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Toxicity of extended courses of linezolid: results of an Infectious Diseases Society of America Emerging Infections Network survey[☆]

Susan E. Beekmann^{a,*}, David N. Gilbert^b, Philip M. Polgreen^a
the IDSA Emerging Infections Network

^a*Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA 52242, USA*

^b*Providence Portland Medical Center, Portland, OR 97213, USA*

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Abstract

Since linezolid was licensed, rare-but-serious adverse events caused by inhibition of mitochondrial protein synthesis have been identified. These events may be more common when the drug is used longer than 28 days, which is the treatment length currently approved by the US Food and Drug Administration. The purpose of this study was to determine how often longer courses of linezolid are prescribed and the nature and relative frequency of adverse events associated with longer courses. Most of the 460 infectious diseases physician respondents had prescribed extended course linezolid (greater than 28 days) at least once, and they reported that 74% of these patients were able to complete the extended course. Hematologic toxicity was the most common adverse event. Peripheral neuropathy and serotonin syndrome (with serotonin reuptake inhibitor use) were encountered more frequently than lactic acidosis. Close monitoring for signs and symptoms of these adverse events should be considered for patients receiving long-term therapy.

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1. Introduction

The US Food and Drug Administration (FDA) listed reversible thrombocytopenia as a possible side effect when linezolid was approved in April 2000. New serious adverse events have been reported since then, including myelosuppression, peripheral and optic neuropathy, and lactic acidosis (Soriano et al., 2005). Available evidence suggests that these adverse events are caused by inhibition of mitochondrial protein synthesis (Garrabou et al., 2007; McKee et al., 2006). Most reported cases have occurred in patients treated for longer than 28 days. In addition, linezolid exposure is a recognized risk factor for development of serotonin syndrome in patients also taking selective serotonin reuptake inhibitors (SSRIs) or other drugs that increase central nervous system serotonin concentrations (Bernard et al., 2003; Das et al., 2008; Taylor et al., 2006).

The FDA approved linezolid therapy for a maximum of 28 days. However, longer periods of therapy may be necessary to treat infections caused by bacteria resistant to other antimicrobial agents, for example, treatment of multi-drug-resistant tuberculosis (von der Lippe et al., 2006). In addition, oral linezolid is used to treat chronic infections such as osteomyelitis or endocarditis to avoid use of intravenous antibiotic therapy.

Little is known about how frequently infectious diseases consultants prescribe linezolid for longer than 28 days. The purposes of this survey were to determine 1) how frequently infectious disease physicians use longer courses of linezolid, 2) how often laboratory or clinical monitoring for toxicity is performed, and 3) the relative frequency of linezolid adverse effects.

2. Methods

In December 2007, we surveyed 1079 members of the Infectious Diseases Society of America (IDSA) Emerging Infections Network (EIN). Nonresponding members were

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* Corresponding author. Tel.: +1-319-384-8622.

E-mail address: susan-beekmann@uiowa.edu (S.E. Beekmann).

sent 2 reminders to complete the survey in January 2007. We asked members to describe how often they prescribed linezolid courses of less than 14 days, 14 to 28 days, 29 to 90 days, and more than 90 days. For members prescribing linezolid, we asked about their practices for monitoring toxicity and the occurrence of serious adverse events. Because of the retrospective nature of this survey, no definitions of adverse events were provided on the survey form; respondents provided answers based on their own judgments. Members reporting patients with thrombocytopenia or anemia/neutropenia were asked to estimate the percentage of their patients that required discontinuation of therapy for these reasons. Other than these 2 percentages of patients, all percentages provided are based on the respective number of respondents. The number of cases of neuropathy and lactic acidosis members had encountered was requested, as was the length of linezolid treatment before cases of lactic acidosis. We also asked members to report concomitant use of SSRIs and serotonin/norepinephrine reuptake inhibitors, and whether serotonin syndrome had been observed. Serotonin syndrome was defined as clonus, hyperreflexia, fever, confusion, and diaphoresis \pm hypotension. Finally, we requested the percentage of patients able to complete courses of linezolid that were longer than 28 days.

