Cefadroxil (Duricef®) capsule and powder for suspension

Classification

First Generation Cephalosporin Antibiotic

Pharmacology

Cefadroxil is a semisynthetic cephalosporin antibiotic for oral administration. Cephalosporin antibiotics inhibit bacterial cell wall synthesis by binding to one or more of the penicillin-binging proteins which inhibits transpeptidation of peptidoglycan synthesis.

Indication

- Treatment of skin and soft tissue infections caused by *staphylococci* and/or *streptococci.*
- Treatment of pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci).
- Treatment of urinary tract infections caused by *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* species.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Rapidly absorbed after oral administration. Time to peak 70-90 minutes.
Distribution	V_d: 0.31 L/kg, 20% protein bound. The urine antibiotic concentration following a 1 g dose was maintained above the MIC for susceptible urinary pathogens for 20 to 22 hours.
Metabolism	Half-life elimination 1 to 2 hours in adults; 1.3-1.8 hours in children, 20-24 hours in adults with renal failure.
Excretion	>90% as unchanged drug in the urine within 24 hours.

Dosage/Administration

Administration with food may reduce gastrointestinal side effects.

Adult Dosing

Urinary Tract Infections:
1 or 2 g per day as single or divided dose for uncomplicated infections. For all other urinary tract infections, the dose is 2 g per day divided twice daily.

Skin and Skin Structure Infections:
1 g per day in single or divided dose.

Pharyngitis and Tonsillitis:
1 g per day in single or divided dose.

Children Dosing

Urinary Tract Infections:
30 mg/kg/day in divided doses every 12 hours; max 2 g per day.

Pharyngitis, Tonsillitis, and Impetigo:
30 mg/kg/day in single or divided dose every 12 hours; max dose 1 g per day.

Other Skin and Skin Structure Infections:
30 mg/kg/day in divided doses every 12 hours; max 1 g per day.

Renal Impairment Dosing

Adjust dose for adults with CrCl 50 mL/min or less as follows- 1 g initial dose followed by a maintenance dose of 500 mg at the following dosage interval based on CrCl:

0 to 10 mL/min= 36 hours

10 to 25 mL/min= 24 hours

25 to 50 mL/min= 12 hours

Note: Other resources indicate dosage adjustment is not needed for those with CrCl 40 mL/min or above and the dosage interval may be every 24 hours for those with CrCl less than 20 mL/min.

Reconstitution Directions for Oral Suspension

Initially tap bottle lightly to loosen powder. Shake well after each portion addition of water as noted below.

100 mL Bottle Size: Suspend in 60 mL water, add water in 2 portions

75 mL Bottle Size: Suspend in 45 mL water, add water in 2 portions

50 mL Bottle Size: Suspend in 30 mL water, add water in 2 portions

After reconstitution store in refrigerator. Shake well before using. Keep container tightly closed. Discard unused portion after 14 days.

Use in Special Populations

Because elderly patients mare more likely to have decreased renal function, care should be taken in dose selection and monitoring renal function should be considered.

No adequate or well controlled studies in pregnant women, although cephalosporin antibiotics are generally considered compatible during pregnancy. Cefadroxil has not been studied for use during labor and delivery.

Caution should be exercised when cefadroxil is administered to a nursing mother although the relative infant dose is low at 2.6% for a standard 1 g per day dose.

Contraindication

Known allergy to the cephalosporin group of antibiotics.

Precautions

- Hypersensitivity reactions to cefadroxil, cephalosporins, penicillins or other drugs. Cross-sensitivity among beta-lactam antibiotics may occur in up to 10% of patients with a history of penicillin allergy. The suspension may contain sulfur dioxide (sulfite) and hypersensitivity reactions may occur.
- *Clostridium difficile associated diarrhea* (CDAD) has been reported with use of antibacterial agents, including cefadroxil, caused by alteration in the normal flora of the colon leading to overgrowth of *C. difficile.*
- Use with caution in the presence of markedly impaired renal function CrCl 50 mL/min or less.
- Use with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Adverse Effects

- Gastrointestinal symptoms such as dyspepsia, nausea, vomiting, abdominal pain and diarrhea. Rarely pseudomembranous colitis symptoms or *Clostridolides diffficile*-associated diarrhea may occur during and after antibiotic treatment.
- Hypersensitivity reactions such as rash, urticaria, angioedema and pruritus have been reported and usually subside after discontinuation of the medication. Rarely anaphylaxis, erythema multiforme, Stevens-Johnson syndrome or eosinophilia may occur. Toxic epidermal necrolysis and serum sickness have also been reported.
- Hepatic dysfunction including cholestasis, elevations in transaminase, alkaline phosphatase, elevated bilirubin, elevated LDH, and rarely idiosyncratic hepatic failure.
- Genitourinary complications including genital pruritus, genital moniliasis, vaginitis.
- Hematologic events including agranulocytosis, neutropenia, thrombocytopenia, aplastic anemia, pancytopenia, hemorrhage, prolonged PT time, positive Coombs' test.
- Renal side effects including elevated BUN, increased creatinine, renal dysfunction, toxic nephropathy.
- Cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, where the dose was not renally adjusted.

