Original Article

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Microbiology Section

Levonadifloxacin: A Novel Approved Drug Exhibiting Potent In vitro Activity against Gram Positive Bacterial Isolates from Patients Admitted in Intensive Care Units

TASNEEM SIDDIQUI[1], RAFAT SHAMIM[2], SANGRAM SINGH PATEL[3], CHINMOY SAHU[4]

ABSTRACT

Introduction: Levonadifloxacin is a novel antibiotic belonging to the benzoquinolizine subclass of fluoroquinolone with potent activity against Methicillin Resistant *Staphylococcus aureus* (MRSA) and Quinolone Resistant *Staphylococcus aureus* (QRSA). Both intravenous levonadifloxacin and its oral formulation have recently been approved in India for the treatment of acute bacterial skin related infections.

Aim: To assess the activity of levonadifloxacin against gram positive clinical isolates collected from Intensive Care Units (ICUs) using the disk-diffusion method.

Materials and Methods: The present descriptive study where non duplicate isolates of *Staphylococcus aureus (S. aureus)* and other gram positive isolates from various clinical samples from all Intensive Care Units (ICUs) were collected from June to December 2020 and subjected to levonadifloxacin susceptibility testing (disk diffusion method) as per the Clinical and Laboratory Standards Institute (CLSI) guidelines, 2020. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 25.0.

Results: A total of 142 gram positive clinical isolates collected from all ICUs of the hospital were analysed. These isolates included coagulase negative *S. aureus* 109 (76.8%), *S. aureus* 21 (14.8%) and *Enterococcus faecalis* 12 (8.4%). All the gram positive isolates of the study were susceptible to levonadifloxacin as per the prespecified interpretive criteria identified based on population pharmacokinetic model and Monte Carlo simulation enabled probability of pharmacodynamic target attainment analysis.

Conclusion: Results of this in vitro study shows good activity of levonadifloxacin against gram positive isolates including difficult to-treat methicillin resistant staphylococcal isolates collected from ICU patients.

Keywords: Antibiotic sensitivity, Drug, Fluoroquinolones, Methicillin resistant *Staphylococcus aureus*

INTRODUCTION

Methicillin resistant *Staphylococcus* are a major cause of healthcare-associated infections [1]. The World Health Organisation (WHO) has estimated a higher likelihood of mortality due to MRSA compared to infections with non resistant Staphylococcal isolates [2].

Recently, changes in the patient population, including increasing number of elderly, chronically ill and immunocompromised patients has led to the recognition of a large variety of infections caused by Coagulase Negative Staphylococci (CoNS) [3,4]. Moreover, the widespread use of Matrix-Assisted Laser Desorption Ionisation-Time-Of-Flight Mass Spectrometry (MALDI-TOF-MS) has allowed a better understanding of the clinical importance of different CoNS species [3,4]. CoNS represent the most common cause of bacteremia associated with indwelling devices, and most of these infections are hospital acquired [1]. Apart from this both CoNS and *S. aureus* cause Skin and Soft tissue Infections (SSSIs) [1,4,5].

Resistant staphylococcal isolates are difficult to treat particularly in ICUs. The two most deployed antibiotics to treat methicillin resistant staphylococcal infections at present are vancomycin and linezolid (teicoplanin and daptomycin to some extent); but both drugs have their limitations like vancomycin is considered as a suboptimal option in critically ill patients due to its weak bactericidal activity, poor penetration into tissues (such as lung), renal toxicity and risk of clinical failure due to Minimum Inhibitory Concentration (MIC) creep [6-8]. Linezolid is a bacteriostatic agent and therefore, not recommended to be used in Blood Stream Infections (BSI). Adverse side effects of linezolid like bone marrow suppression leading to thrombocytopenia requires its usage in shorter duration along with monitoring of safety parameters [9]. Thus, for treatment of methicillin resistant staphylococcal infections, clinicians require improved antibiotics that are bactericidal, having good tissue penetration and are safe especially for the longer duration use.

Levonadifloxacin is a novel antibiotic belonging to the benzoquinolizine subclass of fluoroquinolone with potent activity against MRSA and QRSA. Both intravenous levonadifloxacin and its oral formulation, alalevonadifloxacin, have recently been approved in India to treat acute bacterial infections in skin [10]. Its approval is based on a successfully conducted Phase three clinical study comparing levonadifloxacin with linezolid (Clinical Trial Registry India, CTRI/2017/06/008843) [11]. Good potency of levonadifloxacin against MRSA, QRSA and hetero-vancomycin-intermediate *S. aureus* is attributed to well differentiated mechanism of action involving preferential targeting to DNA gyrase while retaining high affinity toward topoisomerase IV as well [12]. Recently, the potent in vitro activity (MIC) of levonadifloxacin against contemporary Indian MRSA isolates, including the Bengal Bay clones, has been reported [13]. In another report, good in vitro activity of levonadifloxacin against gram positive isolates of BSIs have been reported [14].

