Hypoglycemia in Patients Treated With Linezolid

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Hypoglycemia was not previously known to be a linezolid-associated adverse reaction. A case report describing symptomatic hypoglycemia in a linezolid recipient prompted a review of the US Food and Drug Administration Adverse Event Reporting System, which demonstrated a relationship between linezolid and hypoglycemia. A warning with this information was added to the linezolid package insert.

Keywords. adverse reactions; hypoglycemia; linezolid.

Linezolid, a member of the oxazolidinone class of antibacterial drugs, is approved by the US Food and Drug Administration (FDA) for the treatment of vancomycin-resistant Enterococcus faecium infections, nosocomial and community-acquired pneumonia, and complicated and uncomplicated skin and skin structure infections, including diabetic foot infections [1].

During routine pharmacovigilance, we reviewed a literature report of linezolid-associated symptomatic hypoglycemia in a diabetic patient. This report describes a 64-year-old man with a history of diabetes mellitus who was treated with linezolid for cellulitis. He developed symptomatic hypoglycemia 7 days after initiation of linezolid, which persisted despite modification to his hypoglycemic medication regimen but resolved upon cessation of linezolid [2]. This case report prompted a broader inquiry regarding the relationship between linezolid use and hypoglycemia.

METHODS

We searched the FDA Adverse Event Reporting System (FAERS) for reports of hypoglycemia in linezolid recipients from April 2000 through March 2012 using the Medical Dictionary for Regulatory Activities (MedDRA) [3] preferred terms “hypoglycaemia” and “blood glucose decreased,” with the drug names “linezolid” and “Zyvox.” Data obtained from the reports included demographic information, indication for linezolid usage, concomitant medications (including insulin and oral hypoglycemic agents), comorbidities (especially known diabetes mellitus), temporal relationship of the hypoglycemic event to linezolid exposure, symptoms of hypoglycemia, blood glucose level, and response to linezolid dechallenge.

We graded the strength of association between hypoglycemia and linezolid exposure based on temporal relationship and response to linezolid dechallenge, defined as resolution of hypoglycemia after discontinuation of linezolid. Among diabetic patients, we considered an association “highly probable” if (1) hypoglycemia did not respond to adjustments in hypoglycemic drug regimen and (2) the individual had a positive linezolid dechallenge. We deemed an association “highly probable” in non-diabetic patients who (1) had a positive linezolid dechallenge and (2) no alternative etiology for hypoglycemia. We considered an association “probable” if it met only 1 of the 2 “highly probable” criteria regardless of diabetes history, and “possible” if the event bore a temporal relationship to linezolid exposure but did not meet either of the “highly probable” criteria. Finally, we labeled events that lacked a temporal association to linezolid or had a more plausible explanation as “unlikely” to be related to linezolid exposure. Missing information on a grading criterion was treated as the absence of this criterion. We established these criteria prior to case review. To test our causality assessment algorithm, we compared the outcome of our algorithm to the results obtained with the Naranjo Adverse Drug Reaction Probability Scale [4], which has been used in many publications.

We also conducted a PubMed search to identify additional reports of linezolid-associated hypoglycemia in the medical literature.

RESULTS

We identified 41 unique reports of hypoglycemia among linezolid recipients in the FAERS database. Based on the causality assessment, we categorized 26 cases as unlikely, which we did not further evaluate. Of the remaining 15 cases, we considered the relationship between hypoglycemia and linezolid exposure to be highly probable in 7 cases, probable in 4 cases, and possible in 4 cases (Table 1).

We also scored the cases using the Naranjo scale, which produced similar results: 10 cases with successful linezolid...
dechallenge were classified as probable adverse drug reactions, 5 cases were classified as possible adverse drug reactions, and the remaining 26 cases were classified as doubtful adverse drug reactions.

The median age was 77 years (range, 9–87 years), and 11 patients (73%) were male. Eight subjects (53%) received oral linezolid, 6 subjects (40%) received intravenous linezolid, and route of administration was not provided in 1 case. Twelve of the 15 patients (80%) had diabetes mellitus: 9 were taking oral hypoglycemic drugs, 2 were taking insulin, and treatment information was not available in 1 patient. Monoamine oxidase (MAO) inhibitors were not listed as concomitant medications for any of the 15 subjects, although these lists may be incomplete.

Median time to onset of hypoglycemia was 7 days (range, 2–30 days) from the first linezolid dose; median blood glucose nadir was 32 mg/dL (range, 12–60 mg/dL). Symptoms consistent with hypoglycemia were reported in 6 cases (40%), and information was not provided for the other 9 cases. In 8 of the 12 diabetic patients (75%), hypoglycemia did not respond to adjustments in the diabetic drug regimen, but did resolve after discontinuation of linezolid (positive linezolid dechallenge); data were missing in the other 4 cases. Overall, hypoglycemia resolved after discontinuation of linezolid in 10 cases (67%), and outcomes were missing in 5 cases.

We did not identify any additional reports in the medical literature.

**DISCUSSION**

Based on our review of FAERS, we identified 15 cases of linezolid-associated hypoglycemia. Linezolid’s activity as a weak, nonselective MAO inhibitor confers the possibility of toxicity related to inhibition of these enzymes. The contraindications section of the linezolid package insert cautions against use with other MAO inhibitors [1]. Hypoglycemia is associated with MAO inhibitors, especially those of the hydrazine type [5], but had not previously been associated with linezolid exposure. Hence, linezolid’s activity as an MAO inhibitor may provide a biologic explanation for this phenomenon.

