

Summary: Role of a new oral cephalosporin, cefdinir, for therapy of infections of infants and children

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Cefdinir (Omnicef) is a new oral cephalosporin with a broad spectrum of antimicrobial activity, a pleasant taste, a convenient dosage schedule and a favorable adverse event profile. Cefdinir has been available since 1991 in Japan where it is the most frequently used oral cephalosporin. There are 17 antimicrobial agents currently approved for the indication of acute otitis media, and most are also approved for treatment of group A streptococcal pharyngitis and skin infections. How do we assess a new antimicrobial agent when we have so many other drugs that are already available for the same indications? In this supplement the available data about cefdinir, including *in vitro* activity, pharmacokinetics, safety, palatability and efficacy for acute otitis media and streptococcal pharyngitis are presented. In this report we have summarized those results and presented our conclusions about the role of cefdinir for therapy of infections in infants and children.

IN VITRO ACTIVITY

Guay¹ has provided a comparison of the *in vitro* activity of cefdinir and selected other oral cephalosporins. In comparison with cephalexin, cefaclor, cefixime, cefpodoxime, cefuroxime and ceftibuten, cefdinir had minimum inhibitory concentrations that were comparable or superior to those of the other drugs for group A, B, C, F and G streptococci, viridans streptococci and *Staphylococcus aureus* and *epidermidis*. The *in vitro* activity of cefdinir for *Streptococcus pneumoniae* (including penicillin-susceptible, -intermediate and -resistant strains) was comparable to cefuroxime and cefpodoxime and superior to the other tested cephalosporins. Cefixime and ceftibuten had superior activity against *Haemophilus influenzae*; the activity of cefdinir, cefpodoxime and cefuroxime were comparable and superior

to the activity of cephalexin and cefaclor. None of the cephalosporins was effective *in vitro* against enterococci and *Listeria monocytogenes*.

PHARMACOKINETICS AND PHARMACODYNAMICS

Cefdinir reaches peak concentrations in children of approximately 2 to 3 $\mu\text{g/ml}$ after a 7-mg/kg dose and 3 to 4 $\mu\text{g/ml}$ after a 14-mg/kg dose. The peak concentration after an oral dose is reached at about 2 h, and the half-life ranges between 1.3 and 1.6 h. The drug is primarily excreted unchanged by the kidneys. Few studies are available about diffusion into tissue and body fluids, but one study identified middle ear concentrations that were approximately 15% of corresponding plasma concentrations after single doses of 7 or 14 mg/kg.² The pharmacokinetic/pharmacodynamic breakpoint is considered to be 0.5 $\mu\text{g/ml}$ (M. Jacobs, MD, PhD, personal communication). Based on achievable middle ear concentrations, cefdinir should be effective against all *H. influenzae*, *Moraxella catarrhalis* and penicillin-susceptible *S. pneumoniae* strains and against some penicillin-intermediate resistant pneumococci, a pharmacodynamic profile similar to that of cefuroxime.

TASTE AND PALATABILITY

Powers et al.³ reported on the palatability of cefdinir, amoxicillin/clavulanate, cefprozil and azithromycin in child volunteers ages 4 to 8 years. The children responded to questions of taste and smell using the smile-face scale: cefdinir was superior to amoxicillin/clavulanate for taste and smell; cefdinir was superior to cefprozil for taste and comparable for smell; and cefdinir was superior to azithromycin for taste and smell in the single center study but not in the multicenter program. In general the strawberry milk shake flavor of cefdinir was well-accepted for taste and smell by the participating children.

ACUTE OTITIS MEDIA

There were four studies of cefdinir therapy for acute otitis media presented in this supplement.

The first by Block et al.⁴ compared 5 days of cefdinir (14 mg/kg/day in 2 divided doses) with 10 days of

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cefprozil (30 mg/kg/day in 2 divided doses) treatment in a comparative, investigator-blinded, multicenter study. There were 373 evaluable patients. Clinical cure on Days 9 to 11 was documented in 80 and 82.5% of infants and children who received cefdinir and cefprozil, respectively. Adverse events were similar in the two groups.

The second study was open label in design, and tympanocentesis was performed at diagnosis in 177 patients.⁵ Pathogens were recovered from culture of middle ear fluid in 125 patients. Clinical cure at 2 to 4 days after 5 days of cefdinir (14 mg/kg/day in 2 divided doses) treatment was observed in 84 of 115 (73%) patients with bacteriologically proved disease and in 130 of 168 (77.4%) patients in the overall evaluation. Based on clinical evaluation at the end of therapy, presumed bacteriologic eradication (a second tympanocentesis was not performed) occurred in two-thirds of those with pneumococcal otitis, including 4 of 8 patients with resistant isolates and in 73% of patients with *H. influenzae* otitis media.