Since, 10 µg levonadifloxacin disk has been approved by the CLSI in 2016 [15]. Thus, in this study Kirby-Bauer disk diffusion assay was used to assess the in vitro activity of levonadifloxacin against the bacterial isolates collected from the hospital.

MATERIALS AND METHODS

The present descriptive study which was conducted in Department of Microbiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, between June to December 2020. The study was conducted after obtaining Ethical Committee approval with Letter number- PGI/BE/1561/2021. A total of 142 gram positive clinical isolates collected from all ICUs of the hospital were analysed.

Inclusion criteria: All consecutive, non duplicate isolates of all Staphylococci and Enterococci from BSI, tissue fluids, indwelling catheter tips, skin and soft tissue and pus samples collected from ICUs considered clinically significant were included in the study.

Exclusion criteria: Duplicate isolates were excluded from study.

Study Procedure

Demographic information and clinical details of the patient included in the study were recorded. Culture of clinical specimens and species identification were performed according to laboratory guidelines. Species identifications of all isolates were confirmed by MALDI-TOF-MS using the Biotyper system according to manufacturer recommendations (VITEK MS, bioMérieux, USA). The zone diameter obtained with a 30 µg cefoxitin disk was used to determine methicillin resistance in Staphylococci.

Antimicrobial Susceptibility Testing (AST): Antibiotic sensitivity was done by Kirby-Bauer disk diffusion method as per CLSI, 2020 [16]. MICs were determined using Epsilometer test (E-test) method. It was performed as per manufacturer's instructions.

A 10 µg disk of Levonadifloxacin (Himedia, Mumbai, India) was used; however rest of the comparator antibiotic disks and E-strips were procured from Oxoid India Ltd., and bioMérieux, France respectively. Confirmation of MIC values was done by concurrent testing of CLSI-recommended quality control strains: *S. aureus* American Type Culture Collection (ATCC) 29213 and *Enterococcus faecalis (E. faecalis)* ATCC 29212 [16].

Sensitivity pattern of *Staphylococcus* and *E. faecalis* to the tested antibiotics were determined using breakpoints set by the CLSI, 2020 [16]. Interpretation of zone diameters of levonadifloxacin for *S. aureus* and *E. faecalis* and were done as per zone size ranges [Table/Fig-1] based on population pharmacokinetic model and Monte Carlo simulation enabled probability of pharmacodynamic target attainment analysis [17,18]. As there are no breakpoints for interpretation of levonadifloxacin in case of CoNS so breakpoints of *S. aureus* was used for its interpretation.

Microorganism	Disk diffusion (zone diameter in mm)		
	Susceptible	Intermediate	Resistant
*S. aureus** (methicillin-resistant, methicillin-susceptible, quinolone-resistant, quinolone-susceptible isolates)	≥17	14-16	≤13
E. faecalis†	≥10	-	≤9

[Table/Fig-1]: Susceptibility test interpretive criteria for levonadifloxacin [17,18].
*S.aureus: *Staphylococcus aureus*; †E.faecalis: *Enterococcus faecalis*

STATISTICAL ANALYSIS

Data analysis was performed using SPSS software, version 25.0 for descriptive statistics. Categorical data were described using numbers and percentages.

RESULTS

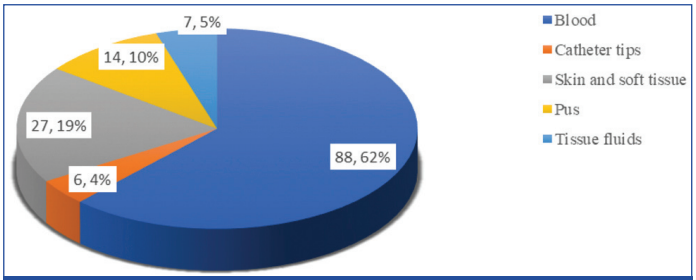
Total 142 gram positive clinical isolates were analysed in the study. The age of the patient population ranged from one month to 81 years with a median age of 36.5 years. The number of males and females enrolled in the study were 92 and 50, respectively with a M:F ratio of 1.8:1. Detailed clinical profile of the patients is illustrated in [Table/Fig-2]. Distribution of clinical sample is shown in [Table/Fig-3].