The Warnings and Precautions section of the linezolid package insert was updated in 2012 to inform providers about the possibility of hypoglycemia in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid. The warning advises providers to counsel patients to report symptoms of hypoglycemia promptly and stop linezolid if symptoms are severe or do not improve with dose adjustments.

### Table 1. Summary of Cases of Linezolid-Associated Hypoglycemia

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>DMa</th>
<th>Hypoglycemic Drugsb</th>
<th>Time to Symptoms, d</th>
<th>Lowest Serum Glucose, mg/dL</th>
<th>HYPO Corrected With DM Drug Adjustmentc</th>
<th>Positive Dechallenged</th>
<th>Causality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>F</td>
<td>No</td>
<td>None</td>
<td>6</td>
<td>52</td>
<td>Not applicable</td>
<td>Yes</td>
<td>Highly probable</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>Yes</td>
<td>Insulin, glyburide, metformin</td>
<td>7</td>
<td>30</td>
<td>No</td>
<td>Yes</td>
<td>Highly probable</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>M</td>
<td>Yes</td>
<td>Insulin</td>
<td>NR</td>
<td>40</td>
<td>No</td>
<td>Yes</td>
<td>Highly probable</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>F</td>
<td>Yes</td>
<td>Insulin</td>
<td>NR</td>
<td>60</td>
<td>No</td>
<td>Yes</td>
<td>Highly probable</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>M</td>
<td>Yes</td>
<td>Acarbose, voglibose, glyburide</td>
<td>19</td>
<td>38</td>
<td>No</td>
<td>Yes</td>
<td>Highly probable</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>M</td>
<td>Yes</td>
<td>Glimepiride, voglibose, glyburide</td>
<td>6</td>
<td>34</td>
<td>No</td>
<td>Yes</td>
<td>Highly probable</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>M</td>
<td>Yes</td>
<td>Glimepiride, metformin, sitagliptin</td>
<td>2</td>
<td>28</td>
<td>No</td>
<td>Yes</td>
<td>Highly probable</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>M</td>
<td>No</td>
<td>None</td>
<td>NR</td>
<td>NR</td>
<td>Not applicable</td>
<td>Yes</td>
<td>Probablea</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>F</td>
<td>No</td>
<td>None</td>
<td>16</td>
<td>NR</td>
<td>Not applicable</td>
<td>NR</td>
<td>Probable</td>
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<tr>
<td>10</td>
<td>87</td>
<td>M</td>
<td>Yes</td>
<td>Glimepiride</td>
<td>14</td>
<td>22</td>
<td>NR</td>
<td>Yes</td>
<td>Probable</td>
</tr>
<tr>
<td>11</td>
<td>NR</td>
<td>M</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>26</td>
<td>NR</td>
<td>Yes</td>
<td>Probable</td>
</tr>
<tr>
<td>12</td>
<td>84</td>
<td>M</td>
<td>Yes</td>
<td>Glimepiride</td>
<td>NR</td>
<td>38</td>
<td>NR</td>
<td>NR</td>
<td>Possible</td>
</tr>
<tr>
<td>13</td>
<td>78</td>
<td>M</td>
<td>Yes</td>
<td>Glimepiride, rosiglitazone</td>
<td>30</td>
<td>12</td>
<td>Yes</td>
<td>NR</td>
<td>Possible</td>
</tr>
<tr>
<td>14</td>
<td>75</td>
<td>M</td>
<td>Yes</td>
<td>Glyburide</td>
<td>NR</td>
<td>28</td>
<td>Yes</td>
<td>NR</td>
<td>Possible</td>
</tr>
<tr>
<td>15</td>
<td>75</td>
<td>F</td>
<td>Yes</td>
<td>Glipizide</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Abbreviations: DM, diabetes mellitus; HYPO, hypoglycemia; NR, not reported.

a Known history of diabetes mellitus.
b Baseline regimen for treatment of diabetes mellitus.
c Includes dose reduction or total cessation of 1 or all components of the baseline hypoglycemic drug regimen.
d Resolution of hypoglycemia after discontinuation of linezolid.

e Classified as probable rather than highly probable because hypoglycemia could be also explained by sepsis in this patient with a hematologic malignancy.
diabetic patients regarding the potential for hypoglycemic reactions while taking linezolid, and indicates that an adjustment or discontinuation of hypoglycemic medications or discontinuation of linezolid may be required.

There are several limitations to this study, most of which are related to limitations of the FAERS database. First, reporting of adverse events to FAERS is voluntary, and many factors can influence whether or not an event will be reported, such as the time since a product has been marketed and publicity about an event. Therefore, the true incidence of linezolid-associated hypoglycemia cannot be estimated. Second, a causal relationship between a product and event cannot be established. Third, the information provided in FAERS reports is highly variable: some reports are quite detailed, whereas others provide little data. Because our classification algorithm was dependent on the information contained in the case reports, missing data may have led to misclassification. Fourth, only a small number of hypoglycemic events was reported among patients treated with linezolid.

In conclusion, our review suggests that there is a potential relationship between linezolid use and hypoglycemia. Healthcare providers should be aware of this possibility when prescribing linezolid, especially in diabetic patients.

Notes

Acknowledgments. The Medical Dictionary for Regulatory Activities (MedDRA) terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA is owned by the International Federation of Pharmaceutical Manufacturers & Associations on behalf of ICH.

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References