Clinical Pharmacology of Antibiotics

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Azithromycin and Clarithromycin: Overview and Comparison With Erythromycin

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Macrolides currently account for 10% to 15% of the worldwide oral antibiotic market.' Erythromycin, the first macrolide antibiotic, was discovered in 1952 from a strain of Streptomyces ***erythreus*** obtained from soil samples in the Phillipines.[2,3] Originally, erythromycin was marketed as an alternative to penicillin because of its activity against gram-positive organisms such as staphylococci, pneumococci, and streptococci. Subsequently, its clinical use broadened to include species of *Mycoplasma, Legionella, Campylobacter,* and *Chlamydia.* Although several other macrolides have been marketed in countries other than the United States, they have failed to achieve erythromycin's widespread use. Unfortunately, erythromycin suffers from several drawbacks, including gastrointestinal side effects, a short serum elimination half-life, and only borderline in vitro activity against common gram-negative respiratory pathogens such as *Haemophilus influenzae.*[4]

Several new macrolides, with improved pharmocodynamic and therapeutic profiles, now exist in various developmental stages. The Food and Drug Administration (FDA) recently approved two of these drugs, azithromycin and clarithromycin, for marketing. This review focuses on these agents, comparing their pharmacokinetic properties and clinical indications with those of erythromycin.

STRUCTURE AND MODE OF ACTION

Each member of the macrolide class of antibiotics contains a macrocyclic lactone ring substituted by one or more sugar moieties. The erythromycin base consists of a 14-membered ring attached to the amino sugar, desosamine, and the neutral sugar, cladinose (Figure). As erythromycin passes through the gastrointestinal tract, it rapidly undergoes acid-catalyzed degradation.[5,6] The new macrolides are erythromycin analogues that resist acid-catalyzed cyclization by modifying the erythromycin base at the functional groups that facilitate the degradation reaction; these include the ketone at C-9, the hydroxyl at C-6, the proton at C-8, and the diol moieties at C-11 and C-12.[7] Several 14-, 15-, and l&membered macrolides were developed using this approach. The l&membered macrolides, josamycin and spiramycin, are in use in Europe.[8] Roxithromycin, an oxime derivative, dirithromycin, and flurithromycin are 14-membered macrolide antibiotics in various stages of development.[4,9-11] In clarithromycin (6-O-methylerythromycin), a methoxy group is substituted for the C-6 hydroxyl group, yielding an acid-stable analogue (Figure).[12] Azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) is produced via rearrangement of the ketone at position C-9 (Figure). Azithromycin, often termed an azalide, differs structurally from the other macrolides by incorporating nitrogen into the lactone ring structure, producing a 15-membered derivative containing a tertiary amino group.[13]

Erythromycin and the other macrolide antibiotics bind to the 50S ribosomal subunit of susceptible organisms, inhibiting the translocation reaction during protein synthesis.[14,15] Erythromycin stimulates the dissociation of peptidyl-tRNA during translocation.[16] Azithromycin acts similarly to erythromycin, because both compete for the same binding site on the 50S ribosome and inhibit mRNA-directed protein synthesis.[17] The primary mechanism of macrolide resistance is the synthesis of ribosomal RNA methy-

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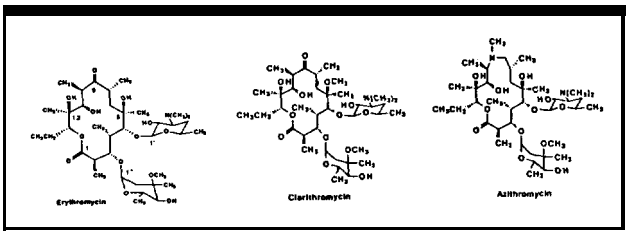

FIGURE. Structures of erythromycin, clarithromycin, and azithromycin (adapted from reference 7).

lases that methylate an adenine residue in the 23S ribosomal RNA of the 50S subunit, leading to macrolide lincosamide-streptogamin B (MLS_B) co-resistance.[18] MLS_B resistance can be plasmid-based or chromosomally located.[19] Plasmids encode for methylases in ***Staphylococcus*** aureus, Streptococcus species, and Bacteroides species; resistance determinants occur rarely on chromosomes in Streptococcus ***pneumoniae.*** Although methylase genes have been characterized in gram-negative organisms, many gram-negative bacteria are inherently resistant to the macrolides on the basis of an impermeable outer membrane alone.[19] In addition, MLS_B resistance may be inducible or expressed constitutively. Both the 14-membered macrolides, including erythromycin and clarithromycin, and the 15-membered azithromycin induce expression of RNA methylases in susceptible bacteria.[17,20] Other mechanisms of macrolide resistance occur infrequently. Erythromycin esterases found in isolates of ***Escherichia coli*** hydrolyze the lactone ring.[21] Another novel mechanism, described in ***S aureus*** and Staphylococcus epidermidis, confers resistance by altering antibiotic efflux.[18]

