Actividad comparativa in vitro entre linezolid y tedizolid frente a aislados clínicos de Staphylococcus aureus resistentes a meticilina y aislados resistentes también a linezolid

Original

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Activity of linezolid and tedizolid against clinical isolates of methicillin-resistant and methicillin and linezolid resistant Staphylococcus aureus: an in vitro comparison

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ABSTRACT

Introduction. The prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in Spain is approximately 20-30%. However, resistance to linezolid is rare, and the main reports are from nosocomial outbreaks. The objective of the present study was to compare the in vitro susceptibility of linezolid with that of tedizolid against MRSA isolates and methicillin- and linezolid-resistant isolates (MLRSA) mediated by the cfr gene.

Material and methods. The in vitro susceptibility of linezolid and tedizolid was determined using the E-test with 18 MRSA strains and 18 cfr-mediated MLRSA strains obtained from clinical isolates in the microbiology service of a tertiary university hospital.

Results. All MRSA strains were susceptible to both antibiotics. Analysis of the MRSA isolates revealed that the MIC50 and MIC90 of linezolid were 1.5 and 2 mg/L, respectively; those of tedizolid were 0.25 and 0.4 mg/L. The MIC50 and MIC90 of tedizolid remained at 0.75 and 1 mg/L against the MLRSA strains (MIC90 ≥ 8 mg/L).

Conclusions. Both for MRSA and for MLRSA, the MICs obtained for tedizolid were at least 2 dilutions lower than those of linezolid, thus demonstrating between 2 and 4 times greater activity in vitro than linezolid.

Key words: Methicillin-resistant Staphylococcus aureus, linezolid-resistant Staphylococcus aureus, linezolid, tedizolid, cfr gene.

Resumen

Introducción. La prevalencia de Staphylococcus aureus resistente a la meticilina (SARM) se sitúa en España en torno al 20 y el 30%. Sin embargo, la resistencia a linezolid se reporta de forma excepcional, salvo en algunos brotes nosocomiales. El objetivo de nuestro estudio fue realizar un análisis comparativo de la sensibilidad in vitro de linezolid y tedizolid frente a aislados de SARM, así como frente a otros también resistentes a linezolid (SARLM) mediados por el gen cfr.

Material y métodos. Se determinó la sensibilidad in vitro a linezolid y tedizolid mediante la técnica de E-test con 18 cepas SARM y 18 cfr-mediated MLRSA obtenidas de aislados clínicos en el Servicio de Microbiología de un Hospital terciario Universitario.

Resultados. Todas las cepas de SARM fueron sensibles a ambos antibióticos. Analizando los aislados clínicos de SARM, las CMI50-CMI90 de linezolid fueron 1,5 y 2 mg/L respectivamente y en el caso de tedizolid de 0,25 y 0,4 mg/L. Frente a las cepas de SARLM (CMI90 ≥ 8 mg/L) las CMI50-CMI90 de tedizolid se mantuvieron en 0,75 y 1 mg/L.

Conclusiones. Tanto en el caso de las SARM como en el de las SARLM, las CMI obtenidas con tedizolid resultaron ser de al menos dos diluciones más bajas, demostrando entre 2 y 4 veces mayor actividad in vitro que linezolid.

Palabras Clave: Staphylococcus aureus resistente a meticilina, Staphylococcus aureus resistente a linezolid, linezolid, tedizolid, cfr gene.

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INTRODUCTION

Resistance to linezolid is increasingly frequent in the hospital environment. This resistance is the result of a genetic change at the binding site of linezolid, namely, 23S ribosomal RNA (rRNA). G2576T is the chromosomal mutation that most commonly leads to this genetic change. Given that all Staphylococcus species have between 4 and 7 copies of the gene that codes for 23S rRNA, several mutated copies are necessary before resistance to the drug is expressed, a circumstance that is unlikely to arise unless the patient receives prolonged treatment. Therefore, resistance of Staphylococcus aureus to oxazolidinones is less frequent than to other antibiotics, such as methicillin.

Resistance to linezolid mediated by the cfr gene, while less common than resistance caused by G2576T, could have a greater clinical impact, since its location in the plasmid potentially facilitates its dissemination in outbreaks. LaMarre et al. and Locke et al. showed the low in vitro fitness cost for Staphylococcus aureus of acquiring and expressing this plasmid gene, thus facilitating its propagation independently of antibiotic pressure. The cfr gene codes for a methyltransferase involved in the methylation of 23S rRNA, thus preventing binding to linezolid as a result of the steric hindrance generated. However, this does not affect the binding capabilities of tedizolid.

In the present study, we compare the in vitro activity of linezolid with that of tedizolid against strains of methicillin-resistant S. aureus (MRSA) and cfr-mediated methicillin- and linezolid-resistant (MLRSA) obtained during a nosocomial outbreak at our center.

