A comparison of linezolid lung tissue concentrations among patients with drug-resistant tuberculosis

Russell Kempker, Emory University
M. Tobias Heinrichs, University of Florida
Ketino Nikolaishvili, National Center for Tuberculosis and Lung Diseases
Irina Sabulua, National Center for Tuberculosis and Lung Diseases
Nino Bablishvili, National Center for Tuberculosis and Lung Diseases
Shota Gogishvili, National Center for Tuberculosis and Lung Diseases
Zaza Avaliani, National Center for Tuberculosis and Lung Diseases
Brent Little, Emory University
Adam Bernheim, Emory University
Hartmut Derendorf, University of Florida

Only first 10 authors above; see publication for full author list.

Journal Title: European Respiratory Journal
Volume: Volume 51, Number 2
Publisher: European Respiratory Society: ERJ | 2018-02-01, Pages 1702166-1702166
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1183/13993003.02166-2017
Permanent URL: https://pid.emory.edu/ark:/25593/tnkk7

Final published version: http://dx.doi.org/10.1183/13993003.02166-2017

Copyright information:
EUROPEAN RESPIRATORY SOCIETY.

Accessed February 28, 2020 11:21 AM EST
A comparison of linezolid lung tissue concentrations among patients with drug-resistant tuberculosis

Russell R. Kempker1, M. Tobias Heinrichs2, Ketino Nikolaishvili3, Irina Sabulua3, Nino Bablishvili2, Shota Gogishvili3, Zaza Avaliani3, Brent P. Little4, Adam Bernheim4, Hartmut Derendorf2, Henry M. Blumberg1,5, Sergo Vashakidze3, and Charles A. Peloquin2

1Division of Infectious Diseases, Dept of Medicine, Emory University School of Medicine, Atlanta, GA, USA.
2University of Florida, College of Pharmacy, Gainesville, FL, USA.
3National Center for Tuberculosis and Lung Disease, Tbilisi, Georgia.
4Dept of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA, USA.
5Depts of Epidemiology and Global Health, Emory Rollins School of Public Health, Emory University, Atlanta, GA, USA.

To the Editor:

Linezolid has become a frequent component of treatment regimens for drug-resistant tuberculosis and is a group C drug in the latest World Health Organization treatment guidelines [1]. However, linezolid has a narrow therapeutic index and there is no consensus on the optimal dose for patients with tuberculosis [2, 3]. A better understanding of lung tissue penetration could provide insight into ideal dosing and the utility of linezolid in patients with severe lung lesions. To evaluate target site lung concentrations of linezolid, we utilised the technique of microdialysis, which facilitates the measurement of unbound (pharmacologically active) extracellular drug concentrations at the site of disease.

Consenting patients with culture-confirmed tuberculosis, already receiving linezolid and undergoing adjunctive surgical resection in Tbilisi, Georgia were enrolled [4, 5]. Patients fasted overnight and received linezolid two hours before surgery. Serum samples were collected immediately before and 1, 4 and 8 h after linezolid administration and at the time of resection. Microdialysis was performed ex vivo on resected lung, immediately after surgical removal. Guided by visual and manual inspection, two semi-permeable microdialysis probes were inserted into both diseased and non-diseased lung tissue. The first probe was placed in the centre of the resected lesion and the second probe was placed in the non-diseased surrounding lung tissue. Four different concentrations of linezolid (0.5, 5, 25 and 100 μg·mL⁻¹) were each infused for every patient for ~35 min, at a rate of 1 μg·min⁻¹, and...
the recovered fluid “dialysate” was collected. Drug concentrations were measured at the University of Florida Infectious Diseases Pharmacokinetics Laboratory, using a validated liquid chromatography-tandem mass spectrometry assay. The six-point standard curves ranged from 0.3–30.0 μg·mL$^{-1}$ with linearity extending above and below this range; recovery of linezolid from human plasma was approximately 87%. A modification of this assay (range 0.3–120 μg·mL$^{-1}$) was used for dialysate samples. Non-compartmental pharmacokinetic analysis was performed. The fraction of the dose absorbed was assumed to be 1 for analysis. Free linezolid serum concentrations were calculated by multiplying the measured serum linezolid concentration by the reported rate of protein binding of 31% (serum concentration × 0.31) [6]. In comparing free serum and tissue drug concentrations, the serum concentration from the time of surgical resection was used. Pre-operative chest computed tomography (CT) scans, when available, were reviewed independently by radiologists. Tissue cultures were performed on resected lung tissues.