PHARMACOKINETICS

A major advantage offered by the new macrolides, compared with erythromycin, is their markedly improved pharmacokinetic properties. Longer half-lives and unique tissue penetration allow once- or twice-daily dosing of these compounds. Oral absorption is adequate for all of the macrolides. Erythromycin's oral bioavailability is variable, depending on the preparation studied. The oral bioavailabilities of clarithromycin and azithromycin are 55% and 37%, respectively.[22,23] If clarithromycin is administered immediately after a meal, however, its bioavailability increases by 25%. Absorption of azithromycin is reduced up to 50% in the presence of food, and peak serum concentrations, but not total absorption, are reduced by concomitant administration of aluminum- and magnesium-containing antacids.[24] Both erythromycin and clarithromycin inhibit theophylline and carbamazepine metabolism; carbamazepine and theophylline concentrations were not altered by a five-day course of azithromycin.[24,25]

TABLE 1
COMPARATIVE SINGLE DOSE PHARMACOKINETICSOF MACROLIDE ANTIBIOTICS IN HUMAN VOLUNTEERS

Drug†	C_{max} (μg/ml)	T_{max} (hours)	$T_{.5}$ (hours)	AUC** (hours x μg/ml)
Clarithromycin	2.41	2	4.9	18.9
14-OH clarithromycin	0.66	—	7.2	6.0
Azithromycin	0.40	2	41‡	3.4
Erythromycin	0.3-2.0	4	1.4	—

* Adapted from references 22,23,26,27.
† Unless indicated, drug was administered orally at a dose of 500 mg.
‡ T_5 after a 500 mg IV dose.
.* Area under the concentration curve.

The single-dose pharmacokinetics of erythromycin, clarithromycin, and azithromycin in human volunteers are shown in Table 1.[22,23,26,27] Clarithromycin, unlike the other macrolides, is metabolized to a microbiologically active form, 14-hydroxyclarithromycin. Azithromycin remains largely unchanged within the body, with minor metabolism into several inactive forms occurring via demethylation. Clarithromycin displays a nonlinear increase in peak serum concentrations as the dose increases; a decrease in metabolite formation with an increase in urinary excretion of the parent compound suggests that the metabolism of clarithromycin to the 14hydroxy derivative is saturable, accounting for these disproportionate pharmacokinetic properties.[28]

Following administration, the macrolide antibiotics accumulate within the extravascular compartment. The volume of distribution of azithromycin is 23 l/kg compared with 1.5 l/kg for erythromycin; no published value for the volume of distribution of clarithromycin is available.29 Both erythromycin and azithromycin concentrate readily within polymorphonuclear leukocytes (PMNs) and macrophages. After two hours of incubation, azithromycin achieved an intracellular to extracellular (I/E) ratio (i.e., intracellular concentration of drug/extracellular concentration of drug) of 79 in human PMNs versus 16 for erythromycin; azithromycin continues to accumulate withii human PMNs for up to 24 hours, reaching an I/E ratio of 226, whereas erythromycin uptake was complete at 30 minutes.[30] Human fibroblasts also concentrate azithromycin, accumulating 21-fold more azithromycin at 72 hours of incubation than erythromycin.[31] In another study that examined the in vitro uptake of radiolabelled antibiotic within human PMNs, erythromycin and clarithromycin demonstrated similar intracellular concentrations, with I/E ratios of 7.3 and 9.2, respectively.[32]

TABLE 2
ANTIBIOTIC CONCENTRATIONS OF MACROLIDE ANTIBIOTICS IN SERUM AND TISSUES

Drug	Dose (mg)	Concentrations† Serum (μg/ml)	Tonsil (mg/kg)	Nasal mucosa (mg/kg)	Lung (mg/kg)
Azithromycin	500 × 1 dose	0.4	1.0 - 9.0‡	1.0 - 9.0‡	1.0 - 9.0‡
Clarithromycin	250 bid x 3 days	1.8 ± 2.2	6.7 ± 2.8	8.3 ± 2.6	—
Clarithromycin	500 bid x 3 days	2.8 2 0.5	—	—	17.5 ± 3.3

* Adapted from references 22,33.
† Values for clarithromycin expressed as mean ± standard deviation.
‡ Range of values obtained from 12-72 hours after a single dose.

Both clarithromycin and azithromycin achieve high tissue concentrations in humans (Table 2). Depending on the tissue site measured, clarithromycin concentrations in tissues are in the range of 2 to 20 times those of serum; azithromycin concentrations in tissues usually exceed serum concentrations by 10- to 100-fold.[22,28] After a single 500 mg dose of azithromycin to healthy volunteers, the tissue concentrations were between 1 and 9 mg/kg at 12 to 72 hours. Four days after a single 500 mg dose, tissue concentrations were as follows: prostate, 0.8-2.3 mg/kg; pulmonary tissue, 2.3-8.1 mg/kg; gynecologic tissue, 0.27-1.48 mg/kg; and tonsillar tissue, 0.26-2.0 mg/kg.[29] Serum and tissue concentrations following administration of 250 mg or 500 mg of clarithromycin twice daily for three days are shown in Table 2.[22,33]