The most common clinical isolate was CoNS 109 (76.8%) followed by *S. aureus* 21 (14.8%) and *E. faecalis* 12 (8.4%) [Table/Fig-4,5].

Of the 109 CoNS isolated most common were *Staphylococcus haemolyticus* 46 (42.2%), *Staphylococcus epidermidis* 44 (40.4%), and *Staphylococcus hominis* 16 (14.7%) and there were two isolates of *Staphylococcus lugdunensis* and one isolate of *Staphylococcus capitis*, respectively.

Patient's clinical profile		Number of isolates (%)
A. Gender	a. Male	92 (64.8%)
	b. Female	50 (35.2%)
B. Age distribution		
<1 year		5 (3.5%)
1-20 years		22 (15.5%)
21-40 years		30 (21.2%)
41-60 years		50 (35.2%)
61-80 years		31 (21.8%)
>80 years		4 (2.8%)
Underlying clinical disorders		
Solid organ malignancy		19 (13.4%)
Haematological malignancy		28 (19.7%)
Renal disease		26 (18.3%)
Gastrointestinal disorders		7 (4.9%)
Respiratory disease		27 (19%)
Neurological disease		4 (2.8%)
Trauma		22 (15.5%)
Liver disease		9 (6.4%)

[Table/Fig-2]: Clinical profile of study population (n=142).



[Table/Fig-3]: Distribution of clinical sample isolates of the study (n=142).

Antimicrobial agents	Number of isolates (n=142)					
	MSSA* (n=13)	MRSA† (n=8)	MS-CoNS‡ (n=11)	MR-CoNS§ (n=98)	VSE‖ (n=6)	VRE** (n=6)
Ampicillin	8	8	7	98	4	6
Ampicillin-salbactum	7	8	5	98	3	6
Amikacin	1	1	0	35	NT††	NT††
Gentamicin	2	3	1	56	4	5
Clindamycin	6	4	4	87	NT††	NT††
Erythromycin	7	8	6	94	NT††	NT††
Doxycycline	0	1	0	77	1	2
Levofloxacin	12	5	2	72	1	6
Linezolid	0	0	0	3	0	5
Daptomycin	0	0	0	0	0	2
Vancomycin	0	0	0	0	0	6
Teicoplanin	0	0	0	0	0	6

[Table/Fig-4]: Susceptibility profiling of comparator antibiotics against clinical isolates of the study.
*MSSA: Methicillin sensitive *Staphylococcus aureus*, †MRSA: Methicillin resistant *Staphylococcus aureus*; ‡MS-CoNS: Methicillin sensitive coagulase negative *Staphylococcus*; §MR-CoNS: Methicillin resistant coagulase negative *Staphylococcus*; ‖VSE: Vancomycin sensitive *Enterococcus*; **VRE: Vancomycin resistant *Enterococcus*, ††NT: Not tested

Antibiotic susceptibility profile of clinical isolates: Amongst the 142 isolates of the study methicillin resistance in *S.aureus* and CoNS was seen in 8 (38.1%) out of 21 and 98 (89.9%) out of 109, respectively. Overall levofloxacin resistant was 98 (69%) isolates. The percentages of levofloxacin resistance were 17 (80.9%) out of 21 in *S. aureus*, 74 (67.9%) out of 109 in CoNS and 7 (58.3%) out of 12 in *E. faecalis* [Table/Fig-5]. All the isolates of *S. aureus* were 100% sensitive to vancomycin, teicoplanin and daptomycin. Susceptibility of other comparator antibiotics tested is shown in [Table/Fig-4]. Based on the diameter of zone of inhibition observed with 10 µg

levonadifloxacin disk, by employing the interpretive criteria provided in [Table/Fig-1], all the isolates including MRSA and MR-CoNS and VRE were susceptible to levonadifloxacin. Additionally all the levofloxacin resistant *S. aureus, CoNS* and *E. faecalis* isolates were susceptible to levonadifloxacin. The [Table/Fig-5] show the range and mean zone diameter values obtained for each of the gram positive organism groups tested in this study. In general, the zone diameter values were ≥20 mm suggesting the potent activity of levonadifloxacin against gram positive isolates.

