Evaluation of linezolid-induced thrombocytopenia based on hospital pharmacometrics

Yasuhiro Tsuji¹, Nick Holford²
¹University of Toyama, Toyama, Japan
²University of Auckland, Auckland, New Zealand

History of MRSA and Antimicrobials

Methicillin
Vancomycin
Linezolid

MRSA Infection spread all over the world

PRS; penicillin-resistant Staphylococci
MRSA; methicillin-resistant Staphylococcus aureus
VRSA; vancomycin-resistant Staphylococcus aureus

High incidence of linezolid induced thrombocytopenia associated with renal dysfunction

Table 1. Studies in the literature that report thrombocytopenia in impaired renal function

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Type of study</th>
<th>Journal</th>
<th>N of patients</th>
<th>Incidence of thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Liu et al.</td>
<td>Retrospective case series</td>
<td>International Journal of Antimicrobial Agents</td>
<td>30</td>
<td>53.3%</td>
</tr>
<tr>
<td>2006</td>
<td>Wei et al.</td>
<td>Retrospective case series</td>
<td>General Hospital</td>
<td>96</td>
<td>51.8%</td>
</tr>
<tr>
<td>2007</td>
<td>Case report</td>
<td>Case report</td>
<td><em>JAMA</em></td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>2010</td>
<td>Nabulsi</td>
<td>Prospective observational</td>
<td>International Journal of Antimicrobial Agents</td>
<td>6</td>
<td>66%</td>
</tr>
<tr>
<td>2010</td>
<td>Nasr</td>
<td>Prospective observational</td>
<td><em>JAMA</em></td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>2011</td>
<td>Case report</td>
<td>Case report</td>
<td><em>Can J Pharm</em></td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>2012</td>
<td>Case report</td>
<td>Case report</td>
<td>Scandinavian Journal of Infectious Diseases</td>
<td>8</td>
<td>62.5%</td>
</tr>
<tr>
<td>2013</td>
<td>Case report</td>
<td>Case report</td>
<td>Scandinavis Journal of Infectious Diseases</td>
<td>8</td>
<td>62.5%</td>
</tr>
<tr>
<td>2013</td>
<td>Nakamura et al.</td>
<td>Prospective observational</td>
<td><em>JAMA</em></td>
<td>36</td>
<td>36.1%</td>
</tr>
</tbody>
</table>
Thrombocytopenia is reversible with linezolid dose adjustment (RF=0.11)

Renal function (RF) was calculated from CLcr/100

Questions

• What factors predict linezolid pharmacokinetics?
• What mechanisms are responsible for linezolid-induced thrombocytopenia?
• How much thrombocytopenia can be explained just by linezolid exposure?
• Is thrombocytopenia made worse in renal impairment in addition to an effect of increased linezolid exposure?

Demographic and disease characteristics of patients studied in Toyama University Hospital, Japan

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Number</th>
<th>Median</th>
<th>95% interval</th>
<th>Lower 2.5%</th>
<th>Upper 97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (Male/Female)</td>
<td>81/51/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration route (i.v./p.o./both)</td>
<td>54/31/14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total concentration (mg/L)</td>
<td>493</td>
<td>11.2</td>
<td>2.0-50.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unbound concentration (mg/L)</td>
<td>380</td>
<td>1.9</td>
<td>0.3-8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline platelet count (10^3/µL)</td>
<td>575</td>
<td>160</td>
<td>22-463</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>69</td>
<td>8</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body weight (kg)</td>
<td>53.2</td>
<td>21.0</td>
<td>99.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>20</td>
<td>4</td>
<td>190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.80</td>
<td>0.20</td>
<td>7.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLcr (mg/min)</td>
<td>59.6</td>
<td>5.6</td>
<td>188.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; CLcr, creatinine clearance
Linezolid population pharmacokinetics: predictable differences

\[ \text{CL (L/h)} = (1.86 \times e^{-0.0205 \times (\text{AGE} - 69)}) + 1.44 \times \text{RF} \times (\text{TBW}/70)^{3/4} \]

