International Journal of Research in Medical Sciences
Naik P et al. Int J Res Med Sci. 2024 Feb;12(2):634-640
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20240027

Review Article

Clarithromycin: overview and its current clinical utility in the treatment of respiratory tract infections

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Received: 20 December 2023
Accepted: 10 January 2024

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ABSTRACT

Upper respiratory tract infection (URTI) is a common reason for medical consultation all over the world. Streptococcus A (Strep A) and other infections can cause sore throat as well as pharyngitis or tonsillitis. It may also result in post-infection sequelae, including acute post-streptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease. As a result, there is a need for an antibiotic that is effective, easy to administer, has a favorable sensitivity pattern, and preferably has some additional pharmacodynamic properties that complement the basic antibacterial profile. Clarithromycin is a macrolide antibacterial agent with broad-spectrum activity against respiratory pathogens. It is especially active against atypical *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella spp*. It is well absorbed and stable at gastric pH. It is metabolized by the cytochrome P450 enzymes and forms 14-hydroxy clarithromycin, which is more active than the parent compound, especially against *Hemophilus influenzae*. It acts by preventing protein synthesis by binding to the 50S subunit of bacterial ribosomes. In dosages of 500 to 1000 mg/day for 5 to 14 days, clarithromycin is effective in the treatment of community-acquired upper and lower respiratory tract infections in hospital and community settings. It exerts significant anti-inflammatory, immunomodulatory, and post-antibiotic effects. It provides a viable option for the treatment of community-acquired respiratory tract infections, in both children and adults.

Keywords: Upper respiratory tract infection, Streptococcus A, Clarithromycin

INTRODUCTION

Respiratory tract infection includes any infectious disease of the upper or lower respiratory tract. The common cold, laryngitis, pharyngitis/tonsillitis, acute rhinitis, acute rhinosinusitis, and acute otitis media (AOM) are all examples of upper respiratory tract infections (URTIs).[1] Upper respiratory tract infection (URTI) is a frequent cause of medical consultation worldwide.[2] Parthasarathy et al reported, in children less than 10 years, the incidence rate of sore throat as 19.2 per 100 person-years.[3]

Streptococcus A (Strep A) and other infections can cause sore throat and pharyngitis or tonsillitis. It may also result in post-infection sequelae, including acute post-streptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease.[4] In primary care, antibiotics are commonly used for RTIs in adults and children.[1] Hence, there is a need for a suitable antibiotic that is effective, easy to administer, has a favorable sensitivity pattern, and also preferably has some additional pharmacodynamic characteristics that add to the basic antibacterial profile.

Macrolides are a large group of antimicrobials derived from *Streptomyces spp*.[5] Erythromycin, the first member of the macrolide class, was brought into therapeutic use in the 1950s.[6] Clarithromycin and azithromycin are second-generation macrolides derived from erythromycin and provide significant advantages over erythromycin in terms of extended-spectrum activity and improved tolerability (Table 1).[6-8]

Table 1: Spectrum of activity and pharmacokinetic parameters of clarithromycin.

Class[6]	Macrolides
Spectrum of activity[7]	Increased activity against certain pathogens. *S. pneumoniae*, viridans streptococci, and group A streptococci
Pharmacokinetics[6]	
Bioavailability (%)	55
C-max (µg/mL)	2.1-2.4
t max (hours)	2
Half-life (hours)	4.3-4.9
AUC (µg/mL× hour)	12-18.9
Protein binding (%)	60-75

Macrolide antibiotics were upgraded with the objective of extending the spectrum of activity, overcoming resistance, improving intracellular penetration, enhancing synergy with the immune system, improving chemical and metabolic stability, serum/tissue pharmacokinetics as well as dosage frequency, reducing drug interaction potential, and improving tolerability. Approaches to achieving these targets included structural modifications of erythromycin (e.g., roxithromycin, azithromycin, clarithromycin, dirithromycin, and flurithromycin) and esterification and/or salt formation of fermentation-derived products [e.g., erythromycin acistrate, midecamycin acetate (miokamycin), rikamycin (rokitamycin)].[9]

Clarithromycin and erythromycin contain a neutral sugar (cladinose) and an amino sugar (desosamine) attached to a 14-member lactone ring of antibiotics.[10,11] Clarithromycin is a semisynthetic derivative of erythromycin produced by methylation at a C-6 hydroxyl group. The structural modification of the acid-degradable erythromycin site reduces the synthesis of hemiketal and spiroketal metabolites, increasing acid stability and reducing gastrointestinal side effects.[8,13] It is well absorbed from the gastrointestinal tract and produces a microbiologically active metabolite, 14-hydroxy clarithromycin.[7,13]

This review covers the antimicrobial activity, clinical pharmacokinetics, clinical utility, and tolerability of clarithromycin in various respiratory diseases.

