



## Cefdinir Use in Children

Marcia L. Buck, Pharm.D., FCCP, FPPAG

Cefdinir, a third-generation extended spectrum oral cephalosporin, was approved by the Food and Drug Administration (FDA) on December 4, 1997. Since that time, it has become one of the most widely prescribed antibiotics for the treatment of pediatric infections.<sup>1</sup> The American Academy of Pediatrics 2013 clinical practice guideline on the diagnosis and management of acute otitis media lists cefdinir as an alternative to amoxicillin as first-line therapy in children with penicillin allergy.<sup>2</sup> In addition to acute otitis media, cefdinir is currently approved by the FDA for the treatment of pharyngitis or tonsillitis in children and adults, as well as uncomplicated skin and skin structure infections.<sup>3</sup> It is also approved for use in community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute maxillary sinusitis in adolescents and adults.

### Mechanism and Spectrum of Activity

Cefdinir is a semisynthetic cephalosporin with activity against a number of both Gram positive and Gram negative aerobic bacteria.<sup>1,3,4</sup> Like other cephalosporins, it inhibits the synthesis of the peptidoglycan layer of bacterial cell walls, altering their structural integrity. Cefdinir has the additional benefit of being stable in the presence of several common beta-lactamases. There are both *in vitro* and clinical data to demonstrate the activity of cefdinir against the following bacteria:

#### **Gram positive organisms**

*Staphylococcus aureus* (methicillin-susceptible)  
*Streptococcus pneumoniae* (penicillin-susceptible)  
*Strep. pyogenes*

#### **Gram negative organisms**

*Haemophilus influenzae*  
*H. parainfluenzae*  
*Moraxella catarrhalis*

Cefdinir has been shown to have *in vitro* activity against the following bacteria, but clinical efficacy in eradicating infections with these organisms has not been established:

#### **Gram positive organisms**

*Staph. epidermidis* (methicillin-susceptible)  
*Strep. agalactiae*  
Viridans group streptococci

#### **Gram negative organisms**

*Citrobacter diversus*  
*Escherichia coli*  
*Klebsiella pneumoniae*  
*Proteus mirabilis*

Cefdinir is inactive against *Enterococcus* and methicillin-resistant *Staph.* species, as well as *Pseudomonas* and *Enterobacter* species.

### Pharmacokinetics

The pharmacokinetic profile of cefdinir in children is similar to that of adults.<sup>1,3,4</sup> Maximum plasma concentrations occur 2 to 4 hours after an oral dose of cefdinir. Children given a 7 mg/kg dose of cefdinir achieved a mean maximum concentration ( $C_{max}$ ) of  $2.3 \pm 0.65$  mcg/mL, slightly higher than the  $C_{max}$  of  $1.6 \pm 0.55$  mcg/mL achieved in adults given a single 300 mg dose. The bioavailability of cefdinir ranges from 16% to 21% for the capsules and 25% for the oral suspension. In adults, administration of cefdinir capsules with a high-fat meal reduces  $C_{max}$  by 16% and area under the concentration time curve (AUC) by 10%. The effect of a high-fat meal is more pronounced with administration of the oral suspension, with reductions in  $C_{max}$  and AUC of 44% and 33%, respectively. These reductions are not believed to be clinically significant.

Cefdinir is 60% to 70% bound to plasma proteins. It is widely distributed, with a mean

volume of distribution of  $0.35 \pm 0.29$  L/kg in adults and  $0.67 \pm 0.38$  L/kg in children 6 months to 12 years of age. In studies conducted in adults, concentrations of cefdinir in tonsil tissue were 24% of simultaneously sampled plasma concentrations, while sinus tissue concentrations were 16% and lung tissue concentrations were 35% of plasma concentrations. In studies of children with acute otitis media, cefdinir concentrations in middle ear fluid were 15% of corresponding plasma concentrations.

Cefdinir is eliminated primarily through renal excretion; it undergoes minimal metabolism. The mean plasma elimination half-life in healthy adults is  $1.7 \pm 0.6$  hours, with a renal clearance of  $2 \pm 1$  mL/min/kg. In a single-dose pharmacokinetic study conducted in children 6 months to 12 years of age, the half-life of cefdinir was  $2.2 \pm 0.6$  hrs after a 7 mg/kg dose and  $1.8 \pm 0.4$  hrs after a 14 mg/kg dose. Renal dysfunction reduces the clearance of cefdinir and results in the need to reduce dosing frequency. Approximately 6% of a cefdinir dose is removed by hemodialysis. No dosage adjustment is needed in patients with hepatic impairment.

