Linezolid-Associated Thrombocytopenia in Children With Renal Impairment

Sara J. Jones,1,a Kristen R. Nichols,2,3,4 Heather L. DeYoung,4,a Elaine G. Cox,4 and Chad A. Knoderer2

1Department of Pharmacy, Lutheran Hospital, Fort Wayne, Indiana; 2Department of Pharmacy Practice, College of Pharmacy and Health Sciences, Butler University, Indianapolis, Indiana; 3Department of Pharmacy, Riley Hospital for Children at Indiana University Health, Indianapolis; and 4Department of Pediatrics, Ryan White Center for Pediatric Infectious Disease, Indiana University School of Medicine, Indianapolis

Corresponding Author: Chad Knoderer, PharmD, Butler University College of Pharmacy and Health Sciences, 4600 Sunset Ave, Indianapolis, IN 46208. E-mail: cknodere@butler.edu.

aS. J. J. and H. L. D. were PharmD candidates at Butler University College of Pharmacy and Health Sciences at time of research completion.


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Impaired renal function has been associated with an increased risk of thrombocytopenia in adults receiving linezolid. Findings from this retrospective cohort demonstrate an association between thrombocytopenia and lower creatinine clearance in children receiving linezolid.

Key words. children; linezolid; pediatric; renal impairment; thrombocytopenia.

BACKGROUND

Linezolid is an oxazolidinone antibiotic used for the treatment of susceptible Gram-positive infections, including those due to methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, or multidrug-resistant Streptococcus pneumonia [1]. It is commonly used in patients with infections due to organisms resistant to vancomycin or in patients with vancomycin allergy or intolerance. Linezolid’s high bioavailability makes it an attractive and effective enteral alternative to intravenous vancomycin [2, 3]. Linezolid is primarily hepatically metabolized with approximately 30% being eliminated unchanged by the kidney [1, 4]. Children under 12 years demonstrate faster clearance than older adolescents [1, 4].

Linezolid-associated thrombocytopenia (LAT) is one adverse effect that may complicate therapy. Incidence is wide ranging in adults with a higher incidence of 31%–66% in adults with renal impairment [5–10]. Incidence in all children has been reported to be 0%–2%, but reports describing the incidence of thrombocytopenia in children with renal impairment are lacking [11, 12]. In general, drugs may exhibit changing pharmacokinetic and pharmacodynamic profiles in children, related to developmental pharmacology, compared with adults. These changes can lead to different dosing strategies and even efficacy or toxicity, but the changes also challenge our ability to extrapolate the adult findings regarding LAT to a pediatric population. The objective of this study was to compare LAT incidence in children with and without renal impairment.

METHODS

This was a retrospective, single-center cohort study. Eligible patients were identified using a pharmacy computer system-generated report of patients who received LZD therapy between January 1, 2007 and March 31, 2012. The study was limited to patients less than 18 years of age who had retrievable serum creatinine and height values. Each eligible patient was only included once, and only data from the first LZD course per patient was included. Medical records were reviewed for demographics, LZD utilization, and clinical and laboratory parameters (including, but not limited to serum creatinine, platelet values, indication, and concomitant vancomycin). Reference range for platelet values at the institution during the time of study was 150 000–450 000 platelets per mm³. To account for the lower 5% (approximate) of reference values, baseline platelet values were categorized as either “low” (<170 000 platelets per mm³) or “normal” (≥170 000 platelets per mm³). Receipt of concurrent drugs

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for which thrombocytopenia is a known effect and presence of other factors known to contribute to thrombocytopenia were also collected (Appendix).

Renal function before and after LZD initiation was recorded. Renal impairment was defined as a creatinine clearance (CrCl) less than 60 ml per min per 1.73 m². The modified Schwartz equation was used to calculate CrCl for patients who started LZD on or after January 1, 2009, which was when our laboratory commenced use of an enzymatic assay to measure serum creatinine. Prior to that time, the Jaffe assay was used, and the original equations proposed by Schwartz were used to calculate CrCl for those patients.

Outcomes
The primary outcome analyzed was development of thrombocytopenia, defined as a platelet count of <100 000 platelets per mm³ or a reduction of greater than 30% from the baseline platelet count [6–8, 13, 14]. The secondary outcome was time to onset, in days, to the first thrombocytopenia occurrence.

