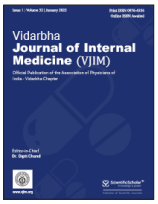
ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://vjim.org/

Vidarbha Journal of Internal Medicine



Drug Update

Levonadifloxacin

Mrunalini Kalikar[1]

[1]Associate Professor, Department of Pharmacology, Government Medical College and Hospital, Nagpur, Maharashtra, India.

ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the major public health concerns in India, MRSA infections continue to be therapeutically challenging both in hospitals and in the community. The currently available therapeutic options for MRSA are unable to provide safe and efficacious treatment with an option of oral switchover in the treatment of MRSA infections, especially in the community. Levonadifloxacin (LND) is a broad-spectrum benzoquinolizine fluoroquinolone with potent activity against quinolone-resistant *S. aureus* and MRSA phenotypes developed by an Indian company Wockhardt. LND and its oral prodrug alalevonadifloxacin have been recently approved in India for the treatment of acute bacterial skin and skin structure infections with concurrent bacteraemia and diabetic foot infections.

Keywords: Levonadifloxacin

INTRODUCTION

The emergence of resistance to antibiotics is considered as a threat to the world's sustainable development.[1] Among various resistant bacterial pathogens isolated around the world, methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the major public health concerns.[2] In India, MRSA infections continue to be therapeutically challenging both in hospitals and in the community.[3] As per published literature, the incidence of MRSA varies from 25% in the Western part of India to 50% in South India. MRSA infection is encountered in both the hospital and community settings.[4]

The currently available options in India for the treatment of MRSA infections include vancomycin, daptomycin, teicoplanin, and linezolid. All these drugs have limitations such as poor lung penetration and nephrotoxicity with vancomycin, myelosuppression with linezolid, and daptomycin skeletal muscle toxicity.[5] With the exception of linezolid, none of these drugs have an oral option. Thus, the currently available therapeutic options are unable to provide safe and efficacious treatment with an option of oral switchover in the treatment of MRSA infections, especially in the community.

Levonadifloxacin (LND) is a broad-spectrum benzoquinolizine fluoroquinolone with potent activity against quinolone-resistant *S. aureus* and MRSA phenotypes developed by an Indian company Wockhardt. LND and its oral prodrug alalevonadifloxacin (ALND) have been recently approved in India for the treatment of acute bacterial skin and skin structure infections with concurrent bacteraemia and diabetic foot infections.[6]

CHEMISTRY

LND belongs to the novel benzoquinolizine subclass of quinolone antibiotics and is being developed as a parenteral formulation in the form of L-arginine salt. In addition, the L-alanine ester prodrug of LND and ALND is being developed as a mesylate salt for oral administration. The molecular weight of LND is 606.6 g/mol and that of ALND is 527.6 g/mol. Structurally, LND differs from ciprofloxacin, moxifloxacin, and levofloxacin by having a benzoquinolizine core attached to a non-basic hydroxypiperidine side chain. Because of its non-basic side chain, LND remains in the unionised form in acidic pH, which facilitates its entry into the bacterial cell. As a result, there is a significant increase in the potency of LND in acidic environments.[7-9] This feature could be beneficial for intracellular activity and antibacterial action in infections with an acidic environment.

LND is *S*-(−)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo; quinolizine-2-carboxylic acid L-arginine salt tetrahydrate is the active S(-) isomer of nadifloxacin recently approved in India.[8] LND exhibits potent *in vitro* activity against contemporary *S. aureus* isolates

***Corresponding author:** Mrunalini Kalikar, Associate Professor, Department of Pharmacology, Government Medical College and Hospital, Nagpur, Maharashtra, India. mrunalinikalikar@yahoo.com

Received: 27 November 2021 **Accepted:** 20 December 2021 **Published:** 31 January 2022 **DOI:** 10.25259/VJIM_19_2021

and Bengal Bay Clone, isolates collected from a large Indian tertiary care hospital.[9] The S(-) isomer of nadifloxacin has been shown to be more potent than the R(+) isomer and twice as active as the racemic form of nadifloxacin against Gram-positive and Gram-negative bacteria.