Monitoring

Culture and susceptibility tests should be initiated prior to and during therapy. Culture and susceptibility information should be considered in selecting or modifying antibacterial therapy when available.

Monitor renal function.

Monitor for possible C. difficile overgrowth including watery and bloody stools (with or without stomach cramps and fever) during and after completion of antibiotic course.

Interactions

- Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics.
- Cefadroxil is an OAT1/3 Substrate.
- Aminoglycosides- may enhance the nephrotoxic effect of aminoglycosides.
- Furosemide- may enhance nephrotoxic effect of cephalosporins.

- Immune Checkpoint Inhibitors (Anti-PD-1, -PD-L1, -CTLA4)- antibiotics may diminish therapeutic effect of immune checkpoint inhibitors.
- Lactobacillus and Estriol- antibiotics may diminish therapeutic effect.
- Probenecid- may increase serum concentration of cephalosporins.
- Vitamin K antagonist (eg, warfarin): Cephalosporins may enhance the anticoagulant effect.

Efficacy

Cefadroxil is active against many gram-positive aerobic cocci, but is much less active against gram-negative bacteria with an antibacterial profile similar to cephalexin. The main advantage of cefadroxil over cephalexin is the longer half-life allowing twice daily dosing versus four times daily dosing. Following equivalent oral doses, serum levels of cefadroxil are higher and more sustained than cephalexin 1.5 hours post ingestion. Cefadroxil has been shown to be active against the following organisms both in vitro and in clinical infections: *Beta-hemolytic streptococci, Staphylococci, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella species, Moraxella catarrhalis*. Cefadroxil has been shown to be effective in clinical trials against these strains for the treatment of urinary tract infections, skin and skin structure infections, as well as pharyngitis/tonsillitis.

Skin and skin structure and musculoskeletal infections

Cefadroxil 30 mg/kg per day was compared to cephalexin 15 mg/kg dosed twice daily (maximum dose 1 g each) for the treatment of gram-positive skin infections in children. Treatment was evaluated in 289 children with the most common skin infection being impetigo. Cefadroxil was found to be significantly better than cephalexin at eradicating the organism, 96% vs. 89% respectively. Clinically, there was no difference treatment response between the two antibiotics with side effects being mild and infrequent with either antibiotic.

Another study compared cefadroxil, cephalexin and other antibiotics and their ability to inhibit growth of MSSA in the laboratory setting. Bacterial samples were obtained from children with bone, joint and/or other musculoskeletal infections caused by MSSA. A total of 48 isolates were obtained from blood (81%), bone (15%) and synovial fluid (4%) with cultures included in the analysis. Cefadroxil and cephalexin inhibited the growth of MSSA at similar concentrations with statistically equivalent MICs ($p=0.28$), suggesting similar antibacterial potency.

According to the Infectious Diseases Society of America (IDSA) treatment guidelines, for impetigo and ecthyma non-purulent skin infections, oral penicillinase-resistant penicillin or first-generation cephalosporins are usually effective.

Uncomplicated urinary tract infection

The safety and efficacy of cefadroxil 1 g twice daily and cephalexin 500 mg four times daily in the treatment of uncomplicated urinary tract infection was evaluated in 660 patients. The trial was a randomized, double-blind design evaluating cure rate based on urine cultures 5 to 9 days post-treatment. Cure rates were similar with the two antibiotics, 93% of cefadroxil patients and 91% of cephalexin patients. Side effects reported were similar between the two groups, 13% cefadroxil and 15% cephalexin. Nausea was more common with cefadroxil and vaginitis was more common with cephalexin. Another study in uncomplicated UTI comparing the two antibiotics with same dosing also found comparable treatment effects; however, this study only included 28 female patients.

IDSA guidelines generally to not recommend use of first-generation cephalosporins in the treatment of uncomplicated urinary tract infections as a first-line treatment. However, if the recommended antimicrobials for UTI are not feasible, cephalosporins can be considered. When cephalosporins are used for the treatment of uncomplicated UTI, a second-generation or third-generation of cephalosporin is generally selected as first-generation cephalosporins such as cefadroxil and cephalexin are less well studied.

Dosage Forms/Cost (AWP)

- Capsule 500 mg: $3.60 per capsule
- Oral suspension 250 mg per 5 mL (100 mL bottle): $60.80
- Oral suspension 500 mg per 5 mL (75 mL bottle): $63.12
- Oral suspension 500 mg per 5 mL (100 mL bottle): $84.17

Safety Considerations

- Look Alike-Sound Alike: Brand name Duricef (no longer available) may be confused with Ultracet
- High Risk-High Alert: No
- Hazardous Drug Status: No

Summary/Conclusion

Cefadroxil is a first-generation cephalosporin available in oral dosage forms similar to the formulary antibiotic cephalexin. Although the two antibiotics have a similar spectrum of antimicrobial activity, cefadroxil requires less frequent administration. Both antibiotics are available generic and are relatively inexpensive.

Recommendation

Cefadroxil capsules and oral suspension are recommended for formulary addition.

References

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