Poster # 499

Toxicity of Extended Course Linezolid: Results of an Emerging Infections Network (EIN) Survey

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Abstract

Background: Since linezolid was licensed in 2000, rare-but-serious adverse events caused by inhibition of mitochondrial protein synthesis have been identified. These toxicities usually take weeks to appear. Also, serotonin syndrome has been reported with concomitant use of linezolid and selective serotonin reuptake inhibitors (SSRIs). How frequently infectious diseases consultants (IDCs) encounter these toxicities is unknown.

Methods: In December 2006, the IDSA EIN surveyed its 1079 member IDCs by facsimile or email regarding frequency of linezolid prescribing and experience with serious adverse events. Non responding IDCs were sent second and third reminders in January 2007.

Results: The 460 IDCs who responded (43% of 1079 members) reported collectively that most (60%) prescribed short-course linezolid (<14 days) at least once a month. 63% of respondents had prescribed at least one extended course (>28 days) of linezolid.

Lactic acidosis had been observed by 5% of all IDCs and by 15% of those who prescribe extended course linezolid at least once a month. Lactic acidosis developed within 5-7 days in one case. Peripheral neuropathy was reported by 17% of IDCs, while optic neuropathy was observed by 3%. New thrombocytopenia was observed by 74% of IDCs and new anemia or neutropenia by 59%, resulting in early discontinuation of 42% and 35% of treatment courses, respectively.

Overall, 47% of IDCs reported concomitant use of SSRIs with linezolid; serotonin syndrome was observed by 23% of those members. IDCs who use linezolid more frequently were more likely to co-administer SSRIs, but were not more likely to observe serotonin syndrome.

Conclusions: Most IDCs have prescribed extended course linezolid on at least one occasion. Lactic acidosis was relatively uncommon, but was reported more frequently by IDCs who routinely prescribe extended course linezolid. Half of the IDCs had co-administered SSRIs with linezoid; about one-quarter of those members had seen at least one case of serotonin syndrome.

Introduction

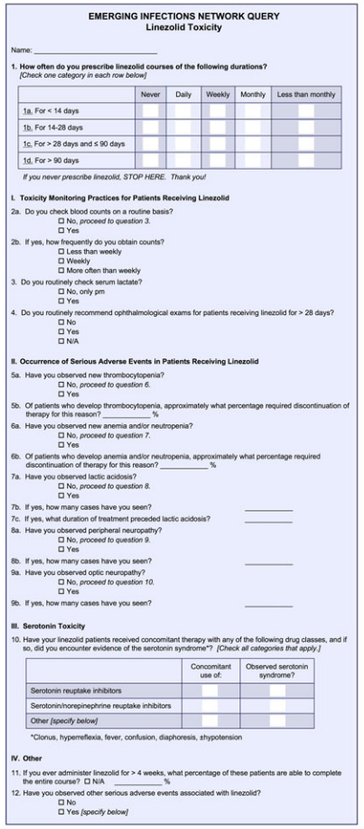
- New rare-but-serious adverse events identified by linezolid postmarketing data, including myelosuppression, peripheral and optic neuropathy, and lactic acidosis (Soriano et al. NEJM 2005; 353:2305)
- These adverse events thought to be caused by the inhibition of mitochondrial protein synthesis (McKee et al. Antimicr Agents Chemo 2006; 50:2042); they take weeks to appear and most reported in patients treated for longer than 28 days
- Serotonin syndrome reported in patients concomitantly treated with linezolid and selective serotonin reuptake inhibitors (SSRIs) or other drugs that increase CNS serotonin concentrations
- Some suggest that SSRIs should be discontinued at least 2 weeks prior to initiating linezolid therapy (Bernard et al. CID 2003; 36:1197), but others suggest that linezolid and an SSRI can be used concomitantly with careful monitoring for serotonin syndrome and prompt discontinuation when suspected (Taylor et al. CID 2006; 43:180)
- Despite FDA approval for a maximum of 28 days of therapy, linezolid is often administered for longer periods because of limited treatment options for some microorganisms (e.g., mycobacteria) and infections (e.g., prosthetic joint infections or osteomyelitis)

