Successful treatment of Panton–Valentine leukocidin-positive methicillin-resistant Staphylococcus aureus pneumonia with high doses of linezolid administered in continuous infusion

Tratamiento eficaz de una neumonía comunitaria producida por un Staphylococcus aureus resitente a meticilina leukocidina Panton-Valentin con altas dosis de linezolid en perfusión continua

Pneumonia caused by methicillin-resistant Staphylococcus aureus (MRSA) strains producing a cytotoxin known as Panton–Valentin leukocidin (PVL) is a severe and difficult to treat disease. Linezolid has excellent epithelial lining fluid (ELF) penetration rates but drug concentrations in critically ill patients are highly variable. We describe the clinical case of a patient with septic shock secondary to a community-acquired PVL-secreting MRSA pneumonia, in which linezolid plasma concentration within the therapeutic range were only reached with the use of higher than recommended doses (600 mg every 8 h) administered in continuous infusion.

A 56-year-old Caucasian man was admitted on February 2, 2015 with a 4-day history of dyspnea, mucopurulent expectoration, and fever (>38°C). His weight was 80 kg (body mass index [BMI] 27.7 kg/m²), smoked 2-3 cigarettes a day, and consumed approximately 7 standard drinks daily. Physical examination revealed sinus tachycardia (160 beats/min), diaphoresis, hypertension (blood pressure [BP] 154/92 mmHg), and marked respiratory distress as well as bilateral crackles and disperse rhonchi up to the apex on lung auscultation. This caused a hypoxemic respiratory insufficiency with an initial PaO₂ of 55 mmHg that did not improve despite an elevated inspired oxygen fraction (FiO₂ 0.5) and noninvasive mechanical ventilation, for which he needed orotracheal intubation and ICU admission. Blood urea nitrogen was 32 mg/dL, serum creatinine 0.88 mg/dL, and glomerular filtration rate (Cockcroft–Gault equation) 106 mL/min, C-reactive protein 25.6 mg/L, procalcitonin 24.17 ng/mL, and lactic acid 5 mmol/L. Other laboratory data were unrevealing. Chest radiography revealed bilateral alveolar and interstitial infiltrates and alveolar condensation in the right upper lobe. The patient was tentatively diagnosed with CAP and was treated empirically with intravenous ceftriaxone (2 g every 24 h), intravenous levofloxacin (0.5 g every 12 h) (positive urinary detection of
pneumococcal antigen), and oseltamivir (positive PCR assay detection of influenza A and B viruses in oropharyngeal swabs). During the first 24 h of ICU admission, the patient’s condition deteriorated, with secondary septic shock and need of vasoactive drugs (norepinephrine 0.2 μg/kg/min). Microbiologically, a MRSA was isolated in cultures from bronchial aspirates and in four blood culture bottles (linezolid minimum inhibitory concentration [MIC] = 2 mg/L) on the day of admission. Each MRSA isolate carried the PVL genes. The MRSA strain was sent to the National Microbiology Center (Institute of Health Carlos III, Madrid). The initial empirical antibiotic treatment was discontinued and linezolid at a standard dose (600 mg every 12 h infused over 60 min) was administered.

Treatment with linezolid was maintained and the remaining antimicrobials were discontinued. Steady state plasma concentrations of linezolid were determined from the third day of treatment using a high-performance liquid chromatography technique, with a minimum plasma concentration state (C_{min}^{ss}) (or pre-dose) of 0.8 mg/L and maximum (C_{max}^{ss}) (at the end of infusion) of 4.8 mg/L, which were considered subtherapeutic (therapeutic range C_{min}^{ss} > 2 mg/L). Although blood cultures became negative on the fifth day of treatment, the patient showed a protracted respiratory clinical course with worsening of radiographic images, and according to drug susceptibility testing, antimicrobial coverage was expanded with intravenous clindamycin (600 mg every 8 h) and ciprofloxacin (400 mg every 8 h). In addition, treatment with linezolid was maintained and the remaining antimicrobials were discontinued.

Table 1: Changes in doses, intervals between doses, forms of administration, and plasma concentrations of linezolid during the patient’s stay in the ICU.

<table>
<thead>
<tr>
<th>Day of sampling</th>
<th>Dose (mg)</th>
<th>Dosing interval</th>
<th>Type and duration of infusion</th>
<th>GFR (mL/min)</th>
<th>C_{min}^{ss} (mg/L)</th>
<th>Platelet count (× 10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 13, 2015</td>
<td>600</td>
<td>12 h</td>
<td>Intermittent (60 min)</td>
<td>176</td>
<td>0.5</td>
<td>112</td>
</tr>
<tr>
<td>February 17, 2015</td>
<td>600</td>
<td>12 h</td>
<td>Intermittent (60 min)</td>
<td>239</td>
<td>&lt;0.5</td>
<td>85</td>
</tr>
<tr>
<td>February 23, 2015</td>
<td>600</td>
<td>8 h</td>
<td>Extended (2 h)</td>
<td>345</td>
<td>&lt;0.5</td>
<td>456</td>
</tr>
<tr>
<td>February 24, 2015</td>
<td>600</td>
<td>6 h</td>
<td>Extended (2 h)</td>
<td>267</td>
<td>1.4</td>
<td>531</td>
</tr>
<tr>
<td>February 26, 2015</td>
<td>600</td>
<td>6 h</td>
<td>Extended (2 h)</td>
<td>301</td>
<td>0.6</td>
<td>540</td>
</tr>
<tr>
<td>March 2, 2015</td>
<td>600</td>
<td>6 h</td>
<td>Continuous (6 h)</td>
<td>301</td>
<td>8.5</td>
<td>544</td>
</tr>
<tr>
<td>March 6, 2015</td>
<td>600</td>
<td>8 h</td>
<td>Continuous (8 h)</td>
<td>275</td>
<td>2.7</td>
<td>527</td>
</tr>
<tr>
<td>March 9, 2015</td>
<td>600</td>
<td>8 h</td>
<td>Continuous (8 h)</td>
<td>333</td>
<td>4.6</td>
<td>467</td>
</tr>
</tbody>
</table>

GFR: glomerular filtration rate.
Strategies for optimizing linezolid plasma levels include an increase in the total dose, by-reducing the dosing interval from 12 h to every 8 or 6 h, or extending the duration of infusion to 2–4 h (extended infusion) or using a continuous infusion.\textsuperscript{9,10} Our patient in whom glomerular filtration rates >200 mL/min were recorded, a $C_{\text{min}} \geq 4 \text{ mg/L}$ were only obtained with the administration of a linezolid dose of 600 mg every 6–8 h in continuous infusion, which coincided with negativization of pulmonary exudate cultures. This high dose, between 1.5 and 2-fold higher than the standard recommended dose was well tolerated, without signs of toxicity, particularly without a decrease in platelet count or hemoglobin levels.

In ICU patients with severe infections and increased renal clearance, linezolid should be administered at high doses and in continuous infusion with close monitorization of plasma drug levels.

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Conflicts of interest

None declared.

References


