Azithromycin

Brand Name: Zithromax
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Azithromycin is a semisynthetic azalide antibiotic, a subclass of macrolide antibiotics. Azalides are distinguished from other macrolides by the addition of nitrogen at position 9a of the lactone ring. Azithromycin differs structurally from erythromycin by a methyl-substituted nitrogen atom incorporated into the macrolide ring. [1] Azithromycin has a broader spectrum of activity than that of erythromycins or clarithromycin. [2]

HIV/AIDS-Related Uses

Azithromycin was approved by the FDA on June 14, 1996, for the prevention of disseminated Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection. Azithromycin may be an effective treatment for symptomatic Cryptosporidiosis in HIV infected patients; however, it is not effective in eradicting cryptosporidial infection.[3]

Non-HIV/AIDS-Related Uses

Azithromycin is used to treat chronic bronchitis or acute otitis media; gonococcal or nongonococcal cervicitis; gonococcal or nongonococcal urethritis; chancroid; pelvic inflammatory disease; pharyngitis or tonsillitis; community-acquired pneumonia; and uncomplicated skin and soft tissue infections. Azithromycin is active against many gram-positive and gram-negative aerobic and anaerobic bacteria, including streptococci, staphylococci, and Haemophilus influenzae.[4]

Pharmacology

Like other macrolides, azithromycin binds the 50S ribosomal subunit of the 70S ribosome of susceptible organisms, inhibiting RNA-dependent protein synthesis. Azithromycin is bactericidal for Streptococcus pyogenes, Streptococcus pneumoniae, and Haemophilus influenzae; it is bacteriostatic for staphylococci and most aerobic gram-negative species.[5] Azithromycin concentrates in phagocytes; penetration of the drug into phagocytic cells is necessary for activity against intracellular pathogens (e.g., Staphylococcus aureus). The site of action appears to be the same as that of the macrolides, clindamycin, lincomycin, and chloramphenicol.[6]

Azithromycin has an expanded spectrum of activity compared with erythromycin and clarithromycin. Azithromycin generally is more active in vitro against gram-negative organisms than erythromycin or clarithromycin and has activity comparable to erythromycin against most gram-positive organisms. Azithromycin is not inactivated by the beta-lactamases produced by Haemophilus influenzae or Moraxella catarrhalis.[7]

Azithromycin is rapidly absorbed from the gastrointestinal (GI) tract after oral administration; absorption of the drug is incomplete but exceeds that of erythromycin. The absolute oral bioavailability of azithromycin is reported to be approximately 34% to 52% with single doses of 500 mg to 1.2 g administered as various oral dosage forms. Limited evidence indicates that the low bioavailability of azithromycin results from incomplete GI absorption rather than acid degradation of the drug or extensive first-pass metabolism.[8] Time to peak concentration in adults is 2.1 to 3.2 hours for oral dosage forms and 1 to 2 hours for intravenous (IV) forms. For oral dosage forms, after a 500 mg loading dose on Day 1, then 250 mg once a day for Days 2 to 5, peak plasma concentrations in healthy adults were approximately 0.41 to 0.38 mcg/ml on Day 1 and 0.24 to 0.26 mcg/ml on Day 5. For IV forms, peak plasma concentrations were approximately 1.1 mcg/ml after a 3-hour IV infusion of 500 mg at a concentration of 1 mg/ml and approximately 3.6 mcg/ml after a 1-hour IV infusion of 500 mg at a concentration of 2 mg/ml.[9] Presence of food in the GI tract may affect the extent of absorption of oral azithromycin; however, the effect of food on absorption depends on the dosage form administered.[10]

Azithromycin is rapidly and widely distributed throughout the body. Azithromycin concentrates intracellularly, resulting in tissue concentrations 10 to 100 times higher than those found in plasma or serum. Azithromycin is highly concentrated in fibroblasts and phagocytic cells.[11] In addition to

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Pharmacology (cont.)

direct tissue uptake, it has been suggested that uptake and release of azithromycin by phagocytic cells contribute to the distribution of the drug into inflamed and infected tissues. Only very low concentrations of azithromycin have been detected in cerebrospinal fluid in patients with noninflamed meninges.[12]