PHARMACOLOGICAL PROPERTIES

Mechanism of action

The mechanism of the action of fluroquinolone (FQN) is well known. FQNs act on two bacterial DNA enzymes: Gyrase and topoisomerase IV. The supercoiling of the DNA is controlled by DNA gyrase and topoisomerase IV; they act by introducing a break in both the strands of DNA in the bacterial chromosome and then, resealing it to stop the supercoiling. Thus, due to the covalent enzyme-DNA complex stabilisation, DNA is cleaved. After this interaction, depending on the concentration, the death of the bacterial cell occurs in two ways: At low concentration by blocking replication and transcription and at higher concentration (over the minimum inhibitory concentration), when the DNA topoisomerase is dissociated/removed, the DNA strands remain free, which leads to the chromosome fragmentation.[10] Due to simultaneous inhibition of DNA gyrase and topoisomerase IV, both representatives exhibit significant antibacterial activity against Gram-negative and Gram-positive bacteria, with an emphasis on MRSA LND has the advantage of being potent against resistant pathogens with a very low frequency of mutation.[4,11-13]

Various *in vitro* and *in vivo* investigations have established LND's antibacterial spectrum against Gram-positive, Gram-negative, atypical and anaerobic pathogens.[14] Preferential targeting of DNA gyrase by LND is beneficial in providing superior potency, especially against quinolone-resistant *S. aureus.* The excellent bioavailability of oral formulations can be helpful in the smooth switch from parenteral to oral therapy. Both medication forms have well-established pharmacokinetics and safety; in the Phase I trial, there were no notable severe or unfavourable clinical or laboratory side effects, indicating that both formulations are well tolerated.[7]

SPECTRUM OF ACTIVITY

Gram-positive pathogens

LND shows potent activity against a variety of Gram-positive aerobic bacteria, including *S. aureus* resistant to methicillin (i.e., MRSA), vancomycin that is, hetero-vancomycin-intermediate *S. aureus* and vancomycin-resistant *S. aureus,* and daptomycin-intermediate/-resistant strains, coagulase-negative staphylococci. Activity against quinolone-resistant *Staphylococcus epidermidis* has also been demonstrated. Moreover, it is active against *Streptococcus pneumoniae*. Moreover, it is active against other streptococcal species as well.

Gram-negative pathogens

LND shows activity against *Acinetobacter baumannii*, *Escherichia coli*, *Haemophilus influenzae, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* that are comparable to other clinically available quinolones.

Atypical pathogens

Activity against *Mycoplasma pneumoniae, Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma* spp. (including macrolide-, tetracycline- and levofloxacin-resistant strains), *Chlamydophila pneumoniae* and *Legionella pneumophila* is established.

Anaerobes

It is active against Gram-positive anaerobes such as *Clostridium perfringens* and *C. difficile*. Similarly, Gram-negative anaerobes such as *Bacteroides fragilis, Prevotella* and *Porphyromonas* strains, and β-lactamase-producing *Fusobacteria* were found to be susceptible to LND.

Activity against bioterror pathogens

LND has demonstrated activity against a wide range of bioterror pathogens, including *Bacillus anthracis*, *Burkholderia pseudomallei*, *Francisella tularensis*, *Burkholderia mallei,* and *Yersinia pestis*.[7]

PHARMACOKINETICS

The approved clinical dose regimens of LND and ALND are formulated as IV and oral dosage regimen, respectively; their approved clinical dose is 800 mg, BID, 90 min infusion, and 1000 mg, BID, oral, respectively. Studies reveal that on administration through a different route, the drug possesses pharmacokinetic properties that are stated below.[11]

Absorption

On ingesting the tablet; the prodrug undergoes ester-mediated biotransformation largely in the liver; the active form of the drug gets absorbed at Tmax of 0.5–2 h. The bioavailability of the drug is 90% in fasting condition and food does not much affect the Cmax of the drug.