In the third study 384 patients received one of three antimicrobial regimens administered for 10 days: Cefdinir 14 mg/kg daily, cefdinir 14 mg/kg/day in 2 divided doses or amoxicillin/clavulanate 40/10 mg/kg/day in 3 divided doses.⁶ Tympanocentesis was performed at the time of diagnosis. Clinical success (cure plus improvement) at 2 to 4 days after completion of therapy was similar (60 to 80%) for the three treatment groups. Presumed eradication of *H. influenzae*, based on clinical outcome, occurred in 64 to 68% of children receiving one of the cefdinir regimens and in 80% of those given amoxicillin/clavulanate. For *S. pneumoniae* infection, presumed eradication occurred in 73% of those given either cefdinir once daily or amoxicillin/clavulanate, but in only 45% of patients who received the twice daily regimen of cefdinir. The reason for this latter observation is unclear.

In the last study performed by Adler et al.⁷ 595 evaluable patients were randomized to one of three regimens: cefdinir 14 mg/kg daily; cefdinir 14 mg/kg/day in 2 divided doses; or amoxicillin/clavulanate 40/10 mg/kg/day in 3 divided doses, all for 10 days. The clinical response rates (cure plus improvement) at 11 to 16 days (89 to 91%) and at 27 to 42 days (91 to 97%) were comparable for children in each of the 3 treatment groups. Adverse events required discontinuation of treatment in 4% of the children in the cefdinir once daily group, 6% in the children in the twice daily cefdinir group and 10% of the children in the amoxicillin/clavulanate group.

STREPTOCOCCAL PHARYNGITIS

Pichichero and Gooch⁸ reviewed the experience with cefdinir therapy for streptococcal pharyngitis based on the results from two previously published studies. The

patients received either the once or twice daily regimen of cefdinir, 14 mg/kg/day, and results were compared with those who received penicillin V, 10 mg/kg 4 times daily. Clinical cure and microbiologic eradication after cefdinir therapy in either dosage schedule for 5 or 10 days were superior to those for penicillin given for 10 days. Adverse events were similar in the treatment groups.

SUMMARY AND CONCLUSIONS

Cefdinir has a favorable spectrum of *in vitro* activity, superior taste and smell for children, administrative advantages in a once or twice daily schedule, an acceptably low rate of adverse events and proven efficacy for treatment of acute otitis media and streptococcal pharyngitis in infants and children.

Where does cefdinir fit in our large armamentarium of effective oral agents for the common infectious diseases of infants and children?

Acute otitis media. Amoxicillin remains the drug of choice for treatment of acute otitis media. In considering regimens for children who failed amoxicillin therapy for acute otitis media, a consensus panel convened by the Centers for Disease Control and Prevention⁹ recommended amoxicillin/clavulanate (high dose), cefuroxime axetil or a three dose regimen of intramuscular ceftriaxone. On the basis of available data from double tympanocentesis studies these three agents are appropriate for children who fail initial amoxicillin therapy. The choice of cefuroxime axetil as the favored oral cephalosporin was based on the excellent *in vitro* profile against likely bacterial pathogens but failed to consider the bitter taste that can diminish compliance in some patients. Cefpodoxime proxetil, an ester compound like cefuroxime axetil, has a similar favorable *in vitro* profile but is similar to cefuroxime axetil in failing taste and smell tests.¹⁰ The problem of palatability is a concern in achieving adequate compliance in pediatric patients for these two products. Cefdinir has an *in vitro* spectrum of activity that is similar to those of cefuroxime and cefpodoxime, but cefdinir has the major advantage of favorable taste and smell. To enhance patient compliance we conclude that cefdinir should be considered the oral cephalosporin of choice for children who fail initial amoxicillin therapy.

Streptococcal pharyngitis. Cefdinir in a 5- and 10-day dosage schedule was effective in infants and children with rates of clinical cure and microbiologic eradication in excess of 90%. Penicillin V in a 10-day dosage schedule had lower rates of microbiologic eradication and in one of two studies lower rates of clinical cure. Although the debate continues about the importance of the superior microbiologic eradication rates achieved by cephalosporins, macrolides and clindamycin in patients with streptococcal pharyngitis, it is appropriate to consider the value of eradicating the

organism in geographic areas where suppurative and nonsuppurative complications have been identified. The 5-day regimen of cefdinir should be attractive for increasing compliance and providing optimal clinical and microbiologic efficacy for infants and children with streptococcal pharyngitis.

In summary cefdinir has a favorable *in vitro* spectrum of activity, excellent taste (strawberry milk shake), favorable pharmacokinetics and proven efficacy for acute otitis media and streptococcal pharyngitis (in a 5-day dosage schedule). Although the clinical trials suggest equivalence to currently available regimens in most instances, the administrative advantages of once or twice daily dosage schedule and excellent taste should make cefdinir an attractive antimicrobial agent for treatment of these common infections of infants and young children.

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