#### Clinical Experience

Early studies with cefdinir in children demonstrated clinical cure rates equivalent to those produced with penicillin, amoxicillin, or azithromycin. In one of the earliest pediatric studies, Tack and colleagues randomized 224 children between 1 and 12 years of age to receive either 7 mg/kg cefdinir twice daily for 5 days or 10 mg/kg penicillin V four times daily for 10 days for the treatment of pharyngitis caused by *Streptococcus pyogenes*.<sup>5</sup> Bacterial eradication was demonstrated in 90% of the cefdinir group and 72% of the penicillin V group ( $p < 0.001$ ). Clinical cure rates were no different, 92% with cefdinir and 91% with penicillin V. Adverse events, primarily diarrhea, occurred in 12.5% and 13.6% in the two groups.

In 2005, Block and colleagues compared cefdinir and azithromycin when given as a 5-day course in children with acute otitis media.<sup>6</sup> A total of 357 children between 6 months and 6 years were randomized to either 7 mg/kg cefdinir given twice daily or azithromycin 10 mg/kg on the first day followed by 5 mg/kg daily thereafter. Clinical cure rates were not significantly different between the groups: 87% with cefdinir and 85% with azithromycin, respectively. Parental satisfaction scores and the frequency of adverse effects were similar in the two groups.

Block and colleagues also compared cefdinir and high-dose amoxicillin/clavulanate in children

with acute otitis media.<sup>7</sup> A total of 318 children 6 months to 6 years of age were randomized in this investigator-blinded comparison study. Patients received either cefdinir 7 mg/kg or amoxicillin/clavulanate 45 mg/kg twice daily for 10 days. At follow-up, intent-to-treat clinical cure rates were 82% for the cefdinir and 85% for amoxicillin/clavulanate ( $p = 0.547$ ). Per protocol cure rates were 82% and 90%, respectively ( $p = 0.045$ ). The authors noted that lower response rates were found in children with recurrent otitis media and in children younger than 24 months of age. Parents rated cefdinir more positively based on ease of use and better taste. Diarrhea was more common in the amoxicillin/clavulanate group (28% versus 18%,  $p = 0.0341$ ).

In 2012, these investigators published a subsequent study in 330 children 6 to 24 months of age with acute otitis media.<sup>8</sup> Patients were randomized to receive cefdinir 7 mg/kg twice daily for 5 days or amoxicillin/clavulanate 45 mg/kg twice daily for 10 days. Clinical cure rates were 71.0% for cefdinir and 86.5% for amoxicillin/clavulanate ( $p = 0.001$ ). In addition to finding 10 days of high-dose amoxicillin/clavulanate more effective than 5 days of cefdinir in this age group, the authors found a negative correlation between clinical cure rates and patient age.

While not an approved indication, cefdinir has been used as prophylaxis in pediatric patients with recurrent urinary tract infections. In a study of 14 infants with vesico-urethral reflux or ureteropelvic junction stenosis given a dose of 3 mg/kg cefdinir daily, the six-month recurrence-free rate was 93%.<sup>9</sup> All of the patients tolerated the therapy without adverse effects. There were no reports of bacterial resistance or fungal infections during treatment. Because of the potential for development of resistance, use of cefdinir in this setting should only be considered in infants or children with recurrent infections that fail to respond to traditional narrow spectrum.

#### Contraindications and Warnings

Cefdinir is contraindicated in patients with a history of a serious hypersensitivity reaction to a cephalosporin.<sup>3</sup> Although the incidence of cross-sensitivity is low, caution should be used if cefdinir is to be given to patients with a history of hypersensitivity to any beta-lactam antibiotic. As with other extended-spectrum antibiotics, the use of cefdinir may promote alterations in normal gastrointestinal bacterial flora, resulting in overgrowth of *Clostridium difficile* and the development of *C. difficile* associated diarrhea (CDAD). While several cases of cefdinir-

associated CDAD have been reported, the frequency of this adverse effect has not been determined.

#### Adverse Effects

The most frequently reported adverse effects in premarketing clinical trials of cefdinir in adolescents and adults included diarrhea (in 15% of patients), vaginal moniliasis (4% of women), nausea (3%), headache (2%), abdominal pain (1%), rash (0.9%), and stomach upset or vomiting (0.7%).<sup>1,3</sup> Overall, 3% of patients discontinued treatment as the result of an adverse effect, most often diarrhea or nausea. Similar adverse effects were reported in pediatric trials, with diarrhea (8%), rash (3%), vomiting (1%), oral thrush (0.9%), abdominal pain (0.8%), vaginitis or vaginal moniliasis (0.3% of girls) or leukopenia (0.3%). Two percent of children discontinued treatment because of an adverse effect, typically diarrhea.

