include diarrhea (3%), nausea (2%), vomiting (1%), pruritis (1%), fever (1%), and headache (1%). As with other cephalosporins, transient leukopenia, neutro-penia, agranulocytosis and thrombocytopenia have been reported.[14] Similar results have also been observed in clinical trials of adult patients.
In addition to the events reported in clinical trials, other adverse reactions have been documented during worldwide postmarketing experience. Encephalopathy, myoclonus, and seizures have been reported in renally impaired patients treated with unadjusted dosing regimens of cefepime.[14]
In the comparative study of cefepime and ceftazidime in the treatment of pyelonephritis by Schaad[9] drug-related adverse events occurred in 14 (9%) and

10 (7%) pediatric patients in the cefepime and ceftazidime groups, respectively (p=0.40). Discontinuations due to drug-related adverse events occurred in 4 (3%) cefepime patients (rash in 3 and nervousness in 1) and in 1 ceftazidime patient (rash).

Laboratory changes seen in adult patients receiving cefepime include positive Coombs's test, decreased phosphorus, increased liver function tests, increased BUN, and abnormal PTT/PT.[3] Similar abnormalities may be expected in pediatric patients.

Cefepime is contraindicated in patients who have shown immediate hypersensitivity reactions to other cephalosporins, penicillins or beta-lactam antibiotics. Since cross-hypersensitivity may occur in up to 10% of patients with a history of penicillin allergy, an alternative therapy should be chosen.[3]

Cost of therapy

The average wholesale price of cefepime is $17.06/gram. The total cost of therapy is comparable to that of ceftazidime.

Summary

Cefepime offers unique advantages for antibacterial therapy in children, with its broad spectrum and ability to eradicate gram-negative bacteria that are resistant to other cephalosporins. Furthermore, it is more active against gram-positive bacteria such as the Staphylococci and Streptococci species. Cefepime is a useful alternative to ceftazidime or other broad spectrum antibiotics in children older than two months of age.

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Literature Review

Antiarrhythmics during Pregnancy

This brief article provides a current review on the treatment options for arrhythmias occurring during pregnancy, focusing on their safety. In addition to reviewing agents by therapeutic class, the authors also discuss the physiologic changes which occur during gestation and the effect of these changes on drug disposition. Joglar JA, Page RL. Treatment of cardiac arrhythmias during pregnancy: safety considerations. **Drug Safety 1999;20:85-94.**

Ibuprofen in Cystic Fibrosis

Ibuprofen has been studied for several years as an inhibitor of inflammatory mediators in patients with cystic fibrosis (CF). To date, there have been only small-scale studies of drug disposition in patients with CF. The authors of this paper attempt to define the pharmacokinetics of ibuprofen in a larger group. The authors studied 98 patients with CF ranging from 1 to 45 years of age (mean age 12.5 yrs). Patients received high dose therapy (20-30 mg/kg/day), as recommended by the United States Cystic Fibrosis Foundation. Peak serum concentrations ranged from 21 to 150 mcg/ml. Clearance correlated with both age and body surface area. When patients were normalized for body surface

area, the effect of age was eliminated. Volume of distribution also correlated with age and body surface area. The authors conclude that ibuprofen pharmacokinetics are highly variable among the CF population. They suggest that individualized dosage regimens, based on therapeutic drug monitoring, may be necessary to achieve adequate concentrations. Murry DJ, Oermann CM, Ou C, et al. Pharmacokinetics of ibuprofen in patients with cystic fibrosis. **Pharmacotherapy 1999;19:340-5.**

MDIs and Adapters in Ventilator Circuits

These two articles describe differing methods of administering albuterol in a ventilated lung model. In the first paper, Avent and colleagues compare the use of a standard inline adapter (Medicomp Straight Swivel) with that of a spacer (Aerochamber) to "fit" a metered-dose inhaler (MDI) to the circuit. In this model, the spacer device delivered significantly more drug to the model lung than the traditional adapter. In the second paper, the same group of investigators compares nebulized versus MDI-administered drug in the same model. In both beclomethasone and albuterol trials, the MDI with the Aerochamber resulted in greater drug delivery. This study, as well as several others previously published, calls into question the utility of nebulized therapy when MDIs may provide a simpler means of drug delivery. Avent ML, Gal P, Ransom JL, et al. Comparing the delivery of albuterol metered-dose inhaler via an adapter and spacer device in an in vitro ventilator lung model. **Ann Pharmacother 1999;33:141-3** and Avent ML, Gal P, Ransom JL, et al. Evaluating the delivery of nebulized and metered-dose inhalers in an in vitro infant ventilator lung model. **Ann Pharmacother 1999;33:144-8.**

Top 200 Brand Products

Every year, lists of the most frequently prescribed medications are published to identify those agents in greatest demand. The top 10 brand products are listed below.

1. Premarin®(conjugated estrogens)
2. Synthroid®(levothyroxine)
3. Prilosec®(omeprazole)
4. Prozac®(fluoxetine)
5. Lipitor®(atorvastatin)
6. Norvasc®(amlodipine)
7. Claritin®(loratadine)
8. Lanoxin®(digoxin)
9. Zoloft®(sertraline)
10. Paxil®(paroxetine)

Anon. List of top 200 drugs includes a few surprises. **Drug Topics 1999;143(5):30,33.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 4/23/99:

1. Abacavir (Ziagen®), an antiretroviral, was added to the formulary.
2. Levofloxacin (Levaquin®), a fluoroquinolone, was added to the formulary.
3. Lyme disease vaccine (LYMErix®) was approved for use in adults, ages 15 to 70 years.
4. Recombinant factor IX (BeneFIX®) was added, restricted to Hematology.
5. Thyrotropin alfa (Thyrogen®) was also added.
6. Zalcitabine (ddC, Hivid®) was removed from the formulary because of lack of use.

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