Distribution

The drug in systemic circulation gets distributed in all parts of the body and body fluids. The mean apparent volume of distribution for IV and oral administration is 32.7 and 55.44 L respectively, and serum protein binding is 70–90%, the alveolar macrophage concentration is 35.3 which even surpasses the MIC 90 values; hence, studies suggest a potency of drug toward treating respiratory infections.

Metabolism

LND is metabolised through Phase II metabolism or biotransformation and involves very less involvement of cytochrome P450 system, the major metabolite formed about 72% of IV dose and 66.77% of an oral dose is excreted as LND sulphate. Various other metabolites observed are glucuronide conjugates such as O-glucuronide and acyl glucuronide and five oxidative metabolites.

Excretion

The drug is finally eliminated out of the body either in changed or unchanged form. In oral and intravenous dose administration, the mean elimination half-life of drug LND is 7.35 h and 6.8 h approximately whereas serum clearance is 5.2 L/h and 4.2 L/h, respectively. After IV dose, 88.2% of the dose is recovered in which 16.2% is unchanged drug and 72% is major metabolite; whereas in oral administration, 97% oral dose is recovered out of which 30.8% is unchanged and 66.7% is metabolite LND sulphate.

CLINICAL ASPECTS

Indian drug regulator, DCGI has approved Wockhardt LND and ALND for acute bacterial skin and skin structure infections including diabetic foot infections and concurrent bacteraemia. The approval is based on a successfully conducted Phase 3 clinical study comparing LND with linezolid (Clinical Trial Registry India, CTRI/2017/06/008843).[9] These are the first novel chemical entity antibiotics researched and developed in India with various international collaborations across the globe. While the non-clinical and Phase 1 studies have been undertaken in the U.S., Europe, and India, the Phase 2 and Phase 3 clinical studies have been successfully completed in India. LND also shows clinically relevant activities against resistant respiratory pathogens such as macrolide and penicillin-resistant *S. pneumoniae*, *Streptococcus pyogenes*, *H. influenzae,* and *Moraxella catarrhalis*. It is also active against anaerobic pathogens as well as atypical respiratory pathogens such as *C. pneumoniae*, *L. pneumophila,* and *M. pneumoniae*.[7] Recently, the potent *in vitro* activity (MIC) of LND against contemporary Indian MRSA isolates, including the Bengal Bay clones, has been reported.[8] In one study, LND showed promising safety and efficacy when used as IV and/or oral therapy for the treatment of secondary bacterial pulmonary infections in COVID-19 patients.[15] The NorA efflux pump does not affect the activity of LND, demonstrating a significant advantage over other quinolones, including ciprofloxacin, norfloxacin, clinafloxacin, and gemifloxacin, which express efflux-mediated fluoroquinolone resistance. LND has undergone extensive clinical development with over 900 patients being exposed to LND at supratherapeutic doses of 2.6 g daily. Moreover, no safety concerns were identified in any study. One study has demonstrated that IV and oral therapy are safe and well tolerated in the treatment of ABSSSI and Gram-positive pathogens including MRSA.[4]