Data Analysis
Groups were compared using independent samples t tests, χ² analyses, and Mann-Whitney tests for non-parametric data. Logistic regression analysis of LAT was utilized using a forced entry method. Demographics, renal function, linezolid dose, duration, route, baseline platelet values, and other factors known to contribute to thrombocytopenia were all examined for potential inclusion into the regression model. Variables were included in the final regression model if found to have a P value < .25 after univariate analysis. P values of less than .05 were considered to be statistically significant. Statistical analyses were conducted using Statistical Package for Social Sciences version 19.0 (SPSS, Inc., Chicago, IL). The study was approved by the Indiana University institutional review board.

RESULTS
One hundred seventy children with a median (interquartile range [IQR]) age (years) and weight (kilogram) of 9 (3–14) and 26.5 (IQR, 13.8–45.1), respectively, were included. Children had a median (IQR) baseline CrCl (ml per min per 1.73 m²) of 103 (IQR, 63.8–130), and baseline renal impairment was present in 22%. The mean (standard deviation) empiric linezolid dose was 25.9 (6.6) mg/kg per day, and therapy was continued for a median (IQR) of 3 (IQR, 1–7) days. Linezolid was most commonly used for bacteremia (23.5%), osteoarticular or skin and soft tissue infection (19.4%), and cystic fibrosis exacerbation (16.5%).

Thrombocytopenia was evaluable in 162 (95%) patients and occurred in 48 (29%). Thrombocytopenia occurred more frequently in patients with baseline renal impairment (57% vs 20%; P < .05). Baseline CrCl (ml per min per 1.73 m²) was significantly lower in patients who developed thrombocytopenia compared to those who did not (median 70 [IQR, 40–124] vs 105 [IQR, 78–130]; P < .05). Seventy-five percent of patients with a low baseline platelet concentration (<170 000 platelets per mm³) at LZD initiation developed thrombocytopenia versus 12.7% of patients with a normal to high baseline platelet value (P < .05). The final regression model included male gender, age <5 years, LZD ≥14 days, baseline renal impairment, and low baseline platelet values. After multivariate logistic regression, baseline renal impairment (odds ratio [OR], 12.7; 95% confidence interval [CI], 3.8–42.9), baseline platelet concentration <170 × 10³ platelets per mm³ (OR, 38.5; 95% CI, 12.3–120.4), and LZD duration ≥14 days (OR, 5.3; 95% CI, 1.7–16.4) were independently associated with LAT. Concurrent thrombocytopenia-associated drugs and presence of other known thrombocytopenia-associated factors were similar between patients with and without thrombocytopenia. Table 1 displays characteristics of children with and without thrombocytopenia.

DISCUSSION
With changing susceptibility patterns of Gram-positive organisms causing infection in children and with its high bioavailability and enteral dosage form, LZD has become a more frequently utilized antibacterial [1–3, 15]. Consistent with adult data, our findings demonstrate LAT is common in children with renal impairment, with 59% of our cohort with baseline renal impairment developing thrombocytopenia after LZD initiation. To our knowledge, this is the first study examining the relationship between renal function and thrombocytopenia in children receiving LZD. Ensuring that linezolid is used only when necessary is one way to combat an increased incidence of thrombocytopenia while also supporting optimal antimicrobial stewardship. At our institution, linezolid requires prior approval from the antimicrobial stewardship program or an infectious diseases physician. It is expected that the majority of linezolid use in our study was appropriate and was likely related to problems with vancomycin including demonstrated resistance (vancomycin-resistant enterococci, elevated minimum inhibitory concentrations in methicillin-resistant S. aureus isolates), acute kidney injury, red man’s syndrome unresponsive to antihistamines, or perceived clinical failure.

Linezolid-associated thrombocytopenia may be due to myelosuppression related to mitochondrial respiration inhibition and immune-mediated platelet destruction, in which
the drug or its metabolites bind to glycoprotein on the platelet surface marking the platelet for destruction and clearance by the reticuloendothelial system [16]. Studies performed in adults demonstrate that LAT occurs more frequently in patients with end-stage renal disease and renal insufficiency [6, 7]. In adults, independent risk factors associated with LAT include end-stage renal disease, LZD duration, and CrCl < 50 ml per min per 1.73 m² [7, 14]. Likewise, children in our cohort with baseline renal impairment had higher thrombocytopenia incidence (57% vs 22%). Baseline renal impairment, baseline platelet concentration < 170 × 10³ platelets per mm³, and LZD duration ≥ 14 days were independently associated with LAT.