Elimination of azithromycin occurs in a polyphasic pattern after a single 500 mg dose.[22] Flux into the extravascular space produces an initial rapid elimination phase, while the slow terminal elimination phase occurs with egress of drug from the tissue compartment into the intravascular space. The terminal serum half-life of azithromycin exceeds 40 hours when measured between 24 and 72 hours after a 500 mg dose; the tissue half-lie is between 24 and 72 hours. Urinary elimination of unchanged drug is miniial, measuring approximately 5% at three days after administration.[25] The serum protein binding of azithromycin is concentration-dependent, declining from 50% to 12% at concentrations of 0.05 μg/ml and 0.5 μg/ml, respectively.[22] Data regarding the serum protein binding of clarithromycin are limited. Clarithromycin is metabolized to the active 14hydroxy form, and urinary excretion of unchanged drug or active metabolite is 30% to 40% of an oral dose.28 The remainder of the drug is excreted through the bile and into the feces. The terminal half-life of clarithromycin varies with dose in a nonlinear manner, with values of 4.39 hours after a single 250 mg dose and 11.27 hours after a 1200 mg dose.[34]

No data are available detailing the effects of hepatic or renal impairment on azithromycin pharmacokinetics. Clarithromycin requires dose adjustment with moderate-to-severe renal impairment. In patients with a creatinine clearance below 30 ml/minute, a 500 mg twice daily schedule of clarithromycin should be adjusted to a 500 mg loading dose, followed by 250 mg twice daily; a 250 mg twice daily schedule should be adjusted to 250 mg once daily.[28] No dosage adjustment of clarithroymcin is required for patients with hepatic impairment and normal renal function.

IN VITRO SPECTRUM OF ACTMTY

The National Committee for Clinical Laboratory Standards sets the breakpoint for susceptibility of an organism to erythromycin at a minimal inhibitory concentration (MIC) ≤0.5 μg/ml, while ≥8 μg/ml is considered resistant. In contrast, breakpoints for susceptibility and resistance of ≤2 μg/ml and ≥8 kg/ml, respectively, are proposed for clarithromycin; these breakpoints are based on achievable serum concentrations.[35] Azithromycin, on the other hand, rapidly accumulates within tissues at high concentrations and has a long tissue half-lie, despite low peak serum concentrations. A susceptible MIC breakpoint of ≤0.12 μg/ml would be applied to azithromycin if based on serum concentrations alone; however, an MIC breakpoint for susceptibility of ≤2 μg/ml and ≥8 μg/ml for resistance has been proposed, based on expected tissue concentrations.[36] Environmental factors, such as pH and the presence of serum may affect the MIC determinations of clarithromycin and azithromycin. In general, MICs increase for all the macrolides as pH decreases; whereas potency improves in an alkaline environment.[37,38] The addition of serum produces a moderate-to-significant improvement in macrolide in vitro activity.[38,39]

Table 3 lists the comparative in vitro data for

TABLE 3
COMPARATIVE IN VITRO ACTIVITIES OF MACROLIDE ANTIBIOTICS*

Organism	MIC_{90} (μg/ml)		
	Erythromycin	Azithromycin	Clarithromycin
B fragilis	4.0	2.0	2.0
Other ***Bacteroides*** species	4.0	1.0	2.0
B pertussis	0.03	0.06	0.03
C jejuni	1.0	0.12	2.0
C perfringens	1.0	0.25	0.5
Corynebacterium species	16	128	4.0
En*terococcus* species†	0.5	2.0	0.5
H influenzae	4.0	0.5	8.0
L pneumophila	2.0	2.0	0.25
L monocytogenes	0.5	2.0	0.25
M catarrhalis	0.25	0.06	0.25
N gonorrhoeae	0.5	0.06	0.5
N *meningitidis*	4.0	2.0	1.0
Peptococcus-Peptostreptococcus	4.0	2.0	4.0
P *acnes*	0.03	0.03	0.03
Methicillin-susceptible S *aureus*†	0.12	0.12	0.06
Methicillin-resistant S aureus	>128	>128	>128
S *epidermidis*†	***8.0***	16	4.0
S agalactiae	0.06	0.12	0.06
S pneumoniae	0.03	0.12	0.015
S pyogenes	0.03	0.12	0.015
Streptococcal species ***viridans*** group	0.06	0.12	0.03

* Adapted from references 37,38.
† Values expressed as MIC_{50};MIC_{90}>128.