METHODS

The articles were sourced from databases like PubMed, Google Scholar, and UpToDate, and a literature search was performed methodically. The selected articles focus on the pharmacokinetics, pharmacodynamics, antimicrobial activity, efficacy, and safety of clarithromycin in respiratory tract infections. Keywords such as 'clarithromycin', 'macrolides', 'atypical organisms', 'upper respiratory tract infection', 'URTI', 'antibiotics', 'inflammation', 'anti-inflammatory', 'immunomodulation', 'pharyngitis', 'tonsillitis', 'acute otitis media' and other identical terms were employed during the search process. The search was made more comprehensive by double-checking the references. The final article types included were randomized controlled trials, clinical trials, reviews, systematic reviews, and meta-analyses. This review presents and summarizes a comprehensive analysis of 36 articles along with findings from the EUCAST database.

ANTIMICROBIAL ACTIVITY

Clarithromycin and its active metabolite, 14-hydroxy clarithromycin, have broad Gram-positive, Gram-negative, atypical, and anti-mycobacterial activity (Table 2).[6,13]

Table 2: List of selected pathogens against which clarithromycin is effective.

Gram-positive organisms	Gram-negative organisms	Atypical organisms/other organisms
Erythromycin-susceptible *Streptococcus pneumoniae*[6]	*Hemophilus influenzae*[13]	
	Moraxella catarrhalis[7]	
	Shigella spp[13]	*Mycoplasma pneumoniae*[6]
Group A, B, C, and G streptococcus[13]	*Campylobacter jejuni*[13]	*Chlamydophila pneumoniae*[6]
	Vibrio cholerae[13]	*Ureaplasma urealyticum*[13]
	Neisseria gonorrhoeae[13]	*Legionella pneumophila*[6]
Methicillin-susceptible *Staphylococcus aureus*[13]	*Helicobacter pylori*[13], *Bordetella pertussis*[6]	

Clarithromycin has better activity than azithromycin in vitro against wild-type *S. pneumoniae* and has similar activity against *M. pneumoniae*, *C. pneumoniae*, and *Legionella. Pneumophila*.[6]

CLINICAL PHARMACOKINETICS

Clarithromycin has better oral absorption, longer serum half-lives, and better tissue and intracellular penetration than erythromycin.[14] Clarithromycin is stable at gastric pH.[7,14] As a result, it has higher bioavailability than erythromycin.[7,15] The oral suspensions and immediate-release tablets can be taken with or without food.[14,16] Clarithromycin extended-release tablets, on the other hand, should be taken with food.[16,17] Clarithromycin has an oral bioavailability of approximately 50 percent when dosed every 12 hours. The mean steady-state peak blood concentration following 500 mg oral dose every 12 hours is 2 to 3 mcg/mL.[14]

Clarithromycin penetrates well into most tissues and fluids, which is associated with its clinical efficacy at different infection sites. Because it concentrates in tissues, concentrations in epithelial-lining fluid and alveolar macrophages are usually higher than in plasma.[6,14] Clarithromycin levels in the lung are six times higher than the plasma concentration.[13]

Clarithromycin undergoes metabolism via hydroxylation, N-demethylation, and hydrolysis in the liver through the cytochrome P450 enzymes.[7,13] The major metabolite, 14-hydroxy clarithromycin, is microbiologically active, and in some species, it is more active than clarithromycin.[13] For example, the 14-hydroxy metabolite inhibited 90% of *H. influenzae* isolates from individuals with community-acquired pneumonia at a dosage of 3 mg/mL, compared to 9 mg/mL for clarithromycin.[18] Twenty to thirty percent of clarithromycin is excreted unchanged in the urine.[16]

Mechanism of Action

By attaching to the 50S component of ribosomes in bacteria, clarithromycin inhibits transpeptidation, translocation, chain elongation, and eventually bacterial protein synthesis.[6,13]