Linezolid clearance is positively correlated with CrCl, and higher linezolid concentrations are observed in patients with diminished renal function [5, 8, 13]. Thrombocytopenia development is associated with the increased linezolid concentrations that result from renal impairment [8–10]. It is concerning that despite the growing evidence associating thrombocytopenia with renal function in LZD recipients, there remain no recommendations for either increased monitoring or dose modifications. Our study was not designed to definitively correlate dose with platelet concentration, and recommending a dose modification based on our findings would be premature. However, increased monitoring may be prudent in children with a degree of renal impairment at LZD initiation.

There are limitations to retrospective studies such as this. The method of data collection and reporting did not allow for consideration of CrCl changes or dose changes over the course of therapy. Creatinine clearance was calculated based upon date of initial LZD dose, and 2 different methods for CrCl estimation were used, but it is not expected that the different equations would significantly alter our findings. In addition, it is not possible to determine whether further decreases in platelet values could be attributable to LZD, as opposed to underlying condition, in those patients who had a low baseline platelet value before starting LZD.

In addition, platelet values could be elevated during infection and subsequently lowered with the course of treatment and should not necessarily be considered a linezolid-associated adverse effect. The sample size in this study is relatively small, but it does represent the only known pediatric cohort. It is noteworthy that our 95% CIs were quite wide and appear wider than those from adult studies. This result may be related to our sample size. The ultimate clinical significance of our regression findings, therefore, must be carefully considered given the CI widths.

CONCLUSIONS

Overall, thrombocytopenia developed in 29% of children receiving LZD in this pediatric cohort and in 57% of children with baseline renal impairment. Linezolid-associated thrombocytopenia appears to be an important adverse effect in children, and it was associated with renal impairment and low baseline platelet concentrations in this pediatric cohort. Close monitoring of renal function should be considered during LZD therapy. Additional studies are needed to determine whether dose modifications are warranted for children receiving LZD with renal impairment.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References


Table 1. Characteristics of Children With and Without Thrombocytopenia

<table>
<thead>
<tr>
<th></th>
<th>No Thrombocytopenia (n = 114)</th>
<th>Thrombocytopenia (n = 48)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>46 (40.4%)</td>
<td>27 (56.3%)</td>
<td>.063</td>
</tr>
<tr>
<td>Age (yr)b</td>
<td>9 (3.1–14.7)</td>
<td>6 (1–13)</td>
<td>.224</td>
</tr>
<tr>
<td>Weight (kg)b</td>
<td>27.3 (13.8–47.3)</td>
<td>23.8 (7.4–44.7)</td>
<td>.407</td>
</tr>
<tr>
<td>LZD dose (mg/kg per day)c</td>
<td>25.6 (6.2)</td>
<td>26.7 (7.6)</td>
<td>.352</td>
</tr>
<tr>
<td>LZD duration (days)b</td>
<td>7 (3–11)</td>
<td>10 (4–21)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Baseline CrClb</td>
<td>105 (78–130)</td>
<td>69.5 (39.8–123.8)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Baseline renal impairmenta</td>
<td>16 (14%)</td>
<td>21 (43.8%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Low baseline plateleta</td>
<td>11 (9.6%)</td>
<td>33 (68.8%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Concomitant thrombocytopenia factorsa</td>
<td>110 (96.5%)</td>
<td>47 (97.9%)</td>
<td>.632</td>
</tr>
</tbody>
</table>

Abbreviations: CrCl, creatinine clearance; SD, standard deviation.

aData reported as n (%).
bData reported as median (interquartile range).
cData reported as mean (SD); CrCl (ml per min per 1.73 m²).


Appendix

Drugs and Other Factors Contributing to Thrombocytopenia

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>Piperacillin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
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</tbody>
</table>

Antiseizure medications
- Carbamazepine
- Phenytoin
- Valproic acid

Chemotherapy
- Heparin and low molecular weight heparin

Conditions
- Anti-phospholipid antibody syndrome
- Aplastic anemia
- Congenital thrombocytopenic disorders
- Disseminated intravascular coagulation
- Hemolytic uremic syndrome
- Human immunodeficiency virus infection
- Myelodysplastic syndrome
- Neonatal alloimmune thrombocytopenia
- Systemic lupus erythematosus
- Splenomegaly
- Thrombotic thrombocytopenic purpura
- Viral infection

Procedures
- Extracorporeal membrane oxygenation
- Cardiopulmonary bypass
- Hemodialysis