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LINEZOLID-ASSOCIATED THROMBOCYTOPENIA IN CHILDREN WITH RENAL IMPAIRMENT

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ABSTRACT

Background: Independent risk factors for linezolid-associated thrombocytopenia are identified in adults, although similar data is lacking in pediatric patients. End-stage renal disease, pre-treatment disease severity score, catheter-related infection, duration of linezolid therapy greater than or equal to 14 days, creatinine clearance less than 50 mL/min/1.73m², and respiratory tract infection have been associated with thrombocytopenia. The objectives of this study were to evaluate and compare the rate of linezolid-associated thrombocytopenia in pediatric patients with and without renal impairment.

Methods: This was a retrospective cohort study of patients less than 18 years who received linezolid between January 1, 2007 and March 31, 2012 and had a documented serum creatinine (SCr) and height. Patients’ electronic medical records were reviewed to capture demographic data, baseline serum creatinine, baseline platelet count, indication for linezolid therapy (including culture and susceptibility data), dosing, and therapy duration. Renal impairment was defined as an estimated creatinine clearance (CrCl) less than 60 mL/min/1.73m². Thrombocytopenia was defined as less than 100 platelets/mm³ or ≥ 20% reduction from baseline.

Results: One hundred seventy seven children with a median (IQR) age of 9 (3 – 14) years were included, and 22% of these had baseline renal impairment. Thrombocytopenia occurred more frequently in patients with baseline renal impairment (57% vs. 21%, p < 0.05). Baseline estimated CrCl (mL/min/1.73m²) was significantly lower in patients who developed thrombocytopenia (median [IQR] 66.29 – 120 vs. 89 (78 – 130), p = 0.004). Seventy-five percent of patients with a low baseline platelet count (<170,000 platelets/mm³) at initiation experienced thrombocytopenia versus 12.1% of patients with normal to high baseline platelet count (p < 0.05).

Conclusion: Linezolid-associated thrombocytopenia in this pediatric cohort was associated with renal impairment and low platelet values upon therapy initiation. These findings illustrate the need for a diligent risk-benefit assessment prior to the initiation of linezolid therapy for children.

BACKGROUND

• Linezolid (LZD) is an alternative to vancomycin for treatment of methicillin-resistant Staphylococcus aureus and Vancomycin-resistant Enterococcus faecium
• Pediatric pharmacokinetics:1
  • Primary hepatic metabolism
  • ~ 30% excreted as unchanged drug in urine
• Age-related changes in clearance
• Linezolid-associated thrombocytopenia (LAT) complicates therapy
• Pediatric incidence and related factors not well defined

Table 1. Selected LAT findings from adult studies

Study | Primary Finding | Reference
--- | --- | ---
Lin (2006) | LAM more frequent in patients with renal insufficiency (OR: 2.32, 95% CI: 1.45 – 3.74) | LAM = Listeria monocytogenes
Matsumoto (2010) | LAM and CrCl strongly correlated (r = 0.933, p < 0.01) | CrCl = creatinine clearance
Takahashi (2011) | CrCl < 50 ml/min independent risk factor for LAT (OR: 2.32, 95% CI: 1.45 – 3.74) | LAT = linezolid-associated thrombocytopenia
Nakai (2013) | LAM more frequent in patients with GFR < 60 ml/min (OR: 3.90, 95% CI: 3.8 – 399.8) | GFR = glomerular filtration rate

STUDY OBJECTIVE

To evaluate and compare the rates of linezolid-associated thrombocytopenia in pediatric patients with and without renal impairment.

METHODS

Design and Setting:
• Retrospective, single center cohort
• Academic, free-standing children’s hospital

Methods:
• Study population
  • Patients less than 18 years of age who received linezolid between January 1, 2007 and March 31, 2012
  • Exclusion criteria:
    • No retrievable SCr• No height

Study Population:
• Patients less than 18 years of age who received linezolid between January 1, 2007 and March 31, 2012
• Exclusion criteria:
  • No retrievable SCr
  • No height

Procedures:
• Demographic and clinical data extracted from medical records included:
  • LZD indication, dosing, and duration
  • SCr, platelet, and white blood cell values collected at baseline and through therapy course
  • Concurrent thrombocytopenia-associated drugs and other known thrombocytopenia-associated factors

