

Clarithromycin

Brand Name: Biaxin

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] [3]

The Prevention of Opportunistic Infections Working Group of the US Public Health Service and Infectious Diseases Society of America (USPHS/IDSA) states that HIV infected adults and adolescents with a CD4 count of less than 50 cells/mm³ should receive 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.[4]

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 indicates that use of ethambutol with clarithromycin may decrease the emergence of clarithromycin-resistant MAC.[5] Adults and adolescents with disseminated MAC should receive lifelong therapy (i.e., secondary prophylaxis or maintenance therapy) unless immune reconstitution occurs as a consequence of highly active antiretroviral therapy (HAART).[6]

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 based on age and CD4 count as indicated in the USPHS/IDSA guidelines. Children with a history of disseminated MAC should be given lifelong prophylaxis to prevent recurrence.[7]

Non-HIV/AIDS-Related Uses

Clarithromycin is indicated in the treatment of 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 due to Streptococcus pyogenes and bacterial and community-acquired pneumonia due to Chlamydia pneumoniae, H. influenzae, M. catarrhalis, Mycoplasma pneumoniae, or S. pneumoniae.

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.[8]

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.[9]

Clarithromycin is rapidly absorbed from the 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.[10]

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 one with significant antibacterial activity.[11] It is

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Pharmacology (cont.)

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 4 to 7 times less active than clarithromycin against MAC isolates; the clinical importance of this is unknown.[12]

Clarithromycin is stable in gastric acid. 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.[13] 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 concentration.[14]

Elimination of clarithromycin is nonlinear and dose-dependent. The elimination half-lives of 250 mg and 500 mg clarithromycin 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.[15] Time to peak concentration is 1 to 4 hours for conventional tablets and 5 to 8 hours for extended-release tablets.[16] Clarithromycin is eliminated by both renal and nonrenal mechanisms.

Hepatic metabolism is extensive and saturable. Following 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.

The serum half-life of clarithromycin is prolonged in patients with impaired renal function. Marked increases in peak serum concentration, area under the concentration-time curve (AUC), and half-life of clarithromycin and 14-hydroxyclearithromycin have been reported in patients with creatinine clearance less than 30ml/min. These patients may require dose reduction.[17]

Clarithromycin is in FDA Pregnancy Category C; no adequate and well-controlled studies in humans have been done.[18] 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.[19]

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.[20]

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.[21]

Pseudomembranous colitis has been reported with clarithromycin use.[22]

Headache is a common adverse effect of clarithromycin therapy.[23]

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 failure is usually reversible, but fatalities have been reported.

Increased prothrombin time and thrombocytopenia have also been reported.[24]

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Drug and Food Interactions

Clarithromycin may be taken with or without food.[25]

Clarithromycin should be used with caution in patients taking carbamazepine and other medications metabolized by the cytochrome P450 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. Generally, addition of clarithromycin increases the serum concentrations of these medications. 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. When used concurrently with clarithromycin, cisapride, pimozole, and terfenadine 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 AUC of ritonavir by 12% to 15%; clarithromycin's AUC increases by 77%. Limited studies have shown that clarithromycin decreases the steady-state AUC of zidovudine by 12%. This effect is partially offset if the two drugs are given 2 to 4 hours apart.[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 44% while the AUC

of rifabutin increased by 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.[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, pimozide, astemizole, or terfenadine is contraindicated.[31]

Clarithromycin should be used with caution in patients with impaired renal function. The elimination of clarithromycin is significantly reduced in patients with creatinine clearance less than 30 ml/min. The dose of clarithromycin should be 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: Tablets (250 and 500 mg), oral suspension (125 and 250 mg/5ml).[34]

Storage: Tablets should be stored in tight containers at a temperature less than 40 C, preferably between 15 and 30 C (59 and 86 F). Oral suspension should be stored away from light between 15 and 30 C (59

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Dosing Information (cont.)

and 86 F).[35]

Chemistry

CAS Name: 6-O-Methylerythromycin[36]

CAS Number: 81103-11-9[37]

Molecular formula: C38-H69-N-O13[38]

C61.02%, H9.30%, N1.87%, O27.81%[39]

Molecular weight: 747.95[40]

Melting point: 217-220 C[41]

Physical Description: Colorless needles from chloroform + diisopropyl ether (1:2); also reported as crystals from ethanol.[42]

Stability: After reconstitution, oral suspension retains potency for 14 days.[43]

Solubility: Practically insoluble in water and slightly soluble in alcohol. Solubility increases with decreasing pH.[44]

Other Names

A-56268 [45]

Abbott-56268[46]

TE-031 [47]

Erythromycin, 6-O-methyl-[48]

Further Reading

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Manufacturer Information

Clarithromycin
Abbott Laboratories
One Hundred Abbott Park Rd
Abbott Park, IL 60064-3500
(800) 633-9110

Biaxin
Abbott Laboratories
One Hundred Abbott Park Rd
Abbott Park, IL 60064-3500
(800) 633-9110

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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