CLINICAL EFFICACY

Streptococcal pharyngitis

Hoban et al conducted a meta-analysis of five outpatient clarithromycin trials for the treatment of streptococcal pharyngitis. The five studies involved 1184 patients with streptococcal pharyngitis, with 600 receiving clarithromycin (250 mg twice daily) and 584 receiving penicillin VK (n=412) or erythromycin (n=172). Although clinical cure or improvement rates were comparable across all treatment groups (Figures 1 and 2), bacteriological cure rates were numerically higher with clarithromycin than with penicillin VK or erythromycin.[19]

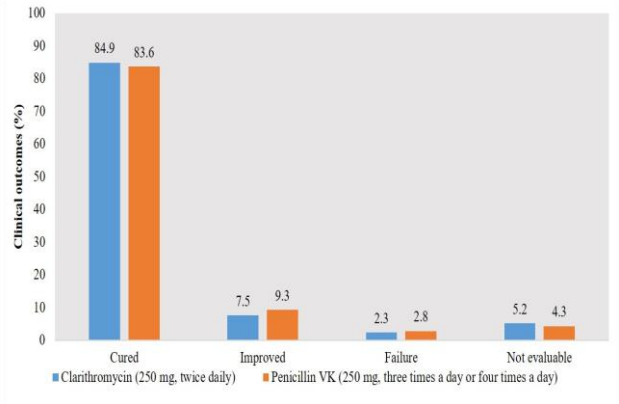

Figure 1: Clinical outcomes in streptococcal pharyngitis studies on treatment with clarithromycin vs. penicillin VK at visit 3 (4–6 days after treatment).

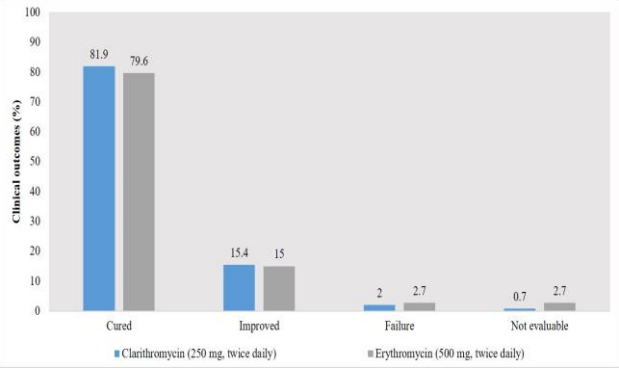

Figure 2: Clinical outcomes in streptococcal pharyngitis studies on treatment with clarithromycin vs. erythromycin at visit 3 (4–6 days after treatment).

In the largest study in this dataset (M86-030), the intergroup difference in bacteriologic cure rate in pharyngitis patients significantly favored clarithromycin over penicillin VK (95% vs. 87%; p=0.009).[19] In a prospective observational study, Gouthami *et al* evaluated the efficacy of clarithromycin, cefuroxime, and levofloxacin for the treatment of URTI. The study included outpatients aged <14 years and was conducted in RVM Hospital, India. A total of 99 subjects participated. Thirty-three participants were assigned to each group i.e., clarithromycin, cefuroxime, and levofloxacin. Clarithromycin and cefuroxime both had a 94% cure rate; however, 73% of clarithromycin participants were cured before three days, and 73% of cefuroxime participants were cured within five days. Levofloxacin, which had a 52% cure rate, was the only therapy group that had treatment failure. Thus, clarithromycin was more effective than cefuroxime and levofloxacin in the treatment of URTI.[20] In another study conducted by Venuta et al in patients with GABHS pharyngitis, clinical and bacteriological response rates of 98 and 95%, respectively, were obtained for clarithromycin recipients and 99 and 95%, respectively, for azithromycin recipients.[21] Kearsley et al found clarithromycin and amoxicillin have similar efficacy, with clinical success rates of 98% and 97%, respectively.

Bacterial eradication for *Streptococcus pyogenes* was observed in 88% and 86% of patients in clarithromycin and amoxicillin groups, respectively.[22]

Otitis media

Arguedas et al concluded in a non-blind trial that clarithromycin and azithromycin are both effective alternative treatments for AOM, with success rates of 96% and 100%, respectively.[23] In another study by Aspin et al, rates of clinical efficacy reported were 93% with clarithromycin when compared to amoxicillin/clavulanic acid (95%).[24]

Sinusitis

Adelglass et al conducted a randomized, investigator-blind study comparing response rates of clarithromycin and levofloxacin in adults with acute bacterial sinusitis. Signs and symptoms were resolved in 93% and 96% of individuals who received clarithromycin and levofloxacin, respectively. At one month after therapy, the relapse rates for clarithromycin and levofloxacin were 7.2% and 4.1%, respectively. In terms of clinical efficacy and recurrence rates, it was established that clarithromycin and levofloxacin were comparable.[25] In a prospective trial, 71% of participants receiving clarithromycin twice daily for up to 12 weeks experienced improvements in their symptoms and rhinoscopic findings. Clarithromycin was proven to be at least as effective in the treatment of chronic sinusitis as the previously tested erythromycin.[12]

Community-acquired pneumonia

Genne et al conducted a non-blind, randomized study in adults to compare the efficacy of intravenous clarithromycin vs oral amoxicillin/clavulanic acid. In the empirical treatment, clarithromycin and amoxicillin-clavulanic acid were found to be equally effective (Figure 3).[26]

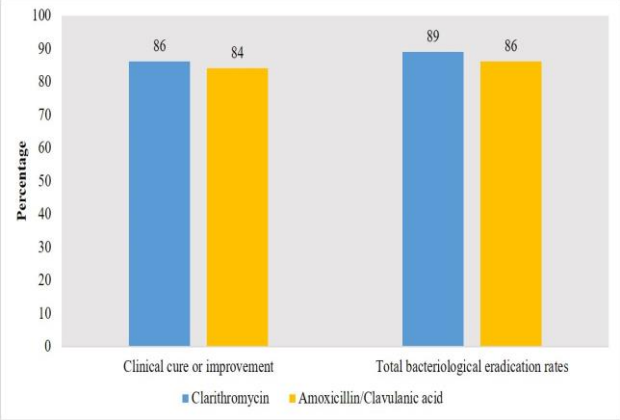

Figure 3: Clinical cure and total bacteriological eradication rates with clarithromycin and amoxicillin/clavulanic acid treatment.

Anti-inflammatory and immunomodulatory effects

Macrolides can reduce long-term inflammation, promote mucus clearance, limit the formation of bacterial biofilm, and increase or decrease immune system activation. Furthermore, macrolides have the potential to impact phagocyte activity by modifying a variety of processes, such as chemotaxis, phagocytosis, oxidative burst, bacterial death, and cytokine production. Macrolides have immunomodulatory properties (Figure 4).[27]

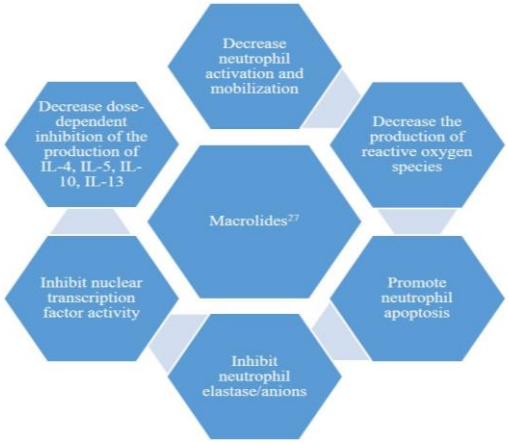

Figure 4: Immunomodulatory effect of macrolides.

Clarithromycin reduces TNF-alpha release from blood monocytes significantly.[25] Clarithromycin reduces the concentration of interleukin IL-4, IL-5, IL-13, chemokine (C-X-C motif) ligand 2 (CXCL2), chemokine ligand 2 (CCL2), chemokine ligand 3 (CCL3), and chemokine ligand 4 (CCL4) in bronchoalveolar lavage.[26] Histological studies show that it considerably lowers inflammatory cell buildup in the bronchoalveolar lavage and lungs. Furthermore, clarithromycin normalizes airway hyper-responsiveness after the reduction in inflammation (Table 3).[28]

Table 3: Advantages of clarithromycin.

Advantages of clarithromycin	
Anti-inflammatory and immunomod-ulatory effects	Significantly reduces TNF-alpha release from blood monocytes. Reduces the concentration of IL-4, IL-5, IL-13, CXCL2, CCL2, CCL3, and CCL4 in bronchoalveolar lavage.
Post-antibiotic effect	Longer in vitro PAEs than erythromycin at similar concentrations (5.5 h vs. 4.2 h)
Active metabolite	14-hydroxy clarithromycin enhances the efficacy against *H. influenzae*
Tolerability	Fewer adverse gastrointestinal events and withdrawals

Post-antibiotic effect

Antibacterial action of macrolides continues after exposure.[12] This type of persistent antibacterial action is referred to as the post-antibiotic effect (PAE) of an agent, which becomes important when the drug concentration falls below the MIC.[12,29] The macrolides exhibit different PAEs depending on the pathogen, drug concentration, time of exposure, pH, and so on. With gram-positive cocci, the duration of the effect is longer than with *Haemophilus influenzae*, and with streptococci, it is longer than with staphylococci. The in vitro PAEs for clarithromycin are longer than those of erythromycin at similar concentrations (5.5 hours vs. 4.2 hours for S. aureus, Table 3).[30]

Sensitivity

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the MIC breakpoints (mg/L) of clarithromycin for Streptococcus groups A, B, C, and G sensitivity is 0.25 mg/l.