3. Results

Four hundred sixty (43%) of 1079 EIN members responded; 19 (4%) members had never prescribed linezolid and were excluded from analysis. Seventeen (4%) prescribed linezolid on a daily basis. Two hundred seventy-eight members (60%) had prescribed linezolid for more than 28 days at least once; 9% of those did so at least once a month.

Hematologic monitoring was performed weekly by 377 (92%) respondents, 12 (3%) routinely checked serum lactate, and 43 (15% of those who prescribed linezolid for more than 28 days) recommended routine ophthalmologic examinations.

Thrombocytopenia associated with linezolid use was reported by 322 (74%) respondents, and an overall average of 42% of their patients required discontinuation of therapy for this reason. New anemia and/or neutropenia was observed by 259 (59%); an overall average of 35% of their patients required discontinuation of linezolid.

Twenty-three members (5%) reported 29 cases of lactic acidosis. The duration of linezolid treatment before lactic acidosis was reported by 22 members and ranged from “5 to 7 days” to “more than a month”; 7 (32%) reported treatment durations of less than 15 days.

Seventy-five members (17%) had observed 104 cases of peripheral neuropathy; 15 (3%) had observed optic neuropathy. Two hundred seven members (47%) reported using SSRIs concomitantly with linezolid; of those, 48 (23%) had observed serotonin syndrome. Serotonin/norepinephrine reuptake inhibitors were concomitantly used with linezolid by 118 (27%) members, of whom 11 (9%) had observed serotonin syndrome. Finally, members who had prescribed linezolid for more than 28 days ($n = 278$) indicated that a mean of 74% of patients completed the entire course despite any toxicities that may have occurred.

Members who prescribed linezolid for more than 28 days on a daily, weekly, or monthly basis reported observing lactic acidosis more frequently than those who prescribe shorter courses of linezolid (Fig. 1). Six of the 39 members (15%) who prescribe linezolid for more than 28 days at least once a month reported observing lactic acidosis compared with 7 of 371 (5%) of those who prescribe longer-duration linezolid on a less-than-monthly basis. Similar trends were seen for members observing peripheral neuropathy associated with linezolid use. Optic neuropathy was seen infrequently, but the highest rate was reported by members who prescribe linezolid for up to 28 days at least monthly (14/264, 5%).

When asked to comment on other adverse events, 21 members listed gastrointestinal intolerance or nausea/vomiting. Rash, neurologic, or psychiatric issues (including confusion or anxiety in patients not on SSRIs and uncontrollable tremors) were mentioned by 6 members

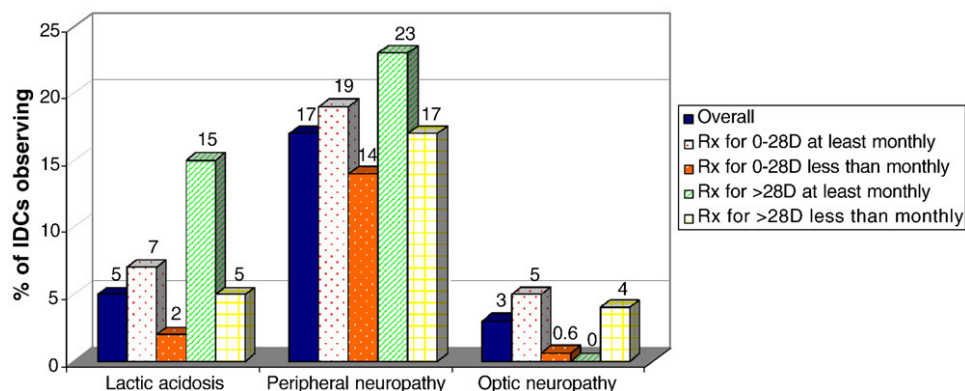


Fig. 1. Occurrence of lactic acidosis and neuropathy events stratified by frequency with which physicians prescribed linezolid.

each. Rare events (1 member each) included sore mouth, myositis with elevated creatine phosphokinase (CPK) after a 3-month course, reversible posterior leukoencephalopathy, small bowel obstruction requiring surgery, severe pancreatitis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, black tongue in a teenager, and *Clostridium difficile* colitis.