Objective

- The primary objective of this query is to identify patterns of serious adverse events associated with longer-duration linezolid therapy

Methods

- Survey (below) distributed in December 2006 to 1079 infectious diseases consultant members in North America
- Non-responding members were sent second and third reminders to complete the survey
- Serotonin syndrome was defined as clonus, hyperreflexia, fever, confusion, diaphoresis ± hypertension



EMERGING INFECTIONS NETWORK QUERY
Linezolid Toxicity

Name: _____

1. How often do you prescribe linezolid courses of the following durations? *[Check one category in each row below]*

	Never	Daily	Weekly	Monthly	Less than monthly
1a. For < 14 days	☐	☐	☐	☐	☐
1b. For 14-28 days	☐	☐	☐	☐	☐
1c. For > 28 days and ≤ 90 days	☐	☐	☐	☐	☐
1d. For > 90 days	☐	☐	☐	☐	☐

If you never prescribe linezolid, STOP HERE. Thank you!

I. Toxicity Monitoring Practices for Patients Receiving Linezolid

2a. Do you check blood counts on a routine basis?
☐ No, *proceed to question 3.*
☐ Yes

2b. If yes, how frequently do you obtain counts?
☐ Less than weekly
☐ Weekly
☐ More often than weekly

3. Do you routinely check serum lactate?
☐ No, only pm
☐ Yes

4. Do you routinely recommend ophthalmological exams for patients receiving linezolid for > 28 days?
☐ No
☐ Yes
☐ N/A

II. Occurrence of Serious Adverse Events in Patients Receiving Linezolid

5a. Have you observed new thrombocytopenia?
☐ No, *proceed to question 6.*
☐ Yes

5b. Of patients who develop thrombocytopenia, approximately what percentage required discontinuation of therapy for this reason? _____ %

6a. Have you observed new anemia and/or neutropenia?
☐ No, *proceed to question 7.*
☐ Yes

6b. Of patients who develop anemia and/or neutropenia, approximately what percentage required discontinuation of therapy for this reason? _____ %

7a. Have you observed lactic acidosis?
☐ No, *proceed to question 8.*
☐ Yes

7b. If yes, how many cases have you seen? _____

7c. If yes, what duration of treatment preceded lactic acidosis? _____

8a. Have you observed peripheral neuropathy?
☐ No, *proceed to question 9.*
☐ Yes

8b. If yes, how many cases have you seen? _____

9a. Have you observed optic neuropathy?
☐ No, *proceed to question 10.*
☐ Yes

9b. If yes, how many cases have you seen? _____

III. Serotonin Toxicity

10. Have your linezolid patients received concomitant therapy with any of the following drug classes, and if so, did you encounter evidence of the serotonin syndrome*? *[Check all categories that apply.]*

	Concomitant use of:	Observed serotonin syndrome?
Serotonin reuptake inhibitors	☐	☐
Serotonin/norepinephrine reuptake inhibitors	☐	☐
Other *[specify below]*	☐	☐

*Clonus, hyperreflexia, fever, confusion, diaphoresis, shypotension

IV. Other

11. If you ever administer linezolid for > 4 weeks, what percentage of these patients are able to complete the entire course? ☐ N/A _____ %

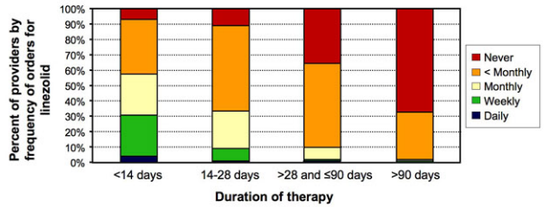
12. Have you observed other serious adverse events associated with linezolid?
☐ No
☐ Yes *[specify below]*

RESULTS

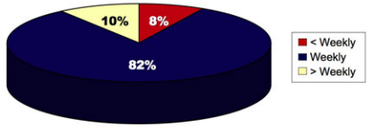
1. Overