Pharmacokinetics Of Linezolid

During Extracorporeal Membrane Oxygenation

Sir,

The extracorporeal membrane oxygenation (ECMO) is increasingly used in the critical setting for patients with respiratory failure and there is a growing body of knowledge describing the associated variations in plasma concentrations of drugs, including antibiotics, due to drug adsorption on the different components of the ECMO circuit. Currently, a multicentre study is ongoing to confirm if the standard antibiotic dosing in adult patients may still be considered appropriate [1]. Linezolid (LNZ) is extensively used in patients with pneumonia in critical care because of its strong activity against *Staphylococcus aureus* and its high pulmonary penetration, but there are no data on LNZ pharmacokinetics during ECMO [2]. Here we report the main pharmacokinetic parameters in three critically ill patients on ECMO treated with LNZ.

Patient 1 was a 61-year-old man, with a body mass index (BMI) of 24, who underwent lung transplantation because of chronic obstructive pulmonary disease and was treated with LNZ for pneumonia caused by meticillin-resistant *S. aureus* (MRSA) with a LNZ minimum inhibitory concentration (MIC) of 1 mg/L. Patient 2 was a 40-year-old woman (BMI = 18) with cystic fibrosis (CF) who was on the transplant list, empirically treated with LNZ and previously colonised by MRSA. Patient 3 was a 32-year-old woman (BMI = 31) with severe pneumonia caused by influenza H1N1 and pulmonary bacterial superinfection by meticillin-susceptible *S. aureus* (LNZ MIC
= 4 mg/L) isolated from bronchoalveolar lavage, previously treated with oxacillin that was stopped because of jaundice.

Plasmatic concentrations of LNZ were studied during ECMO, after informed consent was signed, at steady-state with the standard dosage of 600 mg every 12 h intravenously by 1-h infusion. The area under the curve (AUC) of daily ($\text{AUC}_{0-24}$) plasma concentrations of LNZ was calculated with blood samples collected before (time 0) and 1, 2.5, 4, 6 and 8 h after the intravenous administration. Minimum plasma concentration ($C_{\text{min}}$) is defined as the concentration before the administration and the maximum plasma concentration ($C_{\text{max}}$) is defined as the concentration at the end of the infusion. LNZ was determined in plasma by ultra performance liquid chromatography-photodiode array (UPLC-PDA) method. Pharmacokinetic data were studied using Kinetica software (Thermo Scientific, Waltham, MA) and $\text{AUC}_{0-24}$ was calculated as $\text{AUC}_{0-24} = 2 \times \text{AUC}_{0-12}$ [3]. In Table 1 the main LNZ pharmacokinetic parameters are reported, such as $C_{\text{max}}, C_{\text{min}}, \text{AUC}_{0-24},$ half-life ($t_{1/2}$), clearance (CL), time above the MIC ($t > \text{MIC}$) and volume of distribution ($V_d$); we also reported in Table 1 the LNZ pharmacokinetic parameters calculated with $S. \text{ aureus}$ MICs corresponding to 1, 2 and 4 mg/L for Patients 1, 2 and 3, respectively.

These results show that the calculated pharmacokinetic parameters of LNZ during ECMO are satisfactory when the MRSA MIC is $\leq 1$ mg/L, with $\text{AUC}_{0-24}/\text{MIC}$ ratio $\geq 80$ in all patients [3, 4]. Only patient 3 did not display a full 24-hour plasma concentration above the MIC = 1 mg/L, with $t > \text{MIC}$ corresponding to 66% of the
dosing interval. The rate of achievement of pharmacological parameters decreases for all patients with MIC values > 1 mg/L, as detailed in Table 1, for both AUC$_{0-24}$/MIC ratios and $t >$ MIC.

This is the first report of LNZ plasma concentrations in patients treated with ECMO, where we also included calculated data for different MICs to provide a reference for future patients. According to our data, even if limited, pharmacokinetic targets are not achieved with standard dosage of LNZ when the MRSA MIC is >1 mg/L.

Notwithstanding the limited sample size and heterogeneity of patients, including lung transplant, CF and high BMI, we conclude that plasma pharmacodynamic targets are easily achieved only when the $S. aureus$ MIC is ≤1 mg/L. According to our results, patients infected by $S. aureus$ with MICs > 1 mg/L on ECMO should be considered, pending future confirmation, at considerable risk of inadequate pharmacokinetic coverage. Prolonged or continuous infusion of LNZ might be needed in critically ill patients to increase AUC$_{0-24}$/MIC ratios or $t >$ MIC, as well as increased dosage or combination therapy.

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References


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Table 1.

Pharmacokinetic parameters of linezolid for patients 1, 2 and 3, and calculated data for *Staphylococcus aureus* minimum inhibitory concentrations (MICs) of 1, 2 and 4 mg/L.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>15.67</td>
<td>18.51</td>
<td>15.61</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (mg/L)</td>
<td>4.25</td>
<td>0.47</td>
<td>0.43</td>
</tr>
<tr>
<td>AUC$_{0-24}$ (mg h/L)</td>
<td>212.58</td>
<td>165.65</td>
<td>100.59</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>5.65</td>
<td>7.24</td>
<td>13.35</td>
</tr>
<tr>
<td>$V_d$ (L)</td>
<td>49.7</td>
<td>17.6</td>
<td>46.77</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>6.10</td>
<td>1.68</td>
<td>2.20</td>
</tr>
</tbody>
</table>

Calculated data

| AUC$_{0-24}$/MIC (MIC = 1) | 212.58 | 165.65 | 100.58 |
| AUC$_{0-24}$/MIC (MIC = 2) | 106.29 | 82.83  | 50.30  |
| AUC$_{0-24}$/MIC (MIC = 4) | 53.14  | 41.41  | 25.15  |
| $t>\text{MIC}$ (MIC = 1) (% over 12 h) | 100 | 100 | 66 |
| $t>\text{MIC}$ (MIC = 2) (% over 12 h) | 100 | 75 | 41 |
| $t>\text{MIC}$ (MIC = 4) (% over 12 h) | 100 | 58.3 | 30 |

$C_{\text{max}}$, maximum plasma concentration; $C_{\text{min}}$, minimum plasma concentration; AUC$_{0-24}$: area under the curve of plasma daily concentrations; CL, clearance; $V_d$, volume of distribution; $t_{1/2}$, half-life; $t>\text{MIC}$, time of plasma concentrations above the MIC.