Azithromycin and Clarithromycin

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Macrolide antibiotics have been available and used clinically since 1952. This class of antibiotics originated from a Philippine soil sample. They are called "macrolides" because these drugs possess a large cyclic lactone nucleus. Erythromycin, the most widely used agent in this class, is well established as treatment for a variety of respiratory and cutaneous infections, especially in children. Erythromycin is probably one of the best tolerated and safest antibiotic for use in children. Unfortunately, erythromycin has certain characteristics that are less than ideal including lack of resistance to acid hydrolysis, relatively low bioavailability, propensity to produce gastrointestinal side effects, a relatively narrow spectrum of activity, and a tendency to select resistant organisms, especially gram-positive cocci, in certain clinical settings. Lack of activity against Hemophilus influenzae, type b, limits its use in many settings in which children have not received HIB immunization.

Recently, there has been a resurgence of interest in this class of antibiotics, partially as a result of the emergence of new intracellular pathogens including Legionella, Chlamydia, and Campylobacter species. New compounds have been developed that appear to overcome some of the problems of the older macrolides. A number of chemical modifications resulted in the synthesis of a number of new 14-member and 16-member macrolides, which are similar in antimicrobial activity to erythromycin but are acid-stable. Agents in this group include clarithromycin, roxithromycin, and dirithromycin. A unique 15-member ring compound, azithromycin, also has been introduced.1

Clarithromycin and azithromycin recently have been approved by the US Food and Drug Administration (FDA) for the treatment of respiratory skin and skin structure infections in adults. Neither drug has, as continued on page 162.
TABLE 1

In Vitro Activity of Azithromycin, Clarithromycin, and Erythromycin Against Selected Microorganisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>Azithromycin</th>
<th>Clarithromycin</th>
<th>Erythromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pyogenes</td>
<td>0.12</td>
<td>0.03</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>0.12</td>
<td>0.015</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>0.12</td>
<td>0.03</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>0.125</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>0.06</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Hemophilus influenzae</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td>0.06</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Legionella spp</td>
<td>2</td>
<td>0.25</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>0.25</td>
<td>0.5</td>
<td>≤0.01</td>
<td></td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>0.25</td>
<td>0.008</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>0.25</td>
<td>0.03</td>
<td>0.125</td>
<td></td>
</tr>
</tbody>
</table>

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yet, been approved for use in children, but this is expected to happen shortly. Both drugs offer advantages over erythromycin in terms of pharmacokinetics, tolerance, and antimicrobial coverage.

AZITHROMYCIN

Chemical Properties

Azithromycin differs from erythromycin by the incorporation of a methyl-substituted nitrogen atom into position 9a of the 14-member macrolide ring, giving it a 15-member macrolide with much more acid stability than erythromycin. For this reason, azithromycin is classified as an azalide, rather than as a macrolide antibiotic because macrolides have only carbon and oxygen-containing rings. The insertion of this nitrogen into the ring significantly alters the chemical, microbiologic, and pharmacokinetic properties of the drug. The resulting 15-member ring is dibasic, which permits penetration into phagocytic and other cells.2

Antibacterial Activity

Overall, the antibacterial spectrum of azithromycin is very similar to erythromycin. However, azithromycin is twofold to fourfold less active than erythromycin against staphylococci and streptococci, including Streptococcus pneumoniae3 (Table 1). Erythromycin-resistant staphylococci and streptococci are also resistant to azithromycin. None of the azalide or macrolide antibiotics are active against methicillin-resistant staphylococci. Azithromycin is more active than erythromycin and clarithromycin against H influenzae. Azithromycin has similar activity to erythromycin against Moraxella catarrhalis, Chlamydia trachomatis, Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, Borrelia burgdorferi, Bordetella pertussis, and Neisseria gonorrhoeae.5-5 Azithromycin is more active against aerobic or facultative gram-negative bacilli than either erythromycin or clarithromycin, but this activity is unlikely to be clinically significant, except possibly for treatment of Salmonella infections. Azithromycin also has moderate activity against some atypical mycobacteria, specifically Mycobacterium chelonae. The drug is active against Cryptosporidium in vitro and has been demonstrated to kill cysts of Toxoplasma gondii.7,8

