

CLINICAL CAPSULES

HAART Stabilizes CD4+ Counts

The CD4+ T-cell counts of 31 children aged 2.4 months-16.4 years with HIV-1 remained stable throughout 4 years of highly active antiretroviral therapy (HAART), reported Pieter L.A. Fraaij, M.D., of Erasmus Medical Center-Sophia Children's Hospital, in Rotterdam, the Netherlands, and his colleagues. At baseline, 28 children started HAART that included indinavir and 3 started HAART that included nelfinavir (Clin. Infect. Dis. 2005;40:604-8). In the intent-to-treat analysis, 65% had HIV-1 levels less than 500 copies/mL and 61% had less than 50

copies/mL after 4 years of treatment. Overall, 28 children changed therapies 38 times during the study period, for reasons including 20 cases of treatment failure, 7 cases of drug toxicity, 7 cases of simplification of the drug regimen, 3 cases of refusal or intolerance of medication, and failure to reach appropriate results in 1 case. HAART was changed at least once in 13 children (41%) due to viral failure. Clinical adverse events occurred in 24 children (77%), but they were mostly mild gastrointestinal problems. Seven children changed medications due to toxicity associated with indi-

navir. Six were lost to follow-up, and one child died of serious invasive opportunistic infections 1 year into the therapy.

Varicella Vaccination Cuts Mortality

Mortality due to varicella fell from an average of 0.32 deaths per million between 1990 and 1994 to an average of 0.07 deaths per million between 1999 and 2001 among children aged 1-4 years due to the adoption of universal childhood varicella vaccination in the United States, with the lowest rates for all groups in 2001, said Huong Q. Nguyen and colleagues at the Centers for Disease Control and Prevention (N. Engl. J. Med. 2005;352:450-8). In addition, deaths

due to varicella fell significantly among children aged 10-19 years (67%); and among infants (66%) between the two periods. The decline in mortality was 100% among children aged 1-4 years and aged 5-9 years for children at high risk due to preexisting conditions; however, children with preexisting conditions might have received aggressive treatment when they developed varicella. Overall, mortality was similar across racial and ethnic groups, and similar among children born in the United States compared with foreign-born children.

E. coli Linked to Diarrhea

Diarrheagenic *Escherichia coli* was isolated significantly more often in children with acute gastroenteritis in an emergency department compared with inpatients and controls, said Mitchell B. Cohen, M.D., of Cincinnati Children's Hospital Medical Center, and his associates. In a study of 684 children who presented to an emergency department, 643 inpatient children, and 555 controls, the investigators used DNA probes to evaluate stool samples. A majority in each group was aged 5 years or younger (J. Pediatr. 2005;146:54-61). Diarrheagenic *E. coli* was present in 167 (24%) of 684 ED patients, compared with 78 (14%) of 555 control patients. However, there was no significant difference in prevalence of *E. coli* between the inpatients (13%) and controls (14%). There also was no significant difference in prevalence of *E. coli* between the inpatients and controls in the subset aged 5 years and younger (13.5% vs. 15.4%). In addition, the researchers found a significantly high isolation rate of enteroaggregative *E. coli* in ED patients less than 1 year old, compared with controls (10% vs. 1.4%). "Diarrheagenic *E. coli* may be an important, unrecognized cause of diarrhea in children in the [United States], perhaps accounting for 10% of all acute gastroenteritis," the investigators said. Rotavirus was the most common single etiologic agent, found in 20.3% of inpatients and 20.2% of ED patients, compared with 1.1% of controls.

Urinalysis Predicts Kidney Diseases

Children with a combination of microhematuria and proteinuria were at significantly increased risk for kidney disease or decreased kidney function in a retrospective chart review of 239 children, reported Jayanthi Chandar, M.D., and colleagues at the University of Miami (Clin. Pediatr. 2005;44:43-8). Overall, 109 children had isolated microhematuria, 79 had isolated proteinuria, and 51 had a combination of the two conditions. The 11 children who initially presented with a combination of both conditions had odds ratios of 8.5 for developing kidney disease and 9.8 for decreased kidney function. An additional 17 children presented with proteinuria and later developed microhematuria, and 23 presented with microhematuria and later developed proteinuria, and these children also were at increased risk for kidney problems. A total of 163 children (68%) underwent renal ultrasounds, 16% of which showed genitourinary disease or abnormalities in kidney size or echogenicity. Although urinalysis remains controversial as a screening tool, children with persistent urine abnormalities should be evaluated in order to diagnose kidney disease as soon as possible.

