

Clarithromycin

Brand Name: Biaxin

Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Clarithromycin is a semisynthetic macrolide antibiotic. It differs structurally from erythromycin by methylation of a hydroxyl group at position 6 of the lactone ring. [1]

HIV/AIDS-Related Uses

Clarithromycin is used in the prevention and treatment of Mycobacterium avium complex (MAC) disease due to Mycobacterium avium and Mycobacterium intracellulare. Clarithromycin was approved by the FDA for treatment of MAC on December 23, 1993, and for the prevention of MAC on October 12, 1995.[2]

The Prevention of Opportunistic Infections Working Group of the U.S. Public Health Service and Infectious Diseases Society of America (USPHS/IDSA) state that HIV infected adults and adolescents with a CD4 count less than 50 cells/mm³ should receive primary chemoprophylaxis against disseminated MAC disease; clarithromycin and azithromycin are the preferred agents. The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone and is associated with a higher rate of adverse effects than either drug alone. This combination should not be used for MAC prophylaxis. In addition to its preventive activity for MAC disease, clarithromycin confers protection against respiratory bacterial infections.[3]

The American Thoracic Society recommends that clarithromycin or azithromycin be used with ethambutol and rifabutin for the treatment of disseminated MAC in HIV infected patients. Limited data from clinical trials indicate that use of ethambutol with clarithromycin may decrease the emergence of clarithromycin-resistant MAC. Adults and adolescents with disseminated MAC should receive lifelong therapy (i.e., secondary prophylaxis, maintenance therapy) unless immune reconstitution occurs as a consequence of highly active antiretroviral therapy (HAART).[4]

Clarithromycin and azithromycin are also the preferred prophylactic agents for disseminated

MAC disease in HIV infected children. Prophylaxis should be offered to high-risk children and dosed based on age and CD4 count according to the USPHS/IDSA guidelines. Children with a history of disseminated MAC should be given lifelong prophylaxis to prevent recurrence.[5]

Non-HIV/AIDS-Related Uses

Clarithromycin is indicated in the treatment of acute bacterial exacerbations of chronic bronchitis, otitis media, or acute maxillary sinusitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae. It is also indicated in the treatment of pharyngitis or tonsillitis caused by Streptococcus pyogenes and bacterial and community-acquired pneumonia due to Chlamydia pneumoniae, H. influenzae, M. catarrhalis, Mycoplasma pneumoniae, or S. pneumoniae.[6]

Clarithromycin may be used for the treatment of soft tissue infections due to susceptible strains of Staphylococcus aureus or S. pyogenes and as a treatment adjunct for Helicobacter pylori-associated duodenal ulcers.[7]

Pharmacology

Clarithromycin penetrates the cell wall of susceptible organisms and binds to the 50S subunit of the 70S ribosome, inhibiting translocation of aminoacyl transfer-RNA and protein synthesis. Clarithromycin is generally bacteriostatic but may be bactericidal in high concentrations or against highly susceptible organisms.[8]

Clarithromycin is rapidly absorbed from the gastrointestinal (GI) tract following oral administration. The absolute oral bioavailability of clarithromycin is 50% to 55%. However, this underestimates clarithromycin's systemic activity because of the drug's rapid first-pass metabolism to its active metabolite, 14-hydroxyclearithromycin.[9]

Clarithromycin is extensively metabolized in the liver, primarily by oxidative N-demethylation and hydroxylation at the 14 position. At least seven metabolites have been identified, but the principal metabolite, 14-hydroxyclearithromycin, is the only

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Pharmacology (cont.)

one with significant antibacterial activity.[10] It is as active or only slightly less active than clarithromycin in vitro against most organisms and enhances the antimicrobial activity of clarithromycin against *H. influenzae*. However, 14-hydroxyclearithromycin was four to seven times less active than clarithromycin against MAC isolates; the clinical importance of this is unknown.[11]

