Time-dependent antibacterial effects of linezolid in experimental rabbit endocarditis


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Sir,

Previous studies in a rabbit model of staphylococcal endocarditis have demonstrated significant antibacterial effects with the oxazolidinone linezolid.1,2 In those studies, increases in peak and trough linezolid plasma levels were noted between the first and final doses of the 5 day treatment period. We report results of additional studies to determine the effects of treatment duration on the antibacterial activity and pharmacokinetics of linezolid over a 5 day treatment regimen (75 mg/kg oral three times a day) in this model.

Twenty-four hours following surgery to implant carotid catheters across the aortic valve, rabbits were inoculated with 106 cfu methicillin-resistant Staphylococcus aureus (MRSA). Eighteen hours later, linezolid treatment was initiated. On each day of treatment, periodic plasma samples were obtained from groups of rabbits for pharmacokinetic analysis prior to sacrifice and determination of antibacterial effects at 8 h trough. Compared with controls, no antibacterial effects were observed following the initial linezolid dose on day 1 (Table 1). Pharmacokinetic analysis determined that the initial linezolid dose was rapidly cleared from the blood with a short half-life. Plasma linezolid levels at trough were well below the MIC for the MRSA strain and drug levels in valve vegetation were not determined, the antibacterial effects and maintenance of linezolid plasma levels above the MIC for a 5 day treatment regimen (75 mg/kg oral three times a day) in this model.

Pharmacokinetic analysis prior to sacrifice and determination of antibacterial effects at 8 h trough. Compared with controls, no antibacterial effects were observed following the initial linezolid dose on day 1 (Table 1). Pharmacokinetic analysis determined that the initial linezolid dose was rapidly cleared from the blood with a short half-life. Plasma linezolid levels at trough were well below the MIC for the MRSA strain and drug levels in valve vegetation were not determined, the antibacterial effects and maintenance of linezolid plasma levels above the MIC for a 5 day treatment regimen (75 mg/kg oral three times a day) in this model.

It is important to consider that the pharmacokinetic parameters and trough plasma and vegetation linezolid levels on day 2 indicate substantial drug accumulation after the initial dose(s) on day 1. Rapid tissue distribution and accumulation of linezolid following multiple oral doses has also been reported in a recent clinical study.3 AUC24 to MIC ratios >100 have been shown to correlate with clinical efficacy of aminoglycosides and fluoroquinolones, while Cmax to MIC ratios ≥8 result in a low likelihood of resistance development.4 Linezolid AUC24 to MIC ratios were >100 in the present study, although statistical comparisons did not confirm a correlation with significant antibacterial effects. Studies in standard animal models of lung and thigh infection have shown that the efficacy of β-lactams and macrolides does not correlate with AUC/MIC, but does correlate with the percentage of time that the drug levels were maintained above the MIC for the pathogen used. Preliminary evidence shows a positive correlation between antibacterial effects and maintenance of linezolid plasma levels above the MIC for ~40% of the dosing interval in a neutropenic mouse model of thigh infection.5 In the present endocarditis study, linezolid trough plasma levels were maintained above the MIC for this MRSA strain for the entire dosing interval on each day except day 1. Other rabbit endocarditis studies have stressed the importance of maintaining plasma levels above the MIC to achieve efficacy.6

It is important to consider that the pharmacokinetic requirements for efficacy in experimental endocarditis are more stringent compared with those for lung or thigh infections. Bacterial endocarditis is a deep-seated infection that is difficult to cure for several reasons. The vegetation is avascular, and is comprised of layers of platelets and fibrin, which reduces both neutrophil host-defence mechanisms and penetration of antimicrobial agents. In addition, the metabolic state of the bacteria within the vegetation may be reduced, lowering the effectiveness of drugs that target actively growing bacteria. In this setting, antibacterial agents such as β-lactams that have slow killing rates and no post-antibiotic effect must be administered at short intervals in order to maintain drug levels above the MIC throughout the entire dosing interval. The present study with linezolid demonstrates that maintaining plasma and valve vegetation drug levels above the MIC for the entire dosing interval over multiple days results in progressive reduction in bacterial counts in infected valves. While regional linezolid concentrations within the valve vegetation were not determined, the antibacterial effects and substantial drug concentration in valve homogenates suggest sufficient penetration of the drug.

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The MIC and MBC of linezolid for this strain of MRSA were 2 and >64 mg/L, respectively. Time–kill studies at 8× and 16× the linezolid MIC demonstrated a 1.8 and 2 log reduction in bacterial counts at 24 h. Despite these bacteriostatic effects in vitro, linezolid has been proven to produce significant antibacterial effects in the present, and in previous studies of experimental endocarditis.

References


Table 1. Valve vegetation bacterial counts (log_{10} cfu/g), valve vegetation drug concentration (mg/kg) and pharmacokinetic results in rabbits treated with linezolid 75 mg/kg orally three times a day

<table>
<thead>
<tr>
<th></th>
<th>Control (n=10)</th>
<th>Dose 1 (day 1) (n=5)</th>
<th>Dose 4 (day 2) (n=10)</th>
<th>Dose 7 (day 3) (n=10)</th>
<th>Dose 10 (day 4) (n=9)</th>
<th>Dose 13 (day 5) (n=10)</th>
<th>Dose 15 (final) (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetation counts</td>
<td>8.6±0.7</td>
<td>8.6±0.7</td>
<td>6.1±2.2</td>
<td>5.6±1.3</td>
<td>5.3±1.6</td>
<td>4.6±1.6</td>
<td>3.4±0.4</td>
</tr>
<tr>
<td>Vegetation drug concentration</td>
<td>&lt;0.003</td>
<td>6.7±8.2***</td>
<td>4.5±3.2**</td>
<td>20.2±2.9**</td>
<td>12.9±7.3**</td>
<td>11.5±8.6**</td>
<td>11.5±8.6**</td>
</tr>
<tr>
<td>AUC(0–8 h) (µg·h/mL)</td>
<td>20±14</td>
<td>178±139**</td>
<td>184±50**</td>
<td>322±193**</td>
<td>293±68**</td>
<td>241±79**</td>
<td>241±79**</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>9.8±7.8</td>
<td>37.1±2.8**</td>
<td>38.8±7.8**</td>
<td>56.5±23.1**</td>
<td>48.6±9.7**</td>
<td>44.5±12.8**</td>
<td>44.5±12.8**</td>
</tr>
<tr>
<td>C_{min} (mg/L)</td>
<td>0.4±0.6</td>
<td>10±11.1**</td>
<td>8.1±4.6**</td>
<td>26.3±22.4**</td>
<td>24.5±10.1**</td>
<td>17.1±12.8**</td>
<td>17.1±12.8**</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>1.4±0.9</td>
<td>4.3±3.6**</td>
<td>2.8±1.1**</td>
<td>7.2±5.4**</td>
<td>7.9±5**</td>
<td>5.9±4.3**</td>
<td>5.9±4.3**</td>
</tr>
</tbody>
</table>

*P≤0.05 versus control, **P≤0.05 versus day 1 (lowest level of quantification). Values are means ± S.D.