—Heidi Splette

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

Omnicef® (cefdinir) capsules

Omnicef® (cefdinir) for oral suspension

Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of OMNICEF and other antibacterial drugs, OMNICEF should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

CONTRAINDICATIONS

OMNICEF (cefdinir) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS

BEFORE THERAPY WITH OMNICEF (CEFDINIR) IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFDINIR, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF CEFDINIR IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG β -LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFDINIR OCCURS, THE DRUG SHOULD BE DISCONTINUED. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefdinir, and may range in severity from mild- to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

PRECAUTIONS

General

Prescribing OMNICEF in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other broad-spectrum antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate alternative therapy should be administered. Cefdinir, as with other broad-spectrum antimicrobials (antibiotics), should be prescribed with caution in individuals with a history of colitis.

In patients with transient or persistent renal insufficiency (creatinine clearance <30 mL/min), the total daily dose of OMNICEF should be reduced because high and prolonged plasma concentrations of cefdinir can result following recommended doses.

Information for Patients

Patients should be counseled that antibacterial drugs including OMNICEF should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When OMNICEF is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by OMNICEF or other antibacterial drugs in the future. Antacids containing magnesium or aluminum interfere with the absorption of cefdinir. If this type of antacid is required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the antacid.

Iron supplements, including multivitamins that contain iron, interfere with the absorption of cefdinir. If iron supplements are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the supplement.

Iron-fortified infant formula does not significantly interfere with the absorption of cefdinir. Therefore, OMNICEF for Oral Suspension can be administered with iron-fortified infant formula.

Diabetic patients and caregivers should be aware that the oral suspension contains 2.86 g of sucrose per teaspoon.

Drug Interactions

Antacids: (aluminum- or magnesium-containing): Concomitant administration of 300-mg cefdinir capsules with 30 mL Maalox® TC suspension reduces the rate (C_{max}) and extent (AUC) of absorption by approximately 40%. Time to reach C_{max} is also prolonged by 1 hour. There are no significant effects on cefdinir pharmacokinetics if the antacid is administered 2 hours before or 2 hours after cefdinir. If antacids are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the antacid.

Probenecid: As with other β -lactam antibiotics, probenecid inhibits the renal excretion of cefdinir, resulting in an approximate doubling in AUC, a 50% increase in peak cefdinir plasma levels, and a 50% prolongation in the apparent elimination $t_{1/2}$.

Iron Supplements and Foods Fortified with Iron: Concomitant administration of cefdinir with a therapeutic iron supplement containing

60 mg of elemental iron (as FeSO₄) or vitamins supplemented with 10 mg of elemental iron reduced extent of absorption by 80% and 31%, respectively. If iron supplements are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the supplement. The effect of foods highly fortified with elemental iron (primarily iron-fortified breakfast cereals) on cefdinir absorption has not been studied. Concomitantly administered iron-fortified infant formula (2.2 mg elemental iron/6 oz) has no significant effect on cefdinir pharmacokinetics. Therefore, OMNICEF for Oral Suspension can be administered with iron-fortified infant formula.

There have been reports of reddish stools in patients receiving cefdinir. In many cases, patients were also receiving iron-containing products. The reddish color is due to the formation of a nonabsorbable complex between cefdinir or its breakdown products and iron in the gastrointestinal tract.

Drug/Laboratory Test Interactions

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside, but not with those using nitroferricyanide. The administration of cefdinir may result in a false-positive reaction for glucose in urine using Clinitest®, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used. Cephalosporins are known to occasionally induce a positive direct Coombs' test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of cefdinir has not been evaluated. No mutagenic effects were seen in the bacterial reverse mutation assay (Ames) or point mutation assay at the hypoxanthine-guanine phosphoribosyltransferase locus (HGPRT) in V79 Chinese hamster lung cells. No clastogenic effects were observed *in vitro* in the structural chromosome aberration assay in V79 Chinese hamster lung cells or *in vivo* in the micronucleus assay in mouse bone marrow. In rats, fertility and reproductive performance were not affected by cefdinir at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m²/day).

Pregnancy - Teratogenic Effects

Pregnancy Category B: Cefdinir was not teratogenic in rats at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m²/day) or in rabbits at oral doses up to 10 mg/kg/day (0.7 times the human dose based on mg/kg/day, 0.23 times based on mg/m²/day). Maternal toxicity (decreased body weight gain) was observed in rabbits at the maximum tolerated dose of 10 mg/kg/day without adverse effects on offspring. Decreased body weight occurred in rat fetuses at ≥ 100 mg/kg/day, and in rat offspring at ≥ 32 mg/kg/day. No effects were observed on maternal reproductive parameters or offspring survival, development, behavior, or reproductive function.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Cefdinir has not been studied for use during labor and delivery.