Pharmacokinetics

Azithromycin acts by binding to the 50s ribosomal subunits of susceptible microorganisms and interfering with microbial protein synthesis. After oral dosing, azithromycin is rapidly absorbed and distributed widely throughout the body. The bioavailability after an oral dose is approximately 37%. The presence of food in the stomach and small intestine decreases the bioavailability of azithromycin; each dose should be taken at least 1 hour before or 2 hours after a meal. Serum concentrations after a single 500-mg dose are only 0.4 mg/L at peak, but the drug accumulates inside cells, particularly macrophages and polymorphonuclear leukocytes; tissue levels are much higher. Elimination of azithromycin from serum following a single oral dose is polyphasic and gradual with a long terminal elimination half-life of 68 hours.2 Only 6% of an oral dose can be recovered from the urine; elimination in the bile, metabolism in the liver, and possibly transintestinal elimination account for most of its clearance. The elimination of azithromycin from tissues is much more gradual than elimination from serum. The elimination half-life in tonsillar, urologic, pulmonary, gastric, and gynecologic tissues has been estimated between 56 and 76 hours.2

The sustained tissue levels achieved by azithromycin are unique in many ways and allow for less frequent dosing. Azithromycin appears to be concen-
treated 400- to 1200-fold in phagocytes, which are transported to the site of infection by chemotaxis. Concentration of phagocytes may be especially important for the treatment of infections due to intracellular bacteria such as L pneumophila.

Adverse Reaction Rates
The majority of side effects due to azithromycin appear to be gastrointestinal and are reversible on discontinuation of the drug. Overall, azithromycin appears to be better tolerated than erythromycin with significantly fewer gastrointestinal side effects. The gastrointestinal side effects associated with erythromycin are dose-related abdominal cramps, nausea, vomiting and diarrhea, and appear to be the result of a gastrointestinal motility-stimulating effect of the 14-membered ring macrolides.

Overall, side effects have been reported in 12% of patients receiving azithromycin compared with 14% receiving a comparative drug, usually erythromycin, doxycycline, or a beta-lactam. Ninety-three percent of these side effects have been classified as mild or moderate with less than 1% of patients withdrawing from treatment because of the side effects. Serious adverse effects including anaphylaxis have been rare; to date, only three cases have been reported with more than 2 million courses of azithromycin administered. Transient elevations in transaminase levels have been reported in less than 2% of patients. The only potentially significant pharmacokinetic interaction appears to be with the antihistamine terfenadine (Seldane, Marion Merrell Dow, Kansas City, Missouri). Co-administration of erythromycin and terfenadine may result in increasing terfenadine levels leading to cardiac arrhythmias.

CLARITHROMYCIN
Chemical Properties
Clarithromycin differs from erythromycin by methoxy-substitution at the 6 position of the macrolide ring. This single change in the 14-membered macrolide ring of the erythromycin molecule prevents the rearrangement of the ring, which occurs readily in acid and is at least partly responsible for the gastrointestinal reactions observed with erythromycin. The metabolic derivative, 14-OH clarithromycin, has antimicrobial activity similar to erythromycin and may act synergistically with it.

Antibacterial Activity
Clarithromycin is twofold to fourfold more active than erythromycin against most staphylococci and streptococci, including pneumococci. However, as seen with azithromycin, staphylococci and streptococci that are resistant to erythromycin are also resistant to clarithromycin. Clarithromycin, like erythromycin, has moderate activity against H influenzae, type b, and N gonorrhoeae. The activity against M catarrhalis is similar to that of erythromycin. Clarithromycin is more active in vitro than erythromycin against C trachomatis, C pneumoniae, M pneumoniae, L pneumophila, B burgdorferi, and B pertussis (Table 1). Clarithromycin also has activity against atypical mycobacteria, especially Mycobacterium avium intracellulare. Clarithromycin inhibits M avium at concentrations achievable in lung tissue or in macrophages and also has inhibitory activity against M chelonii and some subspecies of Mycobacterium fortuitum. It is approximately tenfold more active against these organisms than azithromycin.