erythromycin, clarithromycin, and azithromycin against gram-positive and gram-negative organisms.[37,38] Against staphylococcal and streptococcal species, azithromycin is 2- to 4-fold less active in vitro than erythromycin; in contrast, the MIC_{90} of clarithromycin for these organisms is equal to or 4-fold lower than that of erythromycin.[17,37,40,41] Erythromycin-resistant strains of streptococci and staphylococci display cross-resistance and are not inhibited by either clarithromycin or azithromycin. Most strains of methicillin-resistant S aureus are resistant to erythromycin and, consequently, azithromycin and clarithromycin. The macrolide antibiotics are bactericidal against susceptible strains of Streptococcus pyogenes and Streptococcus pneumoniae, but not against staphylococci or enterococci.[17,41-43] Azithromycin is bactericidal against *H influenzae*, demonstrating MIC_{90} values 8 to 16-fold lower than both erythromycin and clarithromycin. However, the major clarithromycin metabolite, 14-hydroxyclarithromycin, is up to 2-fold more potent against *H influenzae* than the parent compound in vitro.[38,44] Standard in vitro susceptibility testing, which ignores this active metabolite, may underestimate the potency of clarithromycin. In addition, the combination of clarithromycin and its 14-hydroxy derivative is synergistic and bactericidal against *H influenzae* in vitro.[45,46]

In addition to *S pneumoniae* and ***H influenzae,*** the new macrolides demonstrate improved in vitro activity against several other respiratory pathogens. Azithromycin is the most active in vitro against *Moraxella catarrhalis* (Table 3). MIC_{90}s for *Mycoplasma pneumoniae* are reported as 0.008 kg/ml, ≤0.001 μg/ml, and ≤0.03 μg/ml for erythromycin,[47] azithromycin,[47] and clarithromycin,[48] respectively. Clarithromycin is 4- to 8-fold more active in vitro against *Chlamydia pneumoniae,* with an MIC_{90} of 0.007-0.03 μg/ml versus 0.06 μg/ml for erythromycin and 0.5 μg/ml for azithromycin.[49-51] Against *Legionella* isolates, clarithromycin is &fold more potent than erythromycin [38,43,52]

Azithromycin, unlike the other macrolides, is active in vitro against many gram-negative aerobes, including E *coli* (MIC_{90} of 1.0-16.0 kg/ml), *Shigella* species (MIC, of 1.0-8.0 kg/ml), Salmonella species (MIC, of 4.0-8.0 kg/ml), and *Yersinia enterocolitica*

(MIC,, of 3.0-8.0 μg/ml).[17,40,53,54] The MIC_{90}s of erythromycin and clarithromycin for these pathogens are all >128 μg/ml.[55] The MIC_{90}s against *Pasteurella multocida* were reported as 2.0 μg/ml for clarithromycin, 2.0-4.0 μg/ml for erythromycin, and 0.10 μg/ml for azithromycin.[17,41]

Azithromycin and clarithromycin are also effective in vitro against many of the etiologic agents of sexually transmitted diseases. Azithromycin is the most active in vitro against *Neisseria* gonorrhoeae. The MIC_{90}s against Haemophilus ducreyi are 0.015 μg/ml for clarithromycin and 0.03 μg/ml for erythromycin; azithromycin is up to 10-fold more active in vitro against *H* ducreyi, with an MIC_{90} of 0.004 μg/ml.[56,57] MIC_{90}s for Chlamydia *trachomatis* are 0.008 μg/ml, 0.128 μg/ml, and 0.25 μg/ml for clarithromycin,[58] erythromycin,[59] and azithromycin,[59] respectively. Although azithromycin may have some in vitro activity against *Treponema pallidum*, no data are available for clarithromycin.[60] Only azithromycin is active in vitro against Mycoplasma *hominis*, demonstrating an MIC_{90} of 4.0 μg/ml.[47,61] MIC_{90}s for *Ureaplasma urealyticum* are 1.0 kg/ml, 1.0 μg/ml, and 0.5 μg/ml for clarithromycin,[61] erythromycin,[47] and azithromycin,[47] respectively.

Against *Borrelia burgdorferi*, the etiologic agent of Lyme disease, the MIC_{90}s of clarithromycin and azithromycin (0.015 kg/ml) are slightly lower than those for erythromycin (0.06 μg/ml).[62] The new macrolides offer comparable in vitro activity against Toxoplasma gondii in both in vitro and animal model systems.[63-65] Azithromycin and clarithromycin also are active against atypical mycobacteria. *Mycobacterium chelonae* species are inhibited by clarithromycin (MIC_{90} 0.25 kg/ml) and azithromycin (MIC, 2.0-8.0 μg/ml).[66] The MIC_{90}s for clarithromycin against Mycobacterium avium complex (MAC) are in the range of 2 to 4 μg/ml.[67,68] The addition of ethambutol or rifampin to clarithromycin may be additive or synergistic, enhancing the killing of MAC within infected macrophages.[69,70] Despite a high MIC,, (64 kg/ml), azithromycin may prove effective in MAC infections because it accumulates within macrophages and tissues at concentrations above its MIC_{90}.[67,71] Mycobacterium tuberculosis is far less susceptible to clarithromycin ($MIC_{90} \geq 32$ μg/ml) and azithromycin (MIC_{90}>128 μg/ml) than are the atypical mycobacteria.[72,73]