Nursing Mothers

Following administration of single 600-mg doses, cefdinir was not detected in human breast milk.

Pediatric Use

Safety and efficacy in neonates and infants less than 6 months of age have not been established. Use of cefdinir for the treatment of acute maxillary sinusitis in pediatric patients (age 6 months through 12 years) is supported by evidence from adequate and well-controlled studies in adults and adolescents, the similar pathophysiology of acute sinusitis in adult and pediatric patients, and comparative pharmacokinetic data in the pediatric population.

Geriatric Use

Efficacy is comparable in geriatric patients and younger adults. While cefdinir has been well-tolerated in all age groups, in clinical trials geriatric patients experienced a lower rate of adverse events, including diarrhea, than younger adults. Dose adjustment in elderly patients is not necessary unless renal function is markedly compromised.

ADVERSE EVENTS

Clinical Trials - OMNICEF Capsules (Adult and Adolescent Patients):

In clinical trials, 5093 adult and adolescent patients (3841 US and 1252 non-US) were treated with the recommended dose of cefdinir capsules (600 mg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. One hundred forty-seven of 5093 (3%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or nausea. Nineteen of 5093 (0.4%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by investigators to be possibly, probably, or definitely related to cefdinir capsules in multiple-dose clinical trials (N = 3841 cefdinir-treated patients):

ADVERSE EVENTS ASSOCIATED WITH CEFDINIR CAPSULES US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N=3841): Incidence $\geq 1\%$, Diarrhea 15%, Vaginal moniliasis 4% of women, Nausea 3%, Headache 2%, Abdominal pain 1%, Vaginitis 1% of women, Incidence <1% but $>0.1\%$, Rash 0.9%, Dyspepsia 0.7%, Flatulence 0.7%, Vomiting 0.7%, Abnormal stools 0.3%, Anorexia 0.3%, Constipation 0.3%, Dizziness 0.3%, Dry mouth 0.3%, Asthenia 0.2%, Insomnia 0.2%, Leukorrhea 0.2% of women, Moniliasis 0.2%, Pruritus 0.2%, Somnolence 0.2%,
^a 1733 males, 2108 females.

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US: **LABORATORY VALUE CHANGES OBSERVED WITH CEFDINIR CAPSULES US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N=3841):** Incidence $\geq 1\%$, \uparrow Urine leukocytes 2%, \uparrow Urine protein 2%, \uparrow Gamma-glutamyltransferase 1%, \downarrow Lymphocytes, \uparrow Lymphocytes 1%, 0.2%, \uparrow Microhematuria 1%, Incidence <1% but $>0.1\%$ \uparrow Glucose^a 0.9%, \uparrow Urine glucose 0.9%, \uparrow White blood cells, \downarrow White blood cells 0.9%, 0.7% \uparrow Alanine aminotransferase (ALT) 0.7%, \uparrow Eosinophils 0.7%, \uparrow Urine specific gravity, \uparrow Urine specific gravity^a 0.6%, 0.2%, \downarrow Bicarbonate^a 0.6%, \uparrow Phosphorus, \downarrow Phosphorus^a 0.6%, 0.3%, \uparrow Aspartate aminotransferase (AST) 0.4%, \uparrow Alkaline phosphatase 0.3%, \uparrow Blood urea nitrogen (BUN) 0.3%, \downarrow Hemoglobin 0.3%, \uparrow Polymorphonuclear (PMMNs), \downarrow PMMNs 0.3%, 0.2%, \uparrow Bilirubin 0.2%, \uparrow Lactate dehydrogenase^a 0.2%, \uparrow Platelets 0.2%, \uparrow Potassium^a 0.2%, \uparrow Urine pH^a 0.2%,
^a N <3841 for these parameters

Clinical Trials - OMNICEF for Oral Suspension (Pediatric Patients):

In clinical trials, 2289 pediatric patients (1783 US and 506 non-US) were treated with the recommended dose of cefdinir suspension (14 mg/kg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. Forty of 2289 (2%) patients discontinued medication due to adverse events considered by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. Discontinuations were primarily for gastrointestinal disturbances, usually diarrhea. Five of 2289 (0.2%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by investigators to be possibly, probably, or definitely related to cefdinir suspension in multiple-dose clinical trials (N=1783 cefdinir-treated patients):