Post-marketing experience has included cases of severe hypersensitivity reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome. Coagulation disorders ranging from thrombocytopenia to idiopathic thrombocytopenic purpura, gastrointestinal bleeding, and disseminated intravascular coagulation have been reported after cefdinir use, but causality has not been definitively established. Cefdinir-induced nephrotoxicity and hepatotoxicity have also been reported.<sup>3,10</sup>

#### Drug Interactions

Cefdinir should not be taken within 2 hours of an antacid containing magnesium or aluminum. Concomitant use may shorten the time to maximum plasma concentration by an hour and reduce AUC by as much as 40%. Administration with oral iron supplements may reduce the extent of cefdinir absorption by 30% to 80%. Giving cefdinir with iron-fortified infant formulas does not produce a significant effect on its absorption.<sup>3</sup> Patients and families should be made aware that non-bloody red stools may occur in patients taking cefdinir with iron supplements or iron-fortified formula.<sup>11,12</sup> The discoloration is the result of cefdinir binding to ferric ions to form a non-absorbable red-colored complex. The discoloration is harmless, but can easily be mistaken for blood. Parents should stop treatment and contact their healthcare provider immediately if the discoloration of the stool is accompanied by signs of abdominal pain, diarrhea, or fever.

Studies of the administration of probenecid with cefdinir have demonstrated a 54% increase in maximum cefdinir concentrations and a 50%

prolongation in elimination half-life.<sup>3</sup> Administration of probenecid during treatment with cefdinir is not recommended.

#### Availability

Cefdinir is available as a generic drug from multiple manufacturers in the United States. It is produced as 300 mg and 600 mg capsules and as a 125 mg/5 mL or 250 mg/5 mL oral suspension.<sup>3</sup> The suspension formulation is manufactured as a powder to be reconstituted with water prior to dispensing. The resulting suspension may be stored at room temperature but must be discarded 10 days after being reconstituted. The original brand name product, Omnicef®, is no longer on the market.

The poor bioavailability of cefdinir oral suspension has led to interest in the creation of a new formulation. Several methods of increasing absorption and reducing dose-to-dose variability have been studied, including the creation of a cyclodextrin-cefdinir complex, microencapsulation, and formation of nonionic surfactant based vesicles (niosomes).<sup>13-15</sup> Veerareddy and colleagues have created cefdinir microcapsules with a mucoadhesive polymer that extends drug release over 12 hours by allowing the drug to remain longer in the upper gastrointestinal tract.<sup>14</sup>

In a recent paper published in the *Journal of Pharmacy and Bioallied Sciences*, Bansal and colleagues described the effectiveness of their cefdinir noisome formulations to provide sustained drug release.<sup>15</sup> In a study using goat intestinal membrane, the authors demonstrated 94% permeation across the membrane over 12 hours. These early studies suggest that it is possible to improve upon current products and create a delivery system that provides greater drug absorption over a longer period of time.

#### Dosing Recommendations

The recommended dose for cefdinir in children 6 months to 12 years of age is 7 mg/kg twice daily or 14 mg/kg once daily for 10 days.<sup>1,3</sup> The 7 mg/kg twice daily regimen may be given for a shorter 5-day period in patients with acute bacterial otitis media or pharyngitis/tonsillitis. In adolescents and adults, the recommended dose is 300 mg twice daily for 10 days for community-acquired pneumonia or uncomplicated skin and skin structure infections. For acute maxillary sinusitis, a dose of either 300 mg twice daily or 600 mg once daily may be given for 10 days. In patients with pharyngitis/tonsillitis or acute exacerbations of chronic bronchitis, the 300 mg twice daily regimen may be given for 5-10 days or the 600 mg once daily regimen for 10 days.

Cefdinir doses should be adjusted in patients with an estimated creatinine clearance less than 30 mL/min/1.73m<sup>2</sup> to compensate for the prolonged elimination half-life seen with renal dysfunction. In these patients, the recommended twice daily dose (7 mg/kg for children and 300 mg in adults) should be given just once daily.<sup>3</sup>

### Summary

Cefdinir produces clinical cure rates in most settings of 80% or greater, with once or twice daily dosing and a relatively mild adverse effect profile, making it an effective choice for the treatment of pharyngitis and tonsillitis, acute otitis media, and most uncomplicated skin and skin structure infections in children. Its broad spectrum of activity, however, poses the risk for worsening bacterial resistance and the development of CDAD. As noted in the recent AAP clinical practice guideline on otitis media, the optimal role for cefdinir is likely to be in the treatment of infections due to organisms resistant to amoxicillin/clavulanate or in children unable to take penicillin or amoxicillin.

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### Formulary Update

There was no August Pharmacy and Therapeutics Committee meeting. The next meeting will be held in September.

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