Eight male patients with a median age of 34 years were enrolled. The median body mass index was 23.8 kg·m$^{-2}$, creatinine clearance was 104.2 mL·min$^{-1}$ and albumin was 4.3 g·dL$^{-1}$. Five patients had multidrug-resistant and three had extensively drug-resistant tuberculosis. Half of the patients were re-treatment cases. At the time of resection, patients were receiving linezolid for a median duration of 194 days. All patients were receiving a linezolid dose of 600 mg once daily and the median linezolid dose by weight was 8.3 mg·kg$^{-1}$ (range 7.6–9.9 mg·kg$^{-1}$). On chest CT scans, five patients showed a nodule; two, a cavity; and one, an infiltrate as the predominant lesion. All lung tissue cultures were negative for Mycobacterium tuberculosis.

Among the eight patients receiving linezolid, the median maximum serum concentration (12.98 μg·mL$^{-1}$), area under the curve (AUC) from time zero to infinity (104 h·μg·mL$^{-1}$), length of time that the drug was present at the maximum concentration in serum (2 h); and half-life (4.5 h) were similar to those reported in the literature. The median free (non-protein-bound) linezolid concentration in diseased lung tissue was 3.57 μg·mL$^{-1}$ (range 0.81–7.09 μg·mL$^{-1}$), and in non-diseased lung, it was 3.85 μg·mL$^{-1}$ (range 1.17–10.24 μg·mL$^{-1}$), with no significant difference between the two (p=0.73). There was a nonsignificant trend towards higher linezolid lung tissue concentrations in new versus previously treated patients in both diseased (4.68 versus 2.81 μg·mL$^{-1}$; p=0.28) and non-diseased lung tissue (5.42 versus 2.92 μg·mL$^{-1}$; p=0.27). The median diseased tissue/serum linezolid concentration was 0.49 (range 0.18–0.92) (table 1).

Our results indicate relatively low lung tissue penetration of linezolid in both diseased and non-diseased lung tissue, among patients with multidrug-resistant tuberculosis. In all patients, the free linezolid concentration in diseased lung was lower than the serum concentrations, as was the case for seven out of eight patients with regards to non-diseased lung compared to serum. Lung tissue penetration of linezolid (lung/serum ratio 0.49) was lower than we what we have previously shown for levofloxacin (1.33) and pyrazinamide (0.77), utilising the same microdialysis method [5, 7]. The trend towards lower lung tissue concentrations of linezolid in re-treatment tuberculosis cases warrants further study. This finding suggests that accumulating lung damage from multiple episodes of tuberculosis might result in a change in lung tissue architecture, thereby reducing drug penetration.
The clinical significance of this relatively low drug penetration of linezolid into lung tissue is unclear. Although linezolid minimum inhibitory concentration (MIC) testing was not performed, the free linezolid drug concentrations in the lung were higher than the suggested epidemiological MIC cut-off of 0.5 mg·L$^{-1}$ in all cases, and above the generally accepted clinical susceptibility breakpoint of 1 mg·L$^{-1}$ in seven patients [8]. In addition, in seven out of eight patients, the linezolid concentration in diseased lung was higher than the mutant prevention concentration found in 90% (MPC90) of M. tuberculosis isolates in one study that used a concentration of 1.2 mg·L$^{-1}$ [9]. The one patient with a linezolid concentration in diseased lung of <1 mg·L$^{-1}$ received the lowest weight-based dose, and correspondingly had the lowest serum drug concentration. In addition, all patients had negative tissue cultures (half of the patients were also receiving bedaquiline), which is in contrast to the high rates of positive lung tissue cultures we found among patients with multidrug-resistant tuberculosis receiving traditional second-line drug regimens [7,10]. While our results suggest that once a day 600 mg dosing could provide adequate lung tissue concentrations, they also urge caution when using doses less than 600 mg.