Clarithromycin is stable in gastric acid. The presence of food delays the rate but not the extent of absorption. Clarithromycin is widely distributed into tissues and fluids; high concentrations are found in nasal mucosa, tonsils, and lungs.[12] Serum concentrations are lower than tissue concentrations because of high intracellular concentrations. Protein binding in vitro is 42% to 72% and decreases with increasing serum drug concentrations.[13]

Elimination of clarithromycin is nonlinear and dose dependent. The elimination half-lives of clarithromycin 250 and 500 mg tablets given every 12 hours are 3 to 4 hours and 5 to 7 hours, respectively. The elimination half-life of 14-hydroxyclearithromycin is slightly longer.[14] Time to peak concentration is 1 to 4 hours for conventional tablets and 5 to 8 hours for extended-release tablets. Clarithromycin is eliminated by both renal and nonrenal mechanisms. Hepatic metabolism is extensive and saturable. After a single 250-mg dose of radiolabeled clarithromycin in healthy men, approximately 38% of the dose (18% as clarithromycin) was excreted in the urine and 40% in feces (4% as clarithromycin) over 5 days.[15]

The serum half-life of clarithromycin is prolonged in patients with impaired renal function. Marked increases in peak serum concentration (C_{max}), area under the concentration-time curve (AUC), and half-life of clarithromycin and 14-hydroxyclearithromycin have been reported in patients with creatinine clearances less than 30 ml/min. These patients may require dose reduction.[16]

Clarithromycin is in FDA Pregnancy Category C.

No adequate and well-controlled studies in pregnant women have been done.[17] In animal studies, clarithromycin has been associated with fetal loss and embryofetal maldevelopment. Clarithromycin should be used during pregnancy only when safer drugs cannot be used or are ineffective. It is not known whether clarithromycin is distributed in human breast milk. However, it is distributed in the milk of lactating animals, and other macrolides are distributed in human milk. Caution should be exercised when clarithromycin is administered to lactating women.[18]

Resistance to macrolide antibiotics usually involves alteration of the antibiotic target site. Resistant bacteria produce an enzyme that leads to methylation of adenine residues in ribosomal RNA and subsequent inhibition of antibiotic ribosomal binding. Erythromycin-resistant organisms are generally resistant to all 14- and 15-membered macrolides because all of the drugs induce the methylase enzyme. Strains of MAC with decreased susceptibility or resistance to clarithromycin have been reported in patients who received the drug for treatment or prevention of MAC infection. MAC isolates resistant to clarithromycin are cross-resistant to azithromycin.[19]

Adverse Events/Toxicity

Clarithromycin is generally well tolerated. In clinical studies, most adverse effects were mild and transient; only about 1% of reported effects were described as severe. The most common adverse effects involve the GI tract and include diarrhea, nausea, abnormal taste, dyspepsia, and abdominal discomfort. Limited clinical data indicate that clarithromycin may cause adverse GI effects less frequently than erythromycin.[20]

Pseudomembranous colitis has been reported with clarithromycin use.[21]

Headache is a common adverse effect of clarithromycin therapy.[22]

Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis and Stevens-Johnson syndrome have occurred. Rare cases of severe hepatic dysfunctions also have been reported. Hepatic dysfunction is usually reversible,

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Adverse Events/Toxicity (cont.)

but fatalities with clarithromycin use have been reported.[23]

Increased prothrombin time and thrombocytopenia have also been reported with the use of clarithromycin.[24]

Drug and Food Interactions

Clarithromycin immediate-release tablets and oral solution may be taken with or without food. Extended-release tablets should be taken with food.[25]

Clarithromycin should be used with caution in patients taking carbamazepine and other medications metabolized by the cytochrome P450 (CYP) enzyme system. Because clarithromycin has been shown to significantly increase the plasma concentrations of these medications, serum concentration should be monitored when coadministered with clarithromycin. Concurrent use of clarithromycin and astemizole is not recommended, as QTc-interval prolongation and torsades de pointes have been reported with concurrent use of astemizole and erythromycin. Cisapride, pimozone, and terfenadine, when used concurrently with clarithromycin, have been associated with cardiac arrhythmias, including QTc-interval prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes. These arrhythmias may be fatal, and concurrent use of clarithromycin with these medications is contraindicated.[26]