CLINICAL USES

Upper Respiratory Tract Infections

The new macrolides compare favorably with established antibiotic regimens in the treatment of upper respiratory tract infections, including pharyngitis, sinusitis, and bronchitis. A five-day course of azithromycin (single 500 mg dose on day 1, followed by 250 mg on days 2 through 5) proved as effective as penicillin V (250 mg every 6 hours for 10 days) in the treatment of adult cases of S pyogenes pharyngitis.[74] Clinical cure or improvement occurred in 99% of patients in both groups, while bacteriologic eradication was seen in over 90% of cases. A ten-day course of either clarithromycin, given as 250 mg twice daily, or penicillin V, given as 500 mg four times daily, was equally effective in treating streptococcal pharyngitis in adolescents and adults; the clinical and bacteriologic success rates were above 90% for both treatment regimens.[75,76] Similar results were seen in children ages 1 to 12 years treated with clarithromycin, 7.5 mg/kg twice daily, versus penicillin V, 13.3 mg/kg three times daily, for ten days.[77,78]

Short-course treatment of sinusitis with azithromycin produces clinical and bacteriologic response rates that are comparable with those of amoxicillin and erythromycin. Once-daily azithromycin (500 mg on day 1, followed by 250 mg on days 2 through 5) and amoxicillin (500 mg three times daily for ten days) both yielded similar clinical (74%) and bacteriologic (100%) cure rates in patients with acute sinusitis confirmed by transantral aspiration; however, this trial documented only one case of *H influenzae* infection.[79] In another study of patients with sinusitis, *H influenzae* isolates, cultured from either high nasal swabs or aspiration specimens, were eradicated in 89% and 90% of cases treated with azithromycin and amoxicillin, respectively.[80] In separate trials, these investigators demonstrated that a five-day regimen of azithromycin was clinically and bacteriologically as effective as a ten-day course of either erythromycin or amoxicillin.[80] In a single-blind, randomized trial, 50 patients with acute maxillary sinusitis received either clarithromycin, 500 mg every 12 hours, or amoxicillin, 500 mg every eight hours, for 9 to 11 days.[81] The clinical response and pathogen eradication rate was approximately 90% in both groups. Although reported as a nonsignificant difference, 14 of 18 (78%) Haemophilus isolates in the clarithromycin-treated patients versus 19 of 21 (90%) Haemophilus isolates in those treated with amoxicillin were eradicated at the end of therapy.

Azithromycin and clarithromycin demonstrate comparable efficacy when matched against either erythromycin or a β-lactam antibiotic in the treatment of bronchitis. In one trial, 48 patients with acute bronchitis and four patients with pneumonia received azithromycin (500 mg on day 1, followed by 250 mg/day on days 2 through 5), and 54 patients with bronchitis and four patients with pneumonia received amoxicillin (500 mg)/clavulanic acid (125 mg) every eight hours, for ten days.[82] The clinical response rate was 9% in the azithromycin-treated group and 87% in

the amoxicillin/clavulanic acid-treated group; the bacteriologic eradication rates were 91% and 89%, respectively. In another study, 72 patients with acute bronchitis and 21 patients with pneumonia were treated with a five-day regimen of either azithromycin or erythromycin.[83] Clinical cure rates of 70% in the azithromycin group and 60% in the erythromycin group were reported along with bacterial eradication rates of 80% and 86%, respectively. Clinical efficacy was similar in both treatment groups, whether patients were diagnosed with pneumonia or bronchitis. The same investigators compared a five-day/five-dose regimen of azithromycin with a seven-day/21-dose amoxicillin regimen in patients with acute bronchitis, and observed combined cure and improvement rates of 96% and 92%, respectively.[83] Clarithromycin (250 mg twice daily for ten days) was also compared with ampicillin (250 mg four times daily) for the therapy of chronic bronchitis exacerbations, yielding clinical success rates of over 90% in both treatment groups.[84] In another study comparing these same two antibiotics in the treatment of chronic bronchitis, the clinical cure rate for clarithromycin was 96% versus 91% for ampicillin.[85] In many of the aforementioned trials, patients with resistant β-lactamase-producing strains of H inffuenzae, against which the macrolides but not the β-lactams were active, were excluded from evaluation. This might have biased the results by inflating the bacterial cure rates reported for the β-lactam antibiotics.

Pneumonia

The limited comparative trials of azithromycin for lower respiratory tract infections grouped patients with pneumonia and bronchitis together. In a randomized trial, 23 of 272 study patients had pneumonia and received either azithromycin (15 patients), 500 mg on day 1 followed by 250 mg on days 2 through 5, or cefaclor (eight patients), 500 mg three times a day for ten days; the study protocol excluded patients with resistant organisms from evaluation.[86] Clinical success rates were better than 90% for both groups. Bacterial eradication rates in patients diagnosed with pneumonia were 94% in the azithromycin group and 100% in the cefaclor group. However, the eradication of H *influenzae* was significantly better with azithromycin (94.5%) than with cefaclor (61.1%). In a previously discussed trial, patients with pneumonia or acute bronchitis received either azithromycin (250 mg every 12 hours on day 1, followed by 250 mg daily on days 2 through 5) or erythromycin (500 mg four times daily for seven to ten days); 21 of 93 patients in the azithromycin group and 21 of 87 in the erythromycin group had pneumonia.[83] Clinical cure of pneumonia was seen in 86% of azithromycin-treated patients versus 74% of those treated with erythromycin.