Microorganism	Number of isolates (n)	Mean zones of inhibition in mm (range)
MSSA	13	30 (26-36)
MRSA	8	28 (24-34)
*LVX-S *S. aureus*	4	28 (26-36)
‡LVX-R *S. aureus*	17	26 (24-32)
MS-CoNS	11	26 (29-31)
MR-CoNS	98	24 (24-29)
*LVX-S-CoNS	27	26 (27-30)
†LVX-MS-CoNS	8	24 (29-31)
‡LVX-R-CoNS	74	24 (24-26)
VSE	6	22 (26-29)
VRE	6	21 (22-26)
*LVX-S-*E. faecalis*	5	22 (26-29)
‡LVX-R-*E. faecalis*	7	20 (22-25)
Total isolates	142	**Interpretation**: All 142 isolates susceptible to levonadifloxacin.

[Table/Fig-5]: Levonadifloxacin disk susceptibility analysis.
*LVX-S: Levofloxacin sensitive; †LVX-MS: Levofloxacin moderately sensitive; ‡LVX-R: Levofloxacin resistant

DISCUSSION

In the present study most common isolates was CoNS (76.8%) followed by *S. aureus* and *E. faecalis* which shows increasing trend of CoNS isolation which was similar to other ICU studies from India [19,20]. Of the 109 CoNS isolated, most common were *S. haemolyticus* (42.2%) followed by *S. epidermidis* and *S. hominis* which was similar to other studies [20,21]. Thirty eight percent methicillin resistance in *S. aureus* was seen which was consistent with other studies [22,23]. We found 89.9% of methicillin resistance CoNS which is consistent with other studies [24,25].

Levofloxacin resistance was noted in 67.9% CoNS, 80.9% *S. aureus* and 58.3% *E. faecalis* in the study. All the isolates of *S. aureus* were 100% sensitive to vancomycin, teicoplanin and daptomycin but 50% isolates of *E. faecalis* were resistant to vancomycin and teicoplanin but these results were in concordance with data from India [26]. The activity of levonadifloxacin against gram positive isolates observed in this study was consistent with various previous reports [13,15,17,18,27-29]. For instance, in a recent report by Appalaraju B et al., levonadifloxacin exhibited potent activity against 390 *S. aureus* isolates (98.7% susceptibility) collected from 15 tertiary hospitals, located in different parts of India including MRSA as well as quinolone resistant phenotypes [29]. In a study, 793 *S. aureus* isolates collected at a large tertiary care hospital at Vellore, Tamil Nadu and all were found to be susceptible to levonadifloxacin [13].

The Deoxyribonucleic Acid (DNA) gyrase and topoisomerase IV are two bacterial enzymes that are critical for bacterial DNA replication. Most quinolones approved to date for gram positive bacteria, are reported to have primary affinity for topoisomerase IV rather than DNA gyrase. Hence, activity of these agents is significantly impacted against those *S. aureus* isolates that carry mutations in topoisomerase IV. On the other hand, levonadifloxacin overcomes ciprofloxacin- and levofloxacin-resistance in *S. aureus* due to its preferential affinity towards DNA gyrase [12].

The 100% susceptibility rate observed for levonadifloxacin in this study supports its use as a therapeutic option for methicillin resistant staphylococcal infections. Additionally, it could also be used as an empirical therapy. In spite of vancomycin and linezolid showing similar high susceptibility rates, vancomycin use is often associated with nephrotoxicity and longer duration use of linezolid leads to myelosuppression. Contrary to vancomycin, levonadifloxacin can be administered to patient with renal or liver impairment without the need for dose adjustments. Moreover, the availability of oral formulation of levonadifloxacin with comparable pharmacokinetics feature allows easy intravenous to oral switch [30]. Enterococci are known to display high level of resistance to most of the antibiotic classes, but in this study all the *Enterococcus* isolates including levofloxacin resistant ones were susceptible to levonadifloxacin.

Limitation(s)

A study recruiting more number of Enterococci isolates is needed to prove activity of levonadifloxacin against *Enterococcus* spp.

CONCLUSION(S)

Results of this in vitro study shows good activity of levonadifloxacin against gram positive isolates including difficult-to-treat methicillin resistant staphylococcal isolates. The 100% susceptibility of isolates to levonadifloxacin observed in this study supports its potential clinical use in the treatment of infections particularly caused by methicillin resistant *Staphylococcus* and other gram positive organisms.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Microbiology, SGPGI, Lucknow, Uttar Pradesh, India.
2. Assistant Professor, Department of Anaesthesiology, SGPGI, Lucknow, Uttar Pradesh, India.
3. Assistant Professor, Department of Microbiology, SGPGI, Lucknow, Uttar Pradesh, India.
4. Associate Professor, Department of Microbiology, SGPGI, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Chinmoy Sahu,
Associate Professor, Department of Microbiology, SGPGI,
Lucknow, Uttar Pradesh, India.
E-mail: sahu.chinmoy@gmail.com

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