Azithromycin is in FDA Pregnancy Category B. Adequate and well-controlled studies have not been done in pregnant women. Reproduction studies done in rats and mice given azithromycin at doses of up to moderately maternally toxic levels (i.e., 200 mg/kg per day) have found no evidence of harm to the fetus. On a mg/m2 basis, these doses are estimated to be four and two times the human daily dose of 500 mg in rats and mice, respectively.[13] Azithromycin has been detected in human milk. Physicians should exercise caution when administering azithromycin to nursing women.[14]

Protein binding to azithromycin varies with concentration but is generally very low to moderate, with approximately 7% binding at 1 mcg/ml, to 50% at 0.02 to 0.05 mcg/ml.[15] Plasma azithromycin concentrations following a single 500 mg oral or IV dose decline in a polyphasic manner, with a terminal elimination half-life average of 68 hours.[16] More than 50% of azithromycin is eliminated through biliary secretion as unchanged drug.[17] Azithromycin is excreted in feces primarily as unchanged drug. The primary route of biotransformation involves N-demethylation of the desoamine sugar or at the 9a position on the macrolide ring. While short-term administration of azithromycin produces hepatic accumulation of the drug and increases azithromycin demethylase activity, current evidence indicates that hepatic cytochrome P-450 induction or inactivation via cytochrome-metabolite complex formation does not occur.[18] Approximately 4.5% of a dose is eliminated in urine as unchanged drug within 72 hours. Approximately 11% to 14% of an IV dose is eliminated in urine as unchanged drug within 24 hours.[19]

Resistance to macrolide antibiotics may be natural or acquired. In studies evaluating prevention of disseminated MAC disease, drug-resistant isolates were detected in 29% to 58% of individuals in whom disease developed while receiving clarithromycin and in 11% of those receiving azithromycin. MAC isolates resistant to azithromycin are resistant to clarithromycin. Erythromycin-resistant staphylococci and streptococci are also resistant to clarithromycin and azithromycin.[20]

Adverse Events/Toxicity

The most frequently reported adverse effect seen with azithromycin use is thrombophlebitis; this effect occurs with the injection form only. Other adverse effects of all dosage forms include acute interstitial nephritis, allergic reactions, pseudomembranous colitis, GI disturbances, dizziness, and headache.[21]

Drug and Food Interactions

When azithromycin is administered in capsule form, food decreases maximum concentration (Cmax) values by approximately 52% and area under the plasma concentration-time curve (AUC) values by approximately 43%. In tablet form, food increases Cmax values by 23% and 34% for the 250 mg and 600 mg tablets, respectively, and has no effect on AUC values. In oral suspension form, food increases the Cmax values by approximately 56% but has no effect on AUC values.[22]

Concurrent use of aluminum- and magnesium-containing antacids decreases the Cmax of azithromycin by approximately 24%, but has no effect on AUC. Oral azithromycin should be administered at least 1 hour before or 2 hours after aluminum- and magnesium-containing antacids.[23]

Contraindications

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotics.[24]

Azithromycin should be administered to patients with hepatic function impairment with caution

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Contraindications (cont.)

because biliary excretion is the major route of elimination for azithromycin.[25]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[26]

Intravenous.[27]

Dosage Form: Film-coated tablets containing anhydrous azithromycin 250, 500, or 600 mg.[28]

Oral suspension containing 100 or 200 mg of anhydrous azithromycin per 5 ml, or 1 g anhydrous azithromycin per single dose packet.[29]

Lyophilized azithromycin in vacuum 10 ml vials containing the equivalent of 500 mg azithromycin.[30]

Storage: Tablets should be stored below 30 C (86 F). Dry powder for reconstitution into azithromycin oral suspension should be stored below 30 C (86 F).[31]

Chemistry

CAS Name: 1-Oxa-6-azacyclopentadecan-15-one, 13-((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-((3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl)oxy)-,[32]

CAS Number: 83905-01-5[33]

Molecular formula: C38-H72-N2-O12[34]

C60.94%, H9.69%, N3.74%, O25.63%[35]

Molecular weight: 748.98[36]

Melting point: 113 to 115 C[37]

Physical Description: White, crystalline powder (dihydrate form).[38]

Stability: After reconstitution with sterile water, azithromycin solution for injection is stable for 24 hours when stored below 30 C (86 F) or for 7 days if stored under refrigeration at 5 C (41 F).[39]

Other Names

Sumamed[40]

Arithromicina[41]

Further Reading

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Manufacturer Information

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Azithromycin

Manufacturer Information (cont.)

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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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