



DONALD G. VIDT, MD, AND ALAN BAKST, PHARM D, EDITORS

The role of azithromycin and clarithromycin in clinical practice

MORTON P. GOLDMAN, PHARM D, AND DAVID L. LONGWORTH, MD

- **BACKGROUND** Azithromycin and clarithromycin are the newest approved macrolide antibiotics.
- **OBJECTIVE** To review the pharmacology, microbiology, and clinical utility of these agents.
- **SUMMARY** These agents have distinct advantages over erythromycin, including an improved pharmacokinetic profile, less toxicity, and a wider spectrum of activity. They are approved for the treatment of respiratory tract infections and uncomplicated skin and skin-structure infections associated with specific organisms. Azithromycin is also indicated for the treatment of nongonococcal urethritis. In addition, these agents may be useful in the treatment of toxoplasmosis, mycobacterial disease, Lyme disease, and legionellosis. Clarithromycin and azithromycin have lower rates of gastrointestinal side effects than erythromycin.
- **CONCLUSIONS** Although clarithromycin and azithromycin show promise in the treatment of some less common infections, they should be considered alternatives to conventional agents in the treatment of respiratory tract, skin, and skin-structure infections caused by the usual pathogens. The expense of these agents may be prohibitive for routine use.

■ INDEX TERMS: CLARITHROMYCIN; AZITHROMYCIN; ERYTHROMYCIN; RESPIRATORY TRACT INFECTIONS; SKIN DISEASES, INFECTIOUS
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From the Departments of Hospital Pharmacy (M.P.G.) and Infectious Disease (D.L.L.), The Cleveland Clinic Foundation.

Address reprint requests to M.P.G., Department of Hospital Pharmacy, S10, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

SINCE ITS DISCOVERY IN the 1950s, erythromycin has been a very important antimicrobial agent for the treatment of a variety of infections. But it has its limitations: its antimicrobial spectrum is relatively narrow, it is bacteriostatic rather than bacteriocidal, its dosing is inconvenient (it must be given four times a day), and many patients experience gastrointestinal intolerance to it.

Of the many new macrolides developed in the past decade, azithromycin and clarithromycin were the first to be marketed in the United States. Their broader antimicrobial spectrum and improved pharmacokinetic and side effect profiles compared with erythromycin make them promising agents for a variety of infections. We will review the pharmacology, microbiology, and clinical use of these agents with emphasis on innovative, nonapproved uses.

CHEMISTRY AND ACTIVITY

Azithromycin and clarithromycin are macrolide antibiotics similar in structure to erythromycin.¹ They act by inhibiting bacterial RNA-dependent protein synthesis

TABLE 1
PHARMACOKINETICS OF MACROLIDE ANTIBIOTICS

	Azithromycin (500 mg) ¹⁸	Clarithromycin (250 mg) ¹⁹	(14 hydroxy- clarithromycin)	Erythromycin (500 mg) ¹⁷
Half-life (hours)*	11-14	2.6-2.7	1.5-3	3.9-4.2
Bioavailability (%)	37	52-55	Variable	Not available
Maximum serum concentration (µg/mL)†	0.4	0.72-0.8	1.9-3.8	0.64-0.65
Time to maximum serum concentration (hours)	2.3	1.72-1.92	1.5	2.17-2.32

*Half-life increases somewhat after multiple-dose administration.

†Maximum serum concentrations increase after multiple doses.

by binding to the 50S-subunit of the 70S-ribosome in the organism.² Comparative microbiologic activity of the new macrolides has been well studied.³⁻⁷ Like erythromycin, azithromycin and clarithromycin possess excellent activity against aerobic gram-positive bacteria, *Mycoplasma pneumoniae*, *Bordetella pertussis*, and species of *Legionella*, *Campylobacter*, and *Chlamydia*. All three macrolides also have significant activity against anaerobic flora and some mycobacterial species. The newer macrolides have improved activity against *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Chlamydia* species. Both of these agents have excellent activity against *Toxoplasma gondii*⁸⁻¹¹; clarithromycin also has increased activity against mycobacterial species compared with the other macrolides.¹²⁻¹⁶ The macrolides are not active against methicillin-resistant staphylococcal species nor against most Enterobacteriaceae.