Definitions:
• Thrombocytopenia (TCP): platelet value < 100 X 10³ platelets/mm³ or ≥ 20% reduction from baseline
• Baseline platelet categorization:
  • Low: < 170 X 10³ platelets/mm³
  • Within normal limits or above: ≥ 170 X 10³ platelets/mm³
• Renal impairment: CrCl ≤ 60 mL/min/1.73m²
• Calculated using Schwartz or Modified Schwartz equations
• Infection resolution:
  • Afebrile at least 48 hours
  • Documented clinical improvement
  • Negative cultures

RESULTS

• Infection resolution occurred in 94% overall
• Renal impairment at LZD initiation present in 22% overall
• TCP incidence evaluable in 161 patients
• Developed in 29.2% (n = 47) overall

Table 3. Characteristics in children with and without TCP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No TCP (n = 114)</th>
<th>TCP (n = 47)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40.4%</td>
<td>56.3%</td>
<td>0.063</td>
</tr>
<tr>
<td>Age [years]</td>
<td>8.8 (3.1 – 14.7)</td>
<td>6.4 (1.1 – 12.8)</td>
<td>0.146</td>
</tr>
<tr>
<td>LZD Dose [mg/kg/day]a</td>
<td>25.6 (6.2)</td>
<td>26.2 (7.7)</td>
<td>0.444</td>
</tr>
<tr>
<td>LZD Duration [days]a</td>
<td>7 (3 – 11.3)</td>
<td>9 (4 – 21)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Baseline CrCl [mL/min/1.73m²]a</td>
<td>105 (78 – 130)</td>
<td>66 (39 – 125)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Baseline renal impairment</td>
<td>14%</td>
<td>43.8%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Low baseline platelet</td>
<td>9.7%</td>
<td>70.2%</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Overall 29% thrombocytopenia in children receiving LZD in this pediatric cohort
• LAT appears to be an important adverse effect in children and adults
• The following variables at LZD initiation may be related to pediatric LAT:
  • Platelet value < 170 X 10³ platelets/mm³
  • CrCl ≤ 60 mL/min/1.73m²
  • An association between therapy duration and TCP was noted
  • Close monitoring of renal function should be considered during LZD therapy
• Additional studies are needed to determine if dose modifications are warranted for children receiving LZD with renal impairment

Table 2. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 170</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>45.9%</td>
</tr>
<tr>
<td>Age [years]a</td>
<td>8.6 (3.1 – 13.8)</td>
</tr>
<tr>
<td>Weight [kg]a</td>
<td>26.5 (13.8 – 45.1)</td>
</tr>
<tr>
<td>Baseline SCr [mg/dL]a</td>
<td>0.51 (0.34 – 0.83)</td>
</tr>
<tr>
<td>Baseline CrCl [mL/min/1.73m²]a</td>
<td>103 (63.8 – 130)</td>
</tr>
<tr>
<td>LZD information</td>
<td></td>
</tr>
<tr>
<td>LZD dose [mg/kg/day]a</td>
<td>25.9 (6.6)</td>
</tr>
<tr>
<td>LZD duration [days]a</td>
<td>3 (1 – 7)</td>
</tr>
<tr>
<td>Enteral route</td>
<td>38.2%</td>
</tr>
<tr>
<td>Infectious Indications</td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>23.6%</td>
</tr>
<tr>
<td>SSTI or Osteoarticular</td>
<td>19.4%</td>
</tr>
<tr>
<td>CF exacerbation</td>
<td>16.5%</td>
</tr>
<tr>
<td>Other/Misc</td>
<td>13%</td>
</tr>
<tr>
<td>CNS</td>
<td>7.1%</td>
</tr>
<tr>
<td>HAP</td>
<td>5.9%</td>
</tr>
<tr>
<td>Fibrile Neutropenia</td>
<td>5.3%</td>
</tr>
<tr>
<td>GI</td>
<td>3.5%</td>
</tr>
<tr>
<td>CAP</td>
<td>2.9%</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

a = Data reported as median (interquartile range [IQR]; b = data reported as mean (standard deviation [SD])