According to the EUCAST reference database of 27/9/2023, 73% of the streptococcus pyogenes tested were sensitive to Clarithromycin.[31] According to another study from North India, 79.4% of Group A beta-hemolytic streptococcus (GABS) specimens were sensitive to Clarithromycin.[32]

Active metabolite

14-hydroxy clarithromycin, which is the active metabolite, enhances the efficacy of clarithromycin against *H. influenzae* by exhibiting a synergistic effect both in vivo and in vitro (Table 3).[33]

Concentrations in middle ear fluid

Gan et al reported that mean middle ear fluid concentrations of clarithromycin (7.5 mg/kg/12 hours for six doses) in 32 children were between 3.0-8.3 µg/g during the dosing interval, while it was 1.5–3.8 µg/g for 14-hydroxy clarithromycin. For both clarithromycin and its metabolite, middle ear fluid concentrations were greater than the mean plasma concentrations. Middle ear fluid concentration to plasma concentration ratios were 8.8 for clarithromycin and 3.8 for 14-hydroxy clarithromycin at 12 hours post-dosing. [34]

Concentrations in epithelial lining fluid

Rodvold et al reported that the concentration of clarithromycin (500 mg twice daily for 9 days) and its active metabolite 14-hydroxy clarithromycin in the alveolar macrophages in healthy adult volunteers was higher than that of azithromycin (500 mg on day 1 and then 250 mg/day for 4 days). [35]

Tolerability profile

Several clinical studies have indicated that clarithromycin is generally well-tolerated and has better tolerability than erythromycin. The most common events associated with the use of clarithromycin are diarrhea, abnormal taste, nausea, dyspepsia, and headache. Clarithromycin is associated with fewer adverse gastrointestinal events and withdrawals over erythromycin and even the amoxicillin/clavulanic acid combination (Table 3).[36]

CLINICAL CONDITIONS AND DOSAGE

Clarithromycin is effective in the treatment of various infections and some are given in Table 4.

Table 4: Clinical indications and dose for clarithromycin.

Clinical indication	Dose and route	Duration of treatment
Streptococcal pharyngitis, group A[16, 36, 37]	Oral, immediate release: 500 mg twice daily	7-14 days
Rhinosinusitis, acute bacterial[16]	Oral, immediate release: 500 mg twice daily	5-7 days
Community-acquired Pneumonia[16]	Oral, immediate release: 500 mg twice daily oral, extended release: 1 g (two 500 mg ER tablets) once daily	Minimum of 5 days; patients should be clinically stable with normal vital signs before therapy is discontinued

CONCLUSION

Respiratory tract infections are one of the most common infections worldwide resulting in significant morbidity and impairments in quality of life. Clarithromycin, a macrolide, is a well-established broad-spectrum antibacterial agent. Food has little effect on its absorption, and it is hydroxylated, N-demethylated, and hydrolyzed in the liver by the cytochrome P450 enzymes. The primary metabolite, 14-hydroxy clarithromycin, is microbiologically active and, in some cases, more effective than clarithromycin against some species, such as *H. influenzae*. It is used in the treatment of streptococcal pharyngitis, otitis media, sinusitis, and community-acquired pneumonia. It exhibits anti-inflammatory, immunomodulatory, and post-antibiotic effects. It has a favorable sensitivity profile of 73% against Streptococcus group A, B, C, and G organisms according to the EUCAST database. Thus, clarithromycin offers a strong viable option in the treatment of

respiratory infections in children and adults and thus judicious use of Clarithromycin seems helpful in avoiding the post-infection sequelae, including acute post-streptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease.

ACKNOWLEDGEMENTS

Dr. Heena Bhojwani for technical support in editing and formatting of this manuscript.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Naik P, Prabhat D, Shrivastava R, Nair A, Khandke DA. Clarithromycin: overview and its current clinical utility in the treatment of respiratory tract infections. Int J Res Med Sci 2024;12:634-40.