PHARMACOKINETICS

The comparative pharmacokinetics of erythromycin, azithromycin, and clarithromycin are summarized in Table 1.¹⁷⁻¹⁹ Azithromycin has the longest half-life of the three, which allows for once-daily administration. Although the maximum serum concentration obtained with azithromycin after oral administration of 500 mg is only 0.4 µg/mL, tissue levels well exceed the serum concentration. The drug is concentrated inside cells, particularly in polymorphonuclear leukocytes and macrophages. Azithromycin has variable protein binding, which is concentration-dependent. The drug is relatively poorly absorbed, with a bioavailability of only 37%. Clarithromycin has a half-life of approximately 3 to 5 hours, which allows for twice-daily dosing. Its maximum serum concentration after a 250-mg dose

is only 0.8 µg/mL; however, it also achieves high tissue concentrations. Clarithromycin is absorbed somewhat better than its macrolide counterparts, with a bioavailability of approximately 55%. All of these agents are metabolized in the liver to some degree, with azithromycin eliminated in the bile and possibly the intestine as well. Clarithromycin un-

dergoes both hydroxylation and N-demethylation, and its 14-hydroxy metabolite is relatively active—perhaps more active against *H influenzae* than the parent compound.^{20,21} These metabolites are primarily eliminated via the kidney.

APPROVED USES FOR AZITHROMYCIN AND CLARITHROMYCIN

Azithromycin and clarithromycin have been approved by the Food and Drug Administration (FDA) for the treatment of pharyngitis, sinusitis, lower respiratory tract infections, and uncomplicated skin and soft-tissue infections associated with various organisms (Table 2). Azithromycin is also indicated for the treatment of nongonococcal urethritis. The effectiveness of these compounds for these indications has been extensively reviewed.^{1,22-25} However, each of the published trials examined relatively few patients, and many of these studies did not have sufficient power to detect potentially significant differences between treatment groups.

Azithromycin

Respiratory tract infections. The standard dosage of azithromycin (500 mg, then 250 mg daily for the next 4 days) has been compared with a 10-day course of penicillin (250 mg every 6 hours) in the treatment of streptococcal pharyngitis. Clinical cure rates and streptococcal eradication rates were similar between the two regimens.²⁶ The same regimen of azithromycin was compared with a 10-day course of amoxicillin (500 mg three times daily) in the treatment of bacterial sinusitis.²⁷ The outcomes in both treatment groups were similar. With the small number of patients studied, however, these data are difficult to interpret.

The standard dose of azithromycin has also been compared with 10-day courses of erythromycin (500 mg four times daily)²⁸ and cefaclor (500 mg three times daily)²⁹ for the treatment of community-acquired pneumonia and bronchitis. The cure rates were comparable with each treatment regimen. Although azithromycin performed well against *H influenzae* in the cefaclor trial, an open-label trial of azithromycin in patients with chronic bronchitis showed frequent persistence and clinical relapse.³⁰

Sexually transmitted diseases. Clinical trials have also shown azithromycin to be as effective as standard therapy in the treatment of sexually transmitted diseases caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Ureaplasma urealyticum*.³¹⁻³³ The dosage regimens ranged from a single 500-mg or 1-g dose to 3 days of therapy. Azithromycin is approved for the treatment of nongonococcal urethritis caused by *C trachomatis* only.

Skin and skin-structure infections. Azithromycin has also been shown to be effective in the treatment of skin and skin-structure infections in two trials.^{28,32,34} The results of standard 5-day courses of azithromycin were not clinically or bacteriologically different from 7-day courses of erythromycin or 10-day courses of cephalexin.

