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ANTIMICROBIAL ACTIVITY OF LEVONADIFLOXACIN IN GRAM POSITIVE COCCI WITH SPECIAL REFERENCE TO MRSA

Microbiology

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ABSTRACT

Background: Levonadifloxacin is a novel benzoquinolizine subclass of quinolone with broad.spectrum activities against problematic pathogens such as methicillin.resistant Staphylococcus aureus, quinolone.resistant S. aureus, vancomycin intermediate S. aureus, and vancomycin.resistant S. aureus. Levonadifloxacin and its oral prodrug, alalevonadifloxacin, have been recently approved in India for the treatment of acute bacterial skin and skin structure infections, including concurrent bacteraemia and diabetic foot infections. The aim of the study is to assess the activity of levonadifloxacin against Gram.positive clinical isolates from our hospital. Nonduplicate isolates of S. aureus and other Gram.positive isolates collected from June 2022 to August 2022 were subjected to levonadifloxacin susceptibility testing (modified Kirby bauer method) as per the Clinical and Laboratory Standards Institute guidelines (CLSI Year 2022).Levonadifloxacin 10 µg impregnated disks were used during the testing. A total of 200 gram positive cocci isolated from different clinical samples. Most common isolates were MRSA followed by MR-CONS. MRSA were mostly isolated from pus specimen and enterococci were isolated from urine specimen. All the gram-positive organisms were susceptible (100%) to levonadifloxacin. The present study showed that levonadifloxacin was highly active against contemporary Gram.positive pathogens and furthermore demonstrated that levonadifloxacin susceptibilities can be reliably determined using the disc.diffusion method. Use of this novel antimicrobial can be used in multi drug resistant (MDR) gram positive organism and monitoring of adverse drug reaction for this drug will be crucial.

KEYWORDS

Levonadifloxacin, gram-positive cocci, vamcomycin, multi drug resistant

INTRODUCTION:

Staphylococcus aureus is a common cause of skin soft tissue infection. In India, the incidence of Methicillin.resistant Staphylococcus aureus (MRSA) is 30-40% in various geographical region of the country [1]. MRSA can be community or hospital acquired and community acquired is more virulent than the later. MRSA is major cause of concern because of resistance to most of first- and second-line drugs particularly in patients with skin and soft tissue infections. At present, the antibiotic resistance is also rising in clinical isolates of methicillin resistance Staphylococcus aures (MSSA).

Coagulase negative Staphlycoccus (CoNS) represent the most common cause of bacteremia associated with indwelling devices, immunodeficient patients and most of these infections are hospital acquired [2].Most of the common antibiotics which are being used are becoming resistant to vancomycin- resistant enterococci (VRE). Most of the human enterococcal infections are caused by E. faecalis and E. faecium, which are also a primary cause of hospital-acquired and multidrug resistant (MDR) infections. In patients with no risk factors, E. faecalis can cause community- acquired endocarditis [3].

Levonadifloxacin is a broad spectrum antibiotic belonging to benzoquinolizine subclass of fluroquinolones. Many studies established potent activity of levonadifloxacin against methicillin. resistant Staphylococcus aureus (MRSA) , quinolone. resistant S. aureus, vancomycin intermediate S. aureus (VISA), and vancomycin.resistant S. aureus (VRSA) [4]. Levonadifloxcin is available in both form intravenous and oral. Its prodrug alalevonadifloxacin is in form of oral formulation for use. These two drugs have recently approved in India for use in patient with soft tissue and skin infection and diabetic foot infection.

MATERIALS AND METHODS:

This is prospective study conducted from July 2022 to October 2022 in bacteriology lab of government tertiary care hospital of Pune.
Sample collection:

Non duplicate isolates of gram positive cocci isolates from clinical samples were included in the study. Gram positive cocci (GPC) were isolated from pus, blood, cerebrospinal fluid (CSF), ascitic fluid, peritoneal fluid, endotracheal tube suction and urine of the patients admitted in the ward and Intensive care Unit (ICU) of the hospital.Study procedure:

Staphylococcus aureus was identified by phenotypic method i.e beta haemolytic golden yellow colony on 5% sheep blood agar. After identification by colony morphology, biochemical test was put (tube coagulase, MR and VP, urease, mannitol fermentation was put for identification of species). Catalase negative growth were tested for bile esculin, arabinose and inulin fermentation. Bacitracin, cotrimoxazole and optochin disc were put on 5% sheep blood agar. Antimicrobial susceptibility test was done by Kirby bauer disc diffusion test as per CLSI 2022 guidelines. On cefoxitin (30ug) disc diffusion susceptibility, the gram-positive organism were classified into methicillin sensitive or methicillin resistant as per CLSI guidelines 2022.

Sensitivity pattern of Staphylococcus and E. faecalis to the tested antibiotics were accessed using breakpoints by the CLSI, 2022. Interpretation of zone diameters of levonadifloxacin for S. aureus and E. faecalis and were done as per zone size ranges [Table 1] based on population pharmacokinetic model and Monte Carlo simulation enabled probability of pharmacodynamic target attainment analysis [5,6]. As there are no breakpoints for interpretation of levonadifloxacin

in case of CoNS, breakpoints of S. aureus was used for its interpretation [7].