CONCLUSION

LND shows promising broad-spectrum antibacterial activity toward many bacteria, particularly toward MRSA, where many antibiotics fail. On the other hand, its oral as well as IV doses have a high therapeutic index which has not been reported to produce any toxicity. Multiple attributes, such as not being a substrate for the NorA efflux pump, preferential DNA gyrase activity, and being devoid of potential adverse effects, may offer a valuable therapeutic option for the management of complex and serious bacterial infections.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Jasovský D, Littmann J, Zorzet A, Cars O. Antimicrobial resistance-a threat to the world's sustainable development. Ups J Med Sci 2016;121:159-64.
2. Gajdács M. The continuing threat of methicillin-resistant *Staphylococcus aureus*. Antibiotics (Basel) 2019;8:52.
3. Sunagar R, Hegde NR, Archana GJ, Sinha AY, Nagamani K, Isloor S. Prevalence and genotype distribution of methicillin-resistant *Staphylococcus aureus* (MRSA) in India. J Glob Antimicrob Resist 2016;7:46-52.
4. Bhatia A, Mastim M, Shah M, Gutte R, Joshi P, Kumbhar D, *et al*. Efficacy and safety of a novel broad-spectrum anti-MRSA agent levonadifloxacin compared with linezolid for acute bacterial skin and skin structure infections: A phase 3, openlabel, randomized study. J Assoc Physicians India 2020;68:30-6.
5. Appelbaum PC. Microbiology of antibiotic resistance in *Staphylococcus aureus*. Clin Infect Dis 2007;45 Suppl 3:S165-70.
6. Appalaraju B, Baveja S, Baliga S, Shenoy S, Bhardwaj R, Kongre V, *et al*. *In vitro* activity of a novel antibacterial agent, levonadifloxacin, against clinical isolates collected in a prospective, multicentre surveillance study in India during 2016-18. J Antimicrob Chemother 2020;75:600-8.
7. Bhagwat SS, Nandanwar M, Kansagara A, Patel A, Takalkar S, Chavan R, *et al*. Levonadifloxacin, a novel broad-spectrum anti-MRSA benzoquinolizine quinolone agent: Review of current evidence. Drug Des Devel Ther 2019;13:4351-65.
8. Bakthavatchalam YD, Shankar A, Muniyasamy R,

Peter JV, Marcus Z, Triplicane Dwarakanathan H, *et al*. Levonadifloxacin, a recently approved benzoquinolizine fluoroquinolone, exhibits potent *in vitro* activity against contemporary *staphylococcus Aureus* isolates and Bengal bay clone isolates collected from a large Indian Tertiary Care Hospital. J Antimicrob Chemother 2020;75:2156-9.
9. Baliga S, Mamtora DK, Gupta V, Shanmugam P, Biswas S, Mukherjee DN, *et al*. Assessment of antibacterial activity of levonadifloxacin against contemporary gram-positive clinical isolates collected from various Indian hospitals using disk-diffusion assay. Indian J Med Microbiol 2020;38:307-12.
10. Rusu A, Lungu IA, Moldovan OL, Tanase C, Hancu G. Structural characterization of the millennial antibacterial (fluoro) Quinolones-shaping the fifth generation. Pharmaceutics 2021;13:1289.
11. Lautre C, Sharma S, Sahu JK. Chemistry, biological properties and analytical methods of levonadifloxacin: A review. Crit Rev Anal Chem 2020;1-9. doi: 10.1080/10408347.2020.1855412. Online ahead of print.
12. Saxena D, Kaul G, Dasgupta A, Chopra S. Levonadifloxacin arginine salt to treat acute bacterial skin and skin structure infection due to *S. aureus* including MRSA. Drugs Today (Barc) 2020;56:583-98.
13. Kongre V, Bhagwat S, Bharadwaj RS. Resistance pattern among contemporary gram positive clinical isolates and *in vitro* antimicrobial resistance. Int J Infect Dis 2021;101:8-119.
14. Tellis M, Joseph J, Khande H, Bhagwat S, Patel M. *In vitro* bactericidal activity of levonadifloxacin (WCK 771) against methicillin-and quinolone-resistant *Staphylococcus aureus* biofilms. J Med Microbiol 2019;68:1129-36.
15. Saseedharan S, Aneja P, Chowti A, Debnath K, Mehta K, Sonone P. Efficacy and safety of intravenous and/or oral levonadifloxacin in the management of secondary bacterial pulmonary infections in COVID-19 patients: Findings of a retrospective, real-world, multi-center study. Sanjith Int J Res Med Sci 2021;9:2935.

How to cite this article: Kalikar M. Levonadifloxacin. Vidarbha J Intern Med 2022;32:55-8.