Clarithromycin

Clarithromycin (250 mg every 12 hours) has been compared with erythromycin (500 mg every 6 hours)³⁵ and penicillin (500 mg every 6 hours)^{36,37} in the treatment of streptococcal pharyngitis; similar cure and bacteriological eradication rates were achieved. To our knowledge, prevention of subsequent rheumatic fever has not been examined for clarithromycin or azithromycin. The same dosage of clarithromycin has also been compared with amoxicillin (500 mg every 8 hours) in the treatment of bacterial sinusitis, with similar results.³⁸

Clinical trials have shown clarithromycin to be as effective as erythromycin^{39,40} or ampicillin^{41,42} in the treatment of community-acquired pneumonia and

TABLE 2
FOOD AND DRUG ADMINISTRATION-APPROVED INDICATIONS
FOR USE OF AZITHROMYCIN OR CLARITHROMYCIN

Disease	Organism	Drug
Pharyngitis or tonsillitis	<i>Streptococcus pyogenes</i>	Clarithromycin, azithromycin
Acute maxillary sinusitis	<i>Streptococcus pneumoniae</i>	Clarithromycin
Exacerbation of chronic bronchitis	<i>Hemophilus influenzae</i>	Clarithromycin, azithromycin
	<i>Moraxella catarrhalis</i>	Clarithromycin, azithromycin
	<i>S pneumoniae</i>	Clarithromycin, azithromycin
Pneumonia (mild)	<i>S pneumoniae</i>	Clarithromycin, azithromycin
	<i>Mycoplasma pneumoniae</i>	Clarithromycin
	<i>H influenzae</i>	Azithromycin
Uncomplicated skin and skin-structure infections	<i>S pyogenes</i>	Clarithromycin, azithromycin
	<i>Streptococcus agalactiae</i>	Azithromycin
Nongonococcal urethritis and cervicitis	<i>Chlamydia trachomatis</i>	Azithromycin

chronic bronchitis, respectively. A number of dosage regimens were studied, and eradication and cure rates were similar between groups.

NONAPPROVED USES FOR AZITHROMYCIN AND CLARITHROMYCIN

Azithromycin and clarithromycin may be useful in the treatment of a variety of other infections, though use for these indications is not approved by the FDA (Table 3). Both drugs have been investigated for activity against and treatment of nontuberculous mycobacteria.¹²⁻¹⁶

Mycobacteriosis

Azithromycin's activity against *Mycobacterium avium-intracellulare* complex has been studied in vitro and in a mouse model.¹⁴ Although its activity in vitro was unimpressive, its cure rate in the mouse model was high. More data are needed to establish azithromycin's place in the treatment of mycobacterial disease, as no clinical data in humans are available.

In vitro studies of clarithromycin's activity against mycobacterial species have been promising. Clarithromycin is a more active agent against *Mycobacterium chelonae* and *Mycobacterium fortuitum* than most other macrolides.¹⁶ Clarithromycin's activity has also been studied in 49 strains of *M avium-intracellulare*.¹⁵ This study concluded that, although active against these organisms, clarithromycin may be bacteriostatic rather than bactericidal. A clinical trial examining the combination of clarithromycin, ciprofloxacin, and amikacin in the treatment of *M avium-intracellulare* complex in pa-

TABLE 3
POTENTIAL USES OF CLARITHROMYCIN AND
AZITHROMYCIN THAT HAVE NOT BEEN APPROVED
BY THE FOOD AND DRUG ADMINISTRATION

Drug	Organism	References
Clarithromycin	<i>Legionella pneumoniae</i> *	44
	<i>Toxoplasma gondii</i> *	8, 11
	<i>Mycobacterium avium-intracellulare</i> *	12-15
	Other mycobacterial species†	16
Azithromycin	<i>Borrelia burgdorferi</i> (Lyme disease)†	43
	<i>Toxoplasma gondii</i> †	9, 10

*Limited human data available

†No human data available

tients with acquired immunodeficiency syndrome (AIDS) has shown this regimen to be effective in treating patients with bacteremia.¹³ Although the sample size was small (12 patients), the results were encouraging.

Toxoplasmosis

The activity of azithromycin and clarithromycin against *T gondii* has also been studied.⁸⁻¹¹ Derouin et al¹⁰ studied azithromycin's activity in experimental toxoplasmosis in a murine model. These authors found that azithromycin significantly potentiates the therapeutic effects of both sulfadiazine and pyrimethamine. Deaths and relapses were less common when azithromycin was added to sulfadiazine or pyrimethamine compared with treatment with any of the three agents alone. Clarithromycin has also been shown to have significant activity against *T gondii* in vitro and in a mouse model.^{8,9}