Our results build on prior research that describes tissue penetration of second-line anti-tuberculosis drugs, utilising the method of microdialysis, which allows for the measurement of free “active” drug at the site of disease. They also add to the scant literature on lung penetration of linezolid. The only prior report of linezolid lung tissue concentrations to our knowledge, was in a paediatric patient with multidrug-resistant tuberculosis who underwent lung resection surgery. This patient received their last dose of linezolid 36 h before surgery, and drug concentrations were obtained using whole tissue homogenates, which measure total drug concentration, including extracellular, intracellular, and protein-bound and non-bound drug. Two early studies among healthy volunteers and patients with obstructive lung disease found that linezolid concentrations were much higher in epithelial lining fluid (ELF), as compared to blood [11, 12]. A subsequent study among patients with ventilator-associated pneumonia, found penetration in ELF of approximately 100% [13]. These findings highlight the challenges associated with inferring linezolid lung tissue concentrations from ELF measurements among patients with tuberculosis, and/or from data obtained from patients without tuberculosis disease, and stress the need for measurements at the site of disease.

Study limitations include a small cohort of patients deemed to be not responding well to treatment, and thus may not be representative of all patients with tuberculosis. We measured linezolid lung concentrations at only one point in time (ex _vivo_), and therefore could not measure key pharmacokinetic parameters, including tissue AUC/MIC and time>MIC. It is also unclear how probe placement variation might have affected the results.

While we found lower linezolid concentrations in the lung versus serum, concentrations in the lung were above the utilised MIC and MPC values in almost all patients. Regarding the clinical implications, our results suggest the cautious use of doses lower than 600 mg in patients with severe tuberculous lung lesions.

**Acknowledgments**

Support statement: This work was supported in part by the National Institutes of Health Fogarty International Center (D43TW007124), National Institute of Allergy and Infectious Diseases (K23AI103044; R21AI122001), the
The findings of this study have been presented in part at the 48th Union World Conference on Lung Health, Guadalajara, Mexico, October 13, 2017.

References

TABLE 1
Free serum and tissue linezolid concentrations and lung to serum drug concentration ratios among patients with drug-resistant pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose mg·kg⁻¹</th>
<th>Free serum concentration at time of resection # μg·mL⁻¹</th>
<th>Non-diseased lung tissue concentration μg·mL⁻¹</th>
<th>Diseased lung tissue concentration μg·mL⁻¹</th>
<th>Diseased lung/serum</th>
<th>Non-diseased lung/serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.23</td>
<td>7.73</td>
<td>10.24</td>
<td>7.09</td>
<td>0.92</td>
<td>1.32</td>
</tr>
<tr>
<td>2</td>
<td>11.54</td>
<td>10.06</td>
<td>4.27</td>
<td>6.60</td>
<td>0.66</td>
<td>0.42</td>
</tr>
<tr>
<td>3</td>
<td>8.33</td>
<td>8.79</td>
<td>3.43</td>
<td>4.27</td>
<td>0.49</td>
<td>0.42</td>
</tr>
<tr>
<td>4</td>
<td>7.50</td>
<td>7.24</td>
<td>2.03</td>
<td>1.30</td>
<td>0.17</td>
<td>0.27</td>
</tr>
<tr>
<td>5</td>
<td>7.69</td>
<td>7.71</td>
<td>6.01</td>
<td>4.22</td>
<td>0.55</td>
<td>0.78</td>
</tr>
<tr>
<td>6</td>
<td>6.19</td>
<td>3.68</td>
<td>1.17</td>
<td>0.81</td>
<td>0.22</td>
<td>0.32</td>
</tr>
<tr>
<td>7</td>
<td>8.33</td>
<td>5.87</td>
<td>1.25</td>
<td>2.91</td>
<td>0.50</td>
<td>0.21</td>
</tr>
<tr>
<td>8</td>
<td>10.53</td>
<td>10.54</td>
<td>4.97</td>
<td>2.75</td>
<td>0.26</td>
<td>0.47</td>
</tr>
<tr>
<td>Median</td>
<td>8.33</td>
<td>7.77</td>
<td>3.85</td>
<td>3.56</td>
<td>0.49</td>
<td>0.41</td>
</tr>
</tbody>
</table>

# : free serum concentration=measured linezolid concentration×0.69.