Several studies indicated that clarithromycin is equivalent to other macrolide antibiotics in the treatment of bacterial pneumonia. In a trial comparing clarithromycin (250 mg every 12 hours for 14 days) with roxithromycin, 76% of patients treated with clarithromycin achieved a clinical cure, including two patients with *Legionella* pneumophila, one with M pneumoniae, and one with Chfamydia *psittaci.*[87] In another study, 44 patients with pneumonia received erythromycin (500 mg four times daily for 14 days) and 64 received clarithromycin (250 mg twice daily for 14 days); the clinical success rates for clarithromycin (89%) and erythromycin (98%) were not significantly different.@ A review of several trials, which used a 250 mg dose of clarithromycin to treat lower respiratory tract infections, revealed that the drug eradicated susceptible H inffuenzae infections less rapidly than ampicillin or erythromycin.[28] However, clarithromycin, given as 500 mg twice daily, was clinically and bacteriologically as effective as either cefixime, cefuroxime axetil, or cefaclor in the therapy of lower respiratory tract infections due to H *influenzae,* indicating the superior efficacy of the high-dose clarithromycin regimen.[28] In the cases discussed above, S pneumoniae, S pyogenes, Haemophilus species, M catarrhalis, and S aureus comprised the majority of pathogens isolated. Clinical data on the atypical pneumonias due to *Mycoplasma, Legionella,* and ***Chlamydia*** species are difficult to gather and, therefore, limited. Because both clarithromycin and azithromycin concentrate within extravascular tissues as well as phagocytic cells, they are uniquely qualified to treat infections caused by these intracellular organisms. In one study, *M pneumoniae* was identified in 13% of patients presenting with community-acquired pneumonias; four of four patients in the clarithromycin-treated group and three of three patients in the erythromycin group achieved a clinical cure.[48] An open, randomized study comparing the efficacy of azithromycin (250 mg every 12 hours on day 1, followed by 250 mg/day on days 2 through 5) and erythromycin (500 mg four times daily for 10 days) in the treatment of atypical pneumonias due to M pneumoniae and ***C*** *psittaci,* revealed clinical success in all treated patients.[89]

Skin and Soft Tissue Infections

A five-day course of azithromycin was equivalent to both erythromycin and cephalexin in the management of acute bacterial infections of skin and soft tissues. In a recent report, patients received either azithromycin (500 mg on day 1, followed by 250 mg daily on days 2 through 5) or 500 mg of cephalexin twice daily for ten days.[90] Clinical success rates for both azithromycin (99%) and cephalexin (96%) were

comparable. However, 6.6% of the initial population was withdrawn from the study after isolation of azithromycin-resistant organisms (versus a 1.4% withdrawal rate for cephalexin resistance). Another trial comparing the efficacy of azithromycin and erythromycin in the treatment of skin and soft tissue infections by azithromycin-sensitive organisms revealed that clinical cure or improvement in patients randomized to azithromycin or erythromycin was 86% and 82%, respectively.[91] S aureus was the most frequent isolate, with overall bacterial eradication rates of 60% for azithromycin and 57% for erythromycin. Clarithromycin was equivalent to erythromycin and cefadroxil in the treatment of skin and skin-structure infections, with clinical success rates of 97% and bacteriological eradication rates of >90% for each antibiotic studied.[28]

Sexually Transmitted Diseases

Use of new macrolide derivatives in the treatment of sexually transmitted diseases has focused primarily on azithromycin. Azithromycin is highly active in vitro against *N* gonorrhoeae, C trachomatis, and U *urealyticum*. Azithromycin exhibits very high tissue concentrations and tissue half-lie, allowing markedly reduced treatment courses. Azithromycin, in three dosing regimens (1 g single dose; 500 mg every 12 hours for one day; 500 mg on day 1, followed by 250 mg daily on days 2 through 3), was compared with a standard seven-day course of doxycycline for the treatment of sexually transmitted C trachomatis and *N* gonorrhoeae infections.[92,93] Overall eradication rates of C trachomatis for all three azithromycin regimens and doxycycline were 96% and 98%, respectively; the single 1 g dose of azithromycin was as effective as the three-day regimen. *N* gonorrhoeae was eradicated in 92% of azithromycin recipients and 100% of those who received doxycycline. In another trial, both a single dose and three-day regimen of azithromycin was compared with a standard course of doxycycline for the treatment of cervicitis caused by *N* gonorrhoeae or C trachomatis; all patients achieved clinical and bacteriologic cures regardless of the treatment regimen.[91] Two additional trials demonstrated the equivalent efficacy of a single 1 g dose of azithromycin and multiple dose doxycycline for treatment of genital infections from C *trachomatis*.[94,95] Single-dose azithromycin (1 or 2 g) was also compared with ceftriaxone (250 mg intramuscularly) in the treatment of uncomplicated genital infection caused by *N* gonorrhoeae.96 Ceftriaxone cured 28 of 28 patients, whereas azithromycin eradicated *N* gonorrhoeae in six of eight men given the 1 g dose and 45 of 45 patients given the 2 g dose. However, nausea and diarrhea occurred frequently with the higher dose. In summary, a single 1 g dose of azithromycin appears to be a viable alternative to doxycycline in the management of chlamydial genital infections. Until further trials document the efficacy of azithromycin against gonococcal infections, however, this single-dose, easily supervised regimen should be coupled to administration of another agent, such as ceftriaxone, that is active against *N* gonorrhoeae infections.