In the only fully published trial in humans, 13 patients with AIDS who had encephalitis caused by *Toxoplasma* were treated with a combination of pyrimethamine and clarithromycin.¹¹ The patients were 18 to 60 years old and had not received therapy for *Toxoplasma* during the 48 hours before enrollment. The regimen consisted of clarithromycin (1 g twice daily), pyrimethamine (a 200-mg load, followed by 75 mg daily), and folinic acid. All patients were to be assessed at 6 weeks. Eight patients completed at least 6 weeks of therapy, and six had a complete response. The five patients who did not complete therapy either voluntarily withdrew or experienced an adverse event possibly related to therapy. It was concluded that outcomes in these 13

patients were similar to results in patients who receive standard therapy.

Lyme disease

Azithromycin in vitro is active against *Borrelia burgdorferi*, the agent of Lyme disease.⁴³ Azithromycin was active in vitro (minimal bactericidal concentration 0.04 mg/L) and was effective in eradicating the organism from experimentally infected hamsters. Data in humans are not yet available.

Legionellosis

Clarithromycin has been studied for the treatment of pneumonia caused by *Legionella* species.⁴⁴ Forty-six Pakistani patients were enrolled in an open trial of clarithromycin at a dosage of 1 g twice daily (for all but one patient). The diagnosis was made by culture, direct fluorescent antibody staining of respiratory secretions, and serologic study. Clinical and radiographic changes were documented at various times during the trial. Almost all patients had clinical cure or improvement as well as radiographic improvement. The adverse reactions reported (13 events in 10 patients) included taste disturbance, gastrointestinal symptoms, headache, dizziness, and mildly elevated serum transaminase concentrations. Clarithromycin was safe and effective in this population. A trial comparing clarithromycin with erythromycin has not yet been performed.

ADVERSE EFFECTS

Adverse effects with these agents have been relatively infrequent compared with erythromycin; mild gastrointestinal side effects have been the most common. Abnormal liver function test results have been noted with both clarithromycin and azithromycin. Eosinophilia and headache have both been reported with the use of clarithromycin. Patients infected with human immunodeficiency virus (HIV) seem to have a higher incidence of adverse effects with clarithromycin than patients who do not have HIV, especially abdominal pain, nausea, vomiting, and skin rash. In the trial of clarithromycin in patients with AIDS and toxoplasma infections,¹¹ 31% of patients experienced severe hematologic abnormalities; however, this may have been due in part to the patients' underlying disease. No hematologic abnormalities have been reported in clarithromycin recipients who are not HIV-positive.

DRUG INTERACTIONS

The pharmacokinetic drug interactions of the macrolides have been extensively reviewed by Periti et al.⁴⁵ Although few drug interactions have been reported with either of the two new macrolide agents, these drugs should be used with caution when combined with agents that have been reported to interact with erythromycin, such as morphine, terfenadine, astemizole, and cyclosporine. Clearance of theophylline and carbamazepine may be decreased with the addition of clarithromycin.

DOSAGE AND COST

The dosage of azithromycin for all approved indications is 500 mg on the first day, followed by 250 mg daily for 4 days.⁴⁶ For nongonococcal urethritis, a single 1-g dose is recommended.⁴⁶ The dosage of clarithromycin for all approved indications is 250 to 500 mg twice daily for 7 to 14 days.⁴⁶

A 7-day course of clarithromycin (250 mg twice a day) costs the patient approximately \$42.00, as does a 5-day course of azithromycin (500 mg for 1 day then 250 mg daily). A 10-day course of erythromycin (500 mg four times daily) costs the patient ap-

proximately \$10.00.

SUMMARY

Clarithromycin and azithromycin are excellent alternatives to conventional agents in the treatment of infections of the respiratory tract, skin, and skin structures caused by susceptible organisms. They are better tolerated and possess a broader spectrum than erythromycin; however, treatment failures have occurred, especially in patients with bronchitis caused by *H influenzae*. Azithromycin is also effective in the treatment of nongonococcal urethritis. These new macrolides are promising additions to the armamentarium for the treatment of various mycobacterial diseases and toxoplasmosis in HIV-infected patients. Carefully performed clinical trials may help to delineate the utility of the macrolides for treating these infections. The expense of these agents may be prohibitive for routine use.

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