Drug Update NEWER MACROLIDES

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MJAFI 1996; 52 : 269-270

Macrolides are antibiotics that have a molecular structure of 12-16 membered lactone ring to which one or more sugars are attached. Erythromycin (EM), introduced in 1952, remained a useful oral drug for some Gram-positive and a limited number of Gram-negative infections. It has significant gastrointestinal toxicity, a short half-life, and a limited antibacterial spectrum. These limitations and its recent application in legionella and helicobacter infections stimulated search for newer and improved macrolides [1]. Clarithromycin (CL), azithromycin (AZ), roxithromycin and dithromycin are the newer semi-synthetic macrolides. AZ is, strictly speaking, an azalide.

Mechanism of Action and Resistance

Like EM, they are bacteriostatic but exhibit bactericidal activity against some organisms in vitro at low pH and inhibit bacterial protein synthesis by causing the peptide chain to dissociate prematurely from the 50S ribosomal subunit during translocation [2]. Drug resistance is by plasmid mediated alteration of binding site at the bacterial ribosomes. Cross-resistance is exhibited by Gram-positive organisms for all macrolides by MLS_B phenotype.

Clinical Pharmacology

Macrolides are acid-stable and well-absorbed orally. Absorption of AZ is decreased by food and antacids. They diffuse well in body tissues except CSF and synovial fluids. AZ is concentrated in tissues and has therapeutic efficacy despite low plasma levels. Half-life of CL and AZ is 3-4 hours and 8-16 hours respectively. CL is metabolized in the liver to a more effective metabolite. Its half life is increased if creatinine clearance is less than 30

mL/min and requires dose adjustment. No dose reduction is recommended in hepatic disease. AZ is considered safe in renal and hepatic disease. Newer macrolides cause less abdominal upset than EM. Headache, dizziness and altered liver functions can occur occasionally. Haematological abnormalities and reversible hearing loss with high doses is reported in HIV positive patients [3]. CL has less significant drug interactions with theophylline, warfarin, digoxin, chlorpromazine, and terfenadine than EM. AZ does not inhibit the hepatic cytochrome p-450 system and is not reported to cause above drug interactions [4,5]. Safety in pregnancy and neonates is not established and caution is required for use in nursing mothers as the drugs are secreted in milk.

Clinical Use

CL 250 mg twice a day for 7-14 days and AZ 500 mg on first day followed by 250 mg for the next 4 days as a single dose are effective in exacerbation of COPD due to *H. influenzae*, *S. pneumoniae* and *Moraxella*; sinusitis and pneumonia due to *S. pneumoniae*, *H. influenzae*, *Legionella*, *Mycoplasma* and *Chlamydia*; streptococcal pharyngitis and soft tissue infections; sexually transmitted diseases (due to *H. ducreyi*, *T. pallidum*, *Ureaplasma*); *H. pylori*, *C. jejuni* infections and Lyme disease. Convenient dosing, better compliance, lesser gastrointestinal adverse effects are the advantages over EM, but the cost of therapy is more [5]. Their more important role is likely to be in treatment of bacillary angiomatosis, toxoplasmosis, and cryptosporidial infection, particularly in HIV positive patients. CL is a useful drug for multibacillary leprosy and atypical mycobacterial infection. AZ holds promise as a single-dose therapy for chlamydial and gonococcal genital tract

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infection.

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