Mycobacterial Infections

The new macrolides are clinically active against specific species of mycobacteria, including M avium, M leprae, and M chelonae. Clarithromycin, as monotherapy, reduced viable colony counts of M avium better than any single regimen in beige mouse models of MAC infection, although it was more active in combination with rifabutin or clofazamine.[68,97,98] Azithromycin also reduced the level of MAC infection in mice when compared with untreated controls.[71] In a small, uncontrolled trial of MAC infection in patients with the acquired immunodeficiency syndrome (AIDS), therapy consisted of clarithromycin 2 g per day plus clofazamine 200 mg per day for two months, followed by clarithromycin 1 g per day plus clofazamine 100 mg per day.[99] All patients showed clinical improvement and subsequent negative blood cultures for mycobacteria, although three died from unrelated causes. In 54 AIDS patients with disseminated MAC infection treated with several clarithromycin-containing regimens (500 mg/day to 2 g/day), the majority displayed a reduction in fever and clinical improvement.[100] In a trial with azithromycin, patients who received monotherapy (500 mg/day) for 10, 20, or 30 days demonstrated a progressive reduction in bacteremia.[101] Clinical symptoms (fever, night sweats, chills) resolved in 14 of 16 patients in the 20- and 30-day treatment arms. In this study, bacteremia returned to baseline in most patients two to three weeks after treatment cessation. Another study involving a small group of MAC-infected AIDS patients used clarithromycin (1 g twice daily) for six weeks, followed by placebo plus rifampin, isoniazid, ethambutol, and clofazamine for six more weeks versus placebo first for six weeks, followed by clarithromycin plus the four drug regimen.[102] Colony counts of MAC in blood dropped dramatically in patients on clarithromycin monotherapy, in contrast to gradual increases observed in the placebo group. In addition, four of seven patients who crossed over into the placebo-containing group developed increased colony counts in quantitative blood cultures. While the new macrolides appear promising in the management of MAC infections in patients with AIDS, further large-scale trials are needed.

Clarithromycin has very good bactericidal activity against M leprae in the mouse foot pad model; activity is additive when clarithromycin is used in

TABLE 4
ADVERSE EFFECTS IN PATIENTS TREATED WITH AZITHROMYCIN OR CLARITHROMYCIN

	Incidence (%)	
Adverse Effect	Azithromycin*	Clarithromycin†
Clinical		
Diarrhea	3.6	3.0
Nausea	2.6	3.0
Abdominal pain	2.5	2.0
Headache	1.3	2.0
Laboratory parameters		
ALT elevation	1.7	<1.0
AST elevation	1.5	<1.0
Total bilirubin elevation	0.7	<1.0
Alkaline phosphatase elevation	0.3	<1.0
WBC decrease	1.1	< 1.0
BUN elevation	0.4	4.0
Creatinine elevation	0.3	<1.0

. Adapted from reference 24 (n = 3,995).
† Adapted from package insert.

combination with rifampin or minocycline.[103,104] Both azithromycin and erythromycin were inactive against M *leprae* infections in one published study.[103] Clarithromycin, 500 mg daily, and minocycline, 100 mg daily, either alone or in combination, demonstrated rapid bactericidal activity as well as clinical efficacy in 36 patients with lepromatous leprosy.[105] Although historically unresponsive to therapy, preliminary reports also suggest that clarithromycin is efficacious against disseminated skin infections caused by M *chelonae*.[106]

Toxoplasmosis

Both clarithromycin and azithromycin completely protected mice from death after intraperitoneal infection with *T gondii*.[64,65] Azithromycin also protected 80% of mice infected intracerebrally with Tgondii, and reduced the number of cysts observed on suspensions of brain tissue when compared with untreated animals.[64] Thirteen AIDS patients in a small, uncontrolled trial received clarithromycin, 2 g per day, plus pyrimethamine, 75 mg per day, for therapy of toxoplasmic encephalitis; 80% of patients improved clinically at six weeks. One of two deaths in this study was directly related to the progression of toxoplasmosis. The majority of study patients experienced side effects, including liver test abnormalities (77%), hearing loss (15%), nausea or vomiting (38%), and skin rash (38%). Although promising, additional trials are required to further evaluate the efficacy and to determine the optimal dosing regimen of the new macrolides in the therapy of toxoplasmic encephalitis.