RESULTS:

In the present study, most of clinical isolates of gram-positive organism were from pus **(figure1)**. A total of 200 gram positive cocci isolated from different clinical samples. Most common isolates were MRSA followed by MR-CONS **(Table 2).** MRSA were mostly isolated from pus specimen and enterococci were isolated from urine specimen. The sensitivity pattern of different Staphylococci species is showed in **Table 3**. The sensitivity pattern of enterococci species is showed in **Table 4**.

DISCUSSION

A total of 200 gram positive organism were analysed in this study. Among them, largest was

S. aureus (n=95) and the MRSA proportion was 36.5%. The rate of MRSA was observed in the study is comparable to study conducted by Balinga et al [7]. All the isolates of S. aureus were 100% sensitive to vancomycin, teicoplanin which similar to study conducted by Shaikh et al [8]. Based on the zone diameter of inhibition observed with 10 µg levonadifloxacin disks, by employing the interpretive criteria Table 1, all the isolates including MRSA were susceptible to levonadifloxacin. In general, the zone diameter values were ≥20 mm suggesting the potent activity of levonadifloxacin against Gram-positive isolates. Against S. aureus isolates, the mean zone diameter ranged from 22 to 29 mm categorizing all the isolates as susceptible to levonadifloxacin. Similarly, other Gram-positive isolates were also levonadifloxacin susceptible with mean zone diameters ranging mostly between 20 and 30 mm. There were differences in mean zone diameters for isolates collected from the different geographical regions which could be ascribed to the differences in the proportions of MRSA. For instance, in a recent report by Appalaraju et al., levonadifloxacin exhibited potent activity against 390 S. aureus isolates (98.7% susceptibility) and Balinga (100% susceptibility)[9,7] Older fluoroquinolones, such as Fluroquinolone resistance in this study is more than 80% in both MRSA and MSSA which is comparative to study conducted by Balinga et al [7].

The activity of levonadifloxacin against Gram-positive isolates observed in this study is consistent with various previous reports [7,10]. This exceptional activity of this drug against Gram-positive oraganism, mainlly against MRSA, is attributed to its distinctive mode of action. The antibacterial action of fluoroquinolones in Gram-positive organisms involves inhibition of bacterial topoisomerases that play a critical role in DNA replication.[11] In contrast to other quinolones, such as ciprofloxacin and levofloxacin, which largely block DNAtopoisomerase IV, levonadifloxacin has a well-defined mechanism of action involving a strong affinity for staphylococcal DNA gyrase as well as topoisomerase IV [4].

Limitation:

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

Table 1: Interpretation of zone diameters of levonadifloxacin

Pathogen	Minimum inhibitory concentration (µg/ml)			Disk diffusion (zone diameter in mm)		
	S	I	R	S	I	R
S. aureus (methicillin−resistant, methicillin−susceptible, quinolone−resistant, quinolone−susceptible isolates)	≤2	4	≥8	≥17	14−16	≤13
S. pyogenes	≤1	2	≥4	≥20	-	≤19
E. faecalis	≤8	-	≥16	≥10	-	≤9
S. dysgalactiae spp. *Dysgalactiae*	≤0.25	-	≥0.5	≥20	-	≤19
S. agalactiae	≤0.5	-	≥1	≥20	-	≤19

S: Susceptibility, I: Intermediate, R: Resistance, S. pyogenes: Staphylococcus pyogenes, E. faecalis: Enterococcus faecalis, S. agalactiae: Streptococcus agalactiae, S. dysgalactiae: Streptococcus dysgalactiae, S. agalactiae: Streptococcus agalactiae

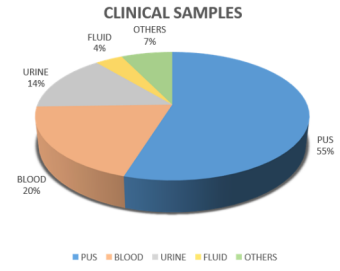

Figure 1. Clinical profile of isolates.

Table 2: Distribution of gram positive isolates in different clinical samples.

Microorganism	Number	Percentage
MRSA	73	36.5
MSSA	22	11
MR- CoNS	43	21.5
MS- CoNS	28	14
Enterococci species	15	7.5
Enterococci feacalis	17	8.5
Enterococci faecium	2	1

Table 3: Antimicrobial sensitivity pattern of Staphycoccus species.

Antibiotics	MRSA	MSSA	MR-CoNS	MS-CoNS
Erythromycin	24.6%	50%	6.9%	75%
Clindamycin	50.7%	81.8%	32.6%	82.1%
Gentamicin	77.1%	93.3%	70%	70%
Cotrimoxazole	80.8%	86.4%	46.5%	96.4%
Ciprofloxacin	13.6%	18.2%	13.9%	57.14
Linezolid	100%	100%	100%	100%
Vancomycin	100%	100%	100%	100%
Levonadifloxacin	100%	100%	100%	100%

Table 4: Antimicrobial sensitivity pattern of Enterococci species

Drugs	Enterococci species	Enterococci faecalis	Enterococci faecium
Ampicillin	53.3%	58.8%	50%
Erythromycin	40%	70.5%	50%
Cotrimoxazole	93.3%	88.2%	50%
Ciprofloxacin			50%
Norfloxacin	60%	76.4%	50%
Nitrofurantoin	60%	47.5%	50%
Linezolid	100%	100%	100%
Vancomycin	100%	100%	100%
Levonadifloxacin	100%	100%	100%

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