4. Discussion

Serious but low-frequency adverse drug effects are often difficult to detect in the clinical trials which lead to FDA licensure. This IDSA EIN survey provides a valuable and unique perspective on linezolid toxicity associated with longer-term use by aggregating the anecdotal observations of hundreds of infectious diseases consultants in North America who use linezolid. It is not a surprise that as the use of linezolid has increased, the case reports of adverse events associated with its use have increased. However, although toxicities from linezolid are described as rare, observation of at least 1 toxicity was reported by 81% of our respondents. For example, new thrombocytopenia was observed by three-quarters of the respondents, and new anemia or neutropenia was reported by more than half of the respondents. Lactic acidosis and optic neuropathy were reported less frequently, but at least 1 case of peripheral neuropathy was observed by 17% of the respondents. Peripheral neuropathy is particularly concerning because it may persist after discontinuation of linezolid (Bishop et al., 2006; Ferry et al., 2005; Narita et al., 2007; von der Lippe et al., 2006). Of the respondents who had coadministered SSRIs with linezolid, approximately one-quarter had observed the serotonin syndrome.

Respondents who prescribed linezolid at least monthly were more likely to encounter adverse events, and respondents who prescribed linezolid for longer durations were the most likely to report thrombocytopenia, anemia and/or neutropenia, lactic acidosis, and peripheral neuropathy. Interestingly, no cases of optic neuropathy were noted by the 39 respondents who most often prescribe longer durations of linezolid therapy.

A recent review found that lactic acidosis occurred after a median of 6 weeks of linezolid therapy, whereas peripheral and optic neuropathies were seen after several months (median, 5 months) (Narita et al., 2007). However, our respondents indicated a much shorter duration of treatment before diagnosis of lactic acidosis, with approximately one-third reporting onset within 2 weeks. Thus, our results suggest that prescribers should be alert to the nonspecific symptoms of lactic acidosis beginning in the 1st week of linezolid therapy, and that they should have a low clinical threshold for monitoring serum bicarbonate levels early during treatment (Bishop et al., 2006; Narita et al., 2007).

Limitations of this survey include a possible reporting bias. Physicians who encountered significant adverse events

may have been more likely to respond. Also, longer-duration linezolid therapy is prescribed on a daily, weekly, or monthly basis by a small number of physicians in our sample ($n = 39$), which could potentially bias our results. This group reported a high frequency of thrombocytopenia, anemia and/or neutropenia, lactic acidosis, and peripheral neuropathy. Finally, we did not specifically define each adverse drug event in the survey; the responding physicians reported adverse events based on their individual definitions.

In summary, our results indicate that adverse events associated with linezolid are common and highlight both the importance of physician vigilance with respect to these possible side effects and the need to inform patients taking linezolid about possible toxicities. Linezolid-associated adverse effects were reported most often among respondents who used longer courses of linezolid. Although the hematologic toxicities were the most common adverse effects, almost 1 in 5 reported at least 1 case of peripheral neuropathy, and 1 in 4 reported serotonin toxicity. Our data suggest that administration of linezolid with concomitant serotonergic agents should be avoided when possible. Close monitoring, particularly for spontaneous clonus (Lawrence et al., 2006), and a high index of suspicion are vital for patients receiving both linezolid and serotonergic agents. Most respondents checked weekly blood counts for patients on linezolid. Given the findings of this study, closer monitoring for signs and symptoms of lactic acidosis and peripheral and optic neuropathy should be considered for patients requiring long-term therapy. In the absence of active postmarketing surveillance for drug toxicities, these results indicate the value gained by organizations such as the IDSA EIN in detecting less frequent but serious adverse drug events. Thus, given that the use of linezolid beyond the approved 28 days is not uncommon, our results indicate the need for either retrospective population-based studies or controlled prospective studies to further investigate toxicities associated with longer-term linezolid use.

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