Other Infections

The clinical spectrum of the new macrolides continues to broaden as further trials and clinical experience become available. For example, in preliminary data, azithromycin, but not clarithromycin, eradicated B *burgdorferi* from intraperitoneally infected gerbils, despite equivalent in vitro activity of the two drugs.[62] No therapy reliably treats *Helicobacter pylori* colonization of the stomach, although clarithromycin monotherapy at a dose of 250 mg four times daily for two weeks reverted the urea breath test to negative in 14 of 14 patients after two days; four of five patients remained negative at one month follow up.[108] However, in another study, azithromycin-treated patients colonized with *H pylori* remained urea test-positive at seven days, with high-level resistance developing in several patients during therapy.[109] Whether or not this resistance also occurs with clarithromycin awaits additional studies.

ADVERSE EFFECTS

The assessment of side effects and laboratory abnormalities for clarithromycin and azithromycin are based on phase I, II, and III trials from the United States and Europe (Table 4).[24] As with erythromycin, gastrointestinal adverse effects for both azithromycin and clarithromycin predominate, but at a significantly reduced rate. In studies comparing erythromycin to clarithromycin, gastrointestinal side effects were 32% and 13%, respectively. Up to 20% of patients withdraw from erythromycin therapy secondary to adverse events versus less than 1% for azithromycin and less than 3% for clarithromycin. Overall, adverse events were reported in 12% of azithromycin recipients. Side effects that occur with more than 1% frequency during azithromycin therapy are diarrhea, nausea, abdominal pain, and headache. Other reactions include skin rash (0.6%) and vaginitis (0.4%). In addition to the adverse gastrointestinal reactions seen with clarithromycin, patients occasionally report headache (2%) and abnormal taste (3%). Laboratory abnormalities with the new macrolides occur infrequently (Table 4). Clarithromycin and erythromycin increase concomitant theophylline and carbamazepine serum concentrations, necessitating careful monitoring of serum concentrations of these drugs. As yet, this effect has not been documented with azithromycin, although one should consider monitoring the serum concentrations of theophylline and carbamazepine during the coadministration of these agents. The macrolide antibiotics as a group may elevate serum digoxin concentrations and should be avoided in patients receiving ergot

alkaloids, because erythromycin has precipitated ergot toxicity. No well-controlled trials have established the safety and efficacy of either clarithromycin or azithromycin in pregnancy or in children less than 12 years of age.

SUMMARY

Azithromycin and clarithromycin are erythromycin analogues that have recently been approved by the FDA. These drugs inhibit protein synthesis in susceptible organisms by binding to the 50S ribosomal subunit. Alteration in this binding site confers simultaneous resistance to all macrolide antibiotics. Clarithromycin is several-fold more active in vitro than erythromycin against gram-positive organisms, while azithromycin is 2- to 4-fold less potent. Azithromycin has excellent in vitro activity against *H influenzae* (MIC_{90} 0.5 kg/ml), whereas clarithromycin, although less active against *H influenzae* (MIC,, 4.0 kg/ml) by standard in vitro testing, is metabolized into an active compound with twice the in vitro activity of the parent drug. Both azithromycin and clarithromycin are equivalent to standard oral therapies against respiratory tract and soft tissue infections caused by susceptible organisms, including S aureus, S pneumoniae, S ***pyogenes,*** *H* intluenzae, and M *catarrhalis*. Clarithromycin is more active in vitro against the atypical respiratory pathogens (e.g., *Legionella*), although insufficient in vivo data are available to demonstrate a clinical difference between azithromycin and clarithromycin. Superior pharmacodynamic properties separate the new macrolides from the prototype, erythromycin. Azithromycin has a large volume of distribution, and, although serum concentrations remain low, it concentrates readily within tissues, demonstrating a tissue half-life of approximately three days. These properties allow novel dosing schemes for azithromycin, because a five-day course will provide therapeutic tissue concentrations for at least ten days. Clarithromycin has a longer serum half-life and better tissue penetration than erythromycin, allowing twice-a-day dosing for most common infections. Azithromycin pharmacokinetics permit a five-day, single daily dose regimen for respiratory tract and soft tissue infections, and a single 1 g dose of azithromycin effectively treats C trachomatis genital infections; these more convenient dosing schedules improve patient compliance. Azithromycin and clarithromycin also are active against some unexpected pathogens (e.g., ***B*** burgdorferi, Tgondii, M avium complex, and M leprae). Clarithromycin, thus far, appears the most active against atypical mycobacteria, giving new hope to what has become a difficult group of infections to treat. Gastrointestinal distress, a well known and major obstacle to patient compliance with erythromycin, is relatively uncommon with the new macrolides. Further clinical data and experiences may better define and expand the role of these new macrolides in the treatment of infectious diseases.

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