MATERIAL AND METHODS

We obtained a total of 18 MRSA and 18 MLRSA strains from clinical samples received in the clinical microbiology department. The MRSA samples were isolated from exudates (9), blood cultures (5), and biopsy samples (4); the MLRSA samples were obtained from respiratory samples (7), blood cultures (5), vascular catheters (2), exudates (3), and cerebrospinal fluid (1). The minimum inhibitory concentration (MIC) was determined.

Table 1  In vitro activity of linezolid and tedizolid against methicillin-resistant Staphylococcus aureus (MRSA) and cfr-mediated methicillin-and linezolid-resistant Staphylococcus aureus (MLRSA).

<table>
<thead>
<tr>
<th>MRSA strains</th>
<th>MIC (mg/L)</th>
<th>MLRSA strains</th>
<th>MIC (mg/L)</th>
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<tbody>
<tr>
<td></td>
<td>Linezolid</td>
<td>Tedizolid</td>
<td>Linezolid</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0.19</td>
<td>1</td>
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<tr>
<td>2</td>
<td>2</td>
<td>0.5</td>
<td>2</td>
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<tr>
<td>3</td>
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<td>0.125</td>
<td>3</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0.19</td>
<td>6</td>
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<tr>
<td>7</td>
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<td>0.19</td>
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<td>8</td>
<td>1.5</td>
<td>0.25</td>
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<tr>
<td>9</td>
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<tr>
<td>10</td>
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<tr>
<td>18</td>
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<tr>
<td>MIC₅₀</td>
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<td>0.25</td>
<td>MIC₅₀</td>
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<tr>
<td>MIC₉₀</td>
<td>2</td>
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<td>MIC₉₀</td>
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<tr>
<td>Range</td>
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<td>[0.19-0.5]</td>
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using the E-test (bioMérieux for linezolid and Liofilchem for tedizolid). Therefore, we sowed a bacterial lawn (0.5 McFarland) on Mueller-Hinton agar dishes and applied E-test strips. The dishes were incubated at 37°C for 18 hours.

RESULTS AND DISCUSSION

All MRSA isolates were susceptible to both oxazolidinones. However, when the strains were analyzed, the MIC$_{50}$ and MIC$_{90}$ of linezolid were 1.5 and 2 mg/L, respectively, whereas those of tedizolid were 0.25 and 0.4 mg/L. Analysis of the MLRSA strains (MIC$_{90}$ to linezolid ≥ 8 mg/L) revealed that the MIC$_{50}$ and MIC$_{90}$ of tedizolid remained at 0.75 and 1 mg/L. Despite the fact that the susceptibility cut-offs defined by the CLSI$^7$ and EUCAST$^8$ are 0.5 for tedizolid and 4 for linezolid, the concentrations obtained with tedizolid proved to be at least 2 dilutions lower, thus demonstrating greater in vitro activity (tables 1 and 2).

We used the E-test, a gradient diffusion method that is rapid, reliable, and widely applied in the routine of the clinical microbiology laboratory. The adequate correlation of this technique with broth microdilution (CLSI reference method) for testing susceptibility to Staphylococcus species has been demonstrated elsewhere$^{9,10}$.

Tedizolid is a novel antibiotic from the oxazolidinone family, which until recently only comprised 1 member, linezolid. It is administered in the form of a phosphate ester, an inactive prodrug that is transformed into its active form via the action of plasma phosphates. Tedizolid is a stable drug within a wide range of pH values that binds to plasma proteins (70-90%) and has an oral bioavailability of more than 90%. Its high-affinity binding to plasma proteins and tendency toward high intracellular concentrations enable it to be administered in a single daily dose of 200 mg$^{11}$. The advantages of tedizolid over linezolid are its more pronounced postantibiotic effect, improved posology, lower frequency of adverse effects, and a lower ability to select resistance mutations$^{12}$.

Tedizolid was recently approved by the FDA and EMA for the treatment of infections of the skin and soft tissue, in which its liposolubility enabled it to reach high concentrations$^{11}$. Linezolid was recently considered to be more widely distributed in tissue, even in areas that are difficult to access, such as necrotic tissue, bone, the blood-brain barrier, pulmonary epithelium, and alveolar macrophages$^{13}$. However, the higher tissue concentrations reached by tedizolid, which are associated with lower myelotoxicity and drug interactions than linezolid$^{14,15}$, make it an interesting alternative in the treatment of infections by MRSA and MLRSA.

Taken together, the in vitro activity we found and the characteristics of the drug in terms of diffusion and safety enable us to conclude that tedizolid could be an alternative in the complex and prolonged regimens used to treat infection by MRSA, even in patients whose resistance to linezolid is mediated by $cfr$.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

DLM is the Director of the Antibiotics Section of the Medical Department of MSD. FJC is a medical advisor on antimicrobial drugs for MSD, Pfizer, Astellas, Novartis, Gilead, and AstraZeneca.

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