Concomitant administration of clarithromycin and antiretroviral agents may alter the pharmacokinetics of both clarithromycin and the antiretroviral agent. Administration of clarithromycin and delavirdine results in a 100% increase in the AUC of clarithromycin but has no effect on delavirdine's pharmacokinetics. Similarly, clarithromycin has no apparent effect on the pharmacokinetics of didanosine. Concurrent use of clarithromycin does increase the C_{max} of ritonavir by 12% to 15%; clarithromycin's AUC and C_{max} increase by 77% and 31%, respectively. Limited studies have shown that clarithromycin decreases the steady-state AUC of zidovudine by a mean 12% and decreases the

C_{max} by approximately 41%. This effect is partially offset if the two drugs are given 2 to 4 hours apart. The manufacturer of clarithromycin states that dosage modification is not necessary for concurrent clarithromycin and HAART in patients with normal renal function. However, the clarithromycin dose should be reduced by 50% in patients with creatinine clearance (CrCl) of 30 to 60 ml/min and by 75% in patients with CrCl below 30 ml/min when administered with HAART.[27]

Concurrent use of clarithromycin and rifabutin or rifampin increases the metabolism of clarithromycin. A study of patients with advanced HIV infection demonstrated inhibition of rifabutin metabolism by clarithromycin and induction of clarithromycin metabolism by rifabutin. The AUC of clarithromycin decreased by an average 44% while the AUC of rifabutin increased by an average 99%.[28]

Concurrent administration of warfarin and clarithromycin has been shown to potentiate the effects of warfarin. Prothrombin time should be monitored closely in patients receiving anticoagulants and clarithromycin concurrently.[29]

Serum concentrations of digoxin increase when digoxin is used concurrently with clarithromycin; serum digoxin concentrations should be monitored.

Clarithromycin increases the AUC of theophylline by 17%, and monitoring of theophylline serum concentration is recommended, especially for patients with theophylline concentrations in the upper therapeutic range.[30]

Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibiotics. Concomitant administration of clarithromycin with cisapride, pimozone, astemizole, terfenadine, or ergotamine and derivatives is contraindicated.[31]

Clarithromycin should be used with caution in patients with impaired renal function, because the elimination of clarithromycin is significantly reduced, especially in patients with CrCl less than 30 ml/min. The dose of clarithromycin should be

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Contraindications (cont.)

halved or the dosing interval should be doubled in these patients.[32]

Clinical Trials

For information on clinical trials that involve Clarithromycin, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Clarithromycin AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[33]

Dosage Form: Film-coated tablets for immediate release containing clarithromycin 250 and 500 mg or for extended release (XL) containing clarithromycin 500 mg.[34]

Oral suspension as granules in sucrose containing 125 and 250 mg per 5 ml.[35]

Storage: Store immediate-release tablets in tight containers at a temperature below 40 C (104 F), preferably between 15 C and 30 C (59 F and 86 F), and protect from light.[36]

Store extended-release tablets between 20 C and 25 C (68 F and 77 F). Excursions are permitted between 15 C and 30 C (59 F and 86 F).[37]

Store oral suspension in a well-closed container away from light between 15 C and 30 C (59 F and 86 F).[38]

Chemistry

CAS Name: 6-O-Methylerythromycin[39]

CAS Number: 81103-11-9[40]

Molecular formula: C38-H69-N-O13[41]

C61.02%, H9.30%, N1.87%, O27.81%[42]

Molecular weight: 747.95[43]

Melting point: 217 to 220 C[44]

Physical Description: White to off-white crystalline powder.[45]

Stability: After reconstitution, oral suspension retains potency for 14 days and does not require refrigeration.[46]

Solubility: Practically insoluble in water and slightly soluble in alcohol at room temperature. Solubility increases with decreasing pH.[47]

Other Names

A-56268[48]

Abbott-56268[49]

TE-031[50]

Further Reading

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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