Pharmacokinetics
Clarithromycin is absorbed after an oral dose from the gastrointestinal tract with a bioavailability of 55%. Absorption is not decreased by the presence of food as it is with azithromycin. Peak serum concentrations are achieved at approximately 1 hour after a 250-mg dose and 2 hours after a 500-mg dose; peak serum concentrations are 11.5 mg/L and 23 mg/L, respectively. The elimination half-life of clarithromycin and the its 14-OH derivative are 5 and 7 hours, respectively. Clarithromycin is metabolized in the liver, and 30% to 40% of an administered dose can be recovered in the urine; patients with a creatinine clearance of ≤30 mL/minute may require a decrease in dosage. The drug also penetrates well in both tissues and cells, including macrophages and polymorphonuclear leukocytes. Clarithromycin is 65% to 70% bound to plasma proteins. Given concurrently, it may increase serum concentrations of theophylline or terfenadine.

Adverse Reaction Rates
Like azithromycin, clarithromycin is well-tolerated and does not appear to cause the high incidence of nausea and other gastrointestinal side effects that occur with erythromycin. Nausea, diarrhea, and abdominal pain have been reported in 3% of patients in clinical trials. Headache and dizziness occur rarely. Reversible loss has been reported with high doses of clarithromycin used to treat M avium infections.

EFFICACY TRIALS
Very few open or comparative studies of the efficacy of azithromycin or clarithromycin have been

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TABLE 2

Dosage and Cost of Azithromycin, Clarithromycin, and Comparative Antimicrobials

<table>
<thead>
<tr>
<th>Drug (Trade Name)</th>
<th>Dosage (Adults)</th>
<th>Wholesale Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>500 mg 1st day, then 250 mg for 4 days</td>
<td>$48.78</td>
</tr>
<tr>
<td>(Zithromax)</td>
<td>1 g once (for genital chlamydial infection)</td>
<td>32.52</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>250 to 500 mg twice daily for 7 days</td>
<td>35.00</td>
</tr>
<tr>
<td>(Biaxin)</td>
<td>250 mg four times daily for 7 days</td>
<td>6.93</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>100 mg twice daily for 7 days</td>
<td>5.39</td>
</tr>
<tr>
<td>(generic)</td>
<td>(generic)</td>
<td></td>
</tr>
</tbody>
</table>

Toxoplasma encephalitis and cryptosporidiosis. Azithromycin is also being evaluated for the treatment of Lyme disease.

Clarithromycin

Clarithromycin has been evaluated in several multicenter treatment trials, mostly in adults but several pediatric studies are in progress. Clarithromycin (250 mg to 500 mg administered orally twice daily for 10 days) was similar in effectiveness to penicillin V in treating pharyngitis, amoxicillin in treating sinusitis, and erythromycin in treating community-acquired pneumonia in adults. In the pneumonia studies, the efficacy of clarithromycin against atypical organisms was difficult to assess because very few patients were culture positive for M pneumoniae, and the diagnosis of C pneumoniae was based on serological evidence only.

CLINICAL APPLICATION

Both azithromycin and clarithromycin are well-tolerated, expensive alternatives to erythromycin for the treatment of streptococcal pharyngitis, community-acquired pneumonia and other respiratory infections, skin and soft-tissue infections, and acute sinusitis in adults. Neither drug is approved as yet for use in individuals less than 18 years of age; however, it is anticipated that both drugs will be approved for pediatric indications in 1993. Limited, unpublished data suggest that azithromycin and clarithromycin are well-tolerated and safe in children. Neither drug is approved for use in pregnant women.