Non-renal CL Renal CL

\[ \text{VC (L)} = 22.9 \times (\text{TBW}/70) \]

\[ \text{Q (L/h)} = 10.9 \times (\text{TBW}/70)^{3/4} \]

\[ \text{VP (L)} = 24.7 \times (\text{TBW}/70) \]

\[ \text{F (Absolute bioavailability)} = 0.922 \]

\[ \text{Fu (Fraction of unbound protein binding)} = 0.823 \]

NONMEM 7.3
Renal function (RF) was calculated from CLcr/100

pc-VPC of total concentration of linezolid

To perform a pcVPC, 100 datasets were simulated using the parameter estimated by the final model

Synthesis and elimination of platelets

Decreased production

Increased destruction

PLATELET

Immune-mediated reaction

Inhibition of the differentiation

Inhibition of megakaryocyte

Platelet

Increased destruction of platelet
Structural PKPD model for linezolid effects by inhibition or stimulation

Gut compartment

Central compartment

Peripheral compartment

Oral dose

Intravenous infusion

Mean transit time

Inhibition

Stimulation

PDI, inhibition of platelets formation

PDS, stimulation of platelets elimination

Influence of impaired renal function on linezolid pharmacodynamics

PDI = 1 - SLOPE × Conc

Platelet production are NOT directly affected by RF

PDI = 1 - SLOPE × EXP(θ × (RF - 1)) × Conc

Renal function (RF) was calculated from CLcr/100

Comparison of PD parameters estimated in this study with previous literature

<table>
<thead>
<tr>
<th>Platelet inhibition models</th>
<th>MTT (h)</th>
<th>γ</th>
<th>PLTZERO (10^3/μL)</th>
<th>SLOPE (1/mg/L)</th>
<th>SMAX (mg/L)</th>
<th>SC50 (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study: proliferation cell</td>
<td>1.06</td>
<td>-0.164</td>
<td>204.3</td>
<td>0.0051</td>
<td>0.3</td>
<td>1.23</td>
</tr>
<tr>
<td>Sasaki et al. proliferation cell</td>
<td>0.33</td>
<td>-0.0167</td>
<td>204.3</td>
<td>0.0051</td>
<td>0.3</td>
<td>1.23</td>
</tr>
<tr>
<td>Boak et al. stem cell</td>
<td>163</td>
<td>-1.02</td>
<td>252.0</td>
<td>0.0055</td>
<td>0.3</td>
<td>1.23</td>
</tr>
</tbody>
</table>

Between-subject variability (%BSV) was calculated from 100 × sqrt (NONMEM OMEGA); MTT, mean transit time; γ, feedback parameter; PLTZERO, baseline platelet count; SLOPE, slope of inhibition effect; SMAX, maximal extent of stimulation effect; SC50, linezolid total concentration producing 50% of the maximum stimulation effect.
To perform a pcVPC, 100 datasets were simulated using the parameter estimated by the final model.

Simulation using mean parameter based on final model (total body weight of 70 kg, CLcr of 6 L/h/70 kg, age 69, linezolid dosage 600 mg q12h).

Mixture fraction of PDI was 0.97 inhibition of platelets formation

Mixture fraction of PDS was 0.03 stimulation of platelets elimination

Conclusion

• Linezolid pharmacokinetics differences are predictable from total body weight, renal function (major) and age (minor)
• The most common mechanism of thrombocytopenia associated with linezolid concentration profile is inhibition of platelet proliferation
• Renal impairment does not have an effect on linezolid pharmacodynamics
• Target concentration intervention should be used to optimize exposure and reduce adverse effects
Present our mixture model

We have evaluated the mixture model which divides into two groups of inhibition and stimulation. It was assumed to occur via one of two mechanisms in each patient.

The differential equations for inhibitory effects of linezolid

The rate of formation of platelets (RFORM) in the platelet formation compartment (PLIFORM) was assumed to be driven either by proliferation of cells in the formation compartment or from a constant stem cell.