ADVERSE EVENTS ASSOCIATED WITH CEFDINIR SUSPENSION US TRIALS IN PEDIATRIC PATIENTS (N=1783): Incidence $\geq 1\%$, Diarrhea 8%, Rash 3%, Vomiting 1%, Incidence <1% but $>0.1\%$, Cutaneous moniliasis 0.9%, Abdominal pain 0.8%, Leukopenia^a 0.3%, Vaginal moniliasis 0.3% of girls, Vaginitis 0.3% of girls, Abnormal stools 0.2%, Dyspepsia 0.2%, Hyperkinesia 0.2%, Increased AST^a 0.2%, Maculopapular rash 0.2%, Nausea 0.2%, 977 males, 806 females.
Laboratory changes were occasionally reported as adverse events.

NOTE: In both cefdinir- and control-treated patients, rates of diarrhea and rash were higher in the youngest pediatric patients. The incidence of diarrhea in cefdinir-treated patients ≤ 2 years of age was 17% (95/557) compared with 4% (51/1226) in those ≥ 2 years old. The incidence of rash (primarily diaper rash in the younger patients) was 8% (43/557) in patients ≤ 2 years of age compared with 1% (8/1226) in those ≥ 2 years old.

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US:

LABORATORY VALUE CHANGES OF POSSIBLE CLINICAL SIGNIFICANCE OBSERVED WITH CEFDINIR SUSPENSION US TRIALS IN PEDIATRIC PATIENTS (N=1783): Incidence $>1\%$ \uparrow Lymphocytes, 2%, 0.8%, \downarrow Lymphocytes 1%, \uparrow Alkaline phosphatase 1%, \downarrow Bicarbonate 1%, \uparrow Eosinophils 1%, \uparrow Lactate dehydrogenase 1%, \uparrow Platelets 1%, \uparrow PMMNs, \downarrow PMMNs 1%, 1%, \uparrow Urine protein 1%, Incidence <1% but $>0.1\%$, \uparrow Phosphorus, \downarrow Phosphorus 0.9%, 0.4%, \uparrow Urine pH 0.8%, \downarrow White blood cells, \uparrow White blood cells 0.7%, 0.3%, \uparrow Calcium^a 0.5%, \downarrow Hemoglobin 0.5%, \uparrow Urine leukocytes 0.5%, \uparrow Monocytes 0.4%, \uparrow AST 0.3%, \uparrow Potassium^a 0.3%, \uparrow Urine specific gravity, \downarrow Urine specific gravity 0.3%, 0.1%, \downarrow Hematocritia 0.2%,^a =1387 for these parameters

Postmarketing Experience

The following adverse experiences and altered laboratory tests, regardless of their relationship to cefdinir, have been reported during extensive postmarketing experience, beginning with approval in Japan in 1991: Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, erythema nodosum, conjunctivitis, stomatitis, acute hepatitis, cholestasis, fulminant hepatitis, hepatic failure, jaundice, increased amylase, shock, anaphylaxis, facial and laryngeal edema, feeling of suffocation, acute enterocolitis, bloody diarrhea, hemorrhagic colitis, melena, pseudomembranous colitis, pancytopenia, granulocytopenia, leukopenia, thrombocytopenia, idiopathic thrombocytopenic purpura, hemolytic anemia, acute respiratory failure, asthmatic attack, drug-induced pneumonia, eosinophilic pneumonia, idiopathic interstitial pneumonia, fever, acute renal failure, nephropathy, bleeding tendency, coagulation disorder, disseminated intravascular coagulation, upper GI bleed, peptic ulcer, ileus, loss of consciousness, allergic vasculitis, possible cefdinir-diclofenac interaction, cardiac failure, chest pain, myocardial infarction, hypertension, involuntary movements, and rhabdomyolysis.

Cephalosporin Class Adverse Events

The following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics in general:

Allergic reactions, anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis. Pseudomembranous colitis symptoms may begin during or after antibiotic treatment (see **WARNINGS**).

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **OVERDOSAGE**). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

Information on cefdinir overdosage in humans is not available. In acute rodent toxicity studies, a single oral 5600-mg/kg dose produced no adverse effects. Toxic signs and symptoms following overdosage with other β -lactam antibiotics have included nausea, vomiting, epigastric distress, diarrhea, and convulsions. Hemodialysis removes cefdinir from the body. This may be useful in the event of a serious toxic reaction from overdosage, particularly if renal function is compromised.

Rx only

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