Both drugs may have greater utility in the treatment of infections due to intracellular pathogens rather than substitutes for beta-lactam antibiotics for common pyogens. The prolonged elimination half-life and high tissue levels achieved with azithromycin hold the promise of once-a-day dosing and shorter courses of therapy than currently available antimicrobial agents allow. Azithromycin clearly has significant advantages over doxycycline or erythromycin for the treatment of uncomplicated genital chlamydial infection in adolescents. As the first single-dose treatment available for these infections, it should have an impact on compliance rates and ultimately control of this sexually transmitted infection.

Azithromycin and clarithromycin should be as effective or more effective than erythromycin for the treatment of respiratory infections due to M pneumoniae, C pneumoniae, and Legionella. Comparative trials in adults and children, using pre- and posttreatment cultures, are just getting underway.

Clarithromycin looks especially promising for the treatment of disseminated M avium infections in patients with AIDS. Studies are also underway examining azithromycin for the treatment of acute and relapsed infections.

published. Many are only available in abstract form, and few have included children.

Azithromycin

Azithromycin administered orally for 5 days at a single dose of 500 mg, then reduced to 250 mg for 4 days was similar in effectiveness to 10 days of penicillin V for the treatment of streptococcal pharyngitis in adults. Other randomized multicenter studies also found azithromycin to be similar in efficacy to amoxicillin for sinusitis, cefaclor for community-acquired pneumonia, and cephalaxin for skin infections in adults. The microbiologic efficacy of azithromycin could not be assessed in the treatment of atypical pneumonia because cultures for C pneumoniae were not performed, and very few patients had culture-confirmed M pneumoniae infection.

Perhaps the most exciting application for azithromycin is as a single-dose treatment for uncomplicated genital chlamydial infection. Two randomized multicenter studies, one in adults and one in adolescents, found that a single 1-g oral dose of azithromycin was equivalent to standard treatment with 7 days of doxycycline in eradicating C trachomatis from the urethra or the cervix. However, the 1-g oral dose has not been sufficiently effective to recommend its use for the treatment of uncomplicated gonorrhea.

Azithromycin was effective against gonorrhea at a 2-g dose but was associated with an unacceptable high rate of gastrointestinal side effects. Studies are underway in children comparing a 5-day course of azithromycin to a 10-day course of amoxicillin for the treatment of otitis media.

Azithromycin is currently being evaluated in some difficult-to-treat infections associated with acquired immunodeficiency syndrome (AIDS), including...
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toxoplasmosis and cryptosporidiosis in individuals with AIDS. Both drugs are currently being evaluated for the treatment of early and late Lyme disease. Because azithromycin has proven effective in animal studies of Salmonella infection, its effectiveness for the treatment of typhoid fever in humans is being tested.

Dose and Cost

Azithromycin is available as 250-mg capsules. The standard course for most respiratory infections in adults is 500 mg once on day one, followed by 250 mg per day for 4 days. The recommended dose of clarithromycin is 250 to 500 mg twice daily for 7 to 10 days. Pediatric suspensions are not as yet available. As shown in Table 2, the wholesale cost of azithromycin and clarithromycin range from $32 to almost $50 for a course of treatment. In contrast, the average cost of an erythromycin treatment regimen is approximately $7. The average cost of 7 days of doxycycline treatment for genital chlamydial infection is $5.39.2,25

Potential concerns about the use of these agents include the development of widespread resistance among streptococcal and staphylococcal species, as has occurred with the use of erythromycin. Controlled trials will help to establish the role of azithromycin and clarithromycin in difficult-to-treat infections that occur in immunocompromised patients and in infections caused by atypical pathogens occurring in normal hosts. Their greater gastrointestinal tolerance and broader antimicrobial spectrum may make these drugs suitable alternatives to many currently available drugs for common outpatient respiratory infections. However, cost, convenience, compliance, and tolerance must all be considered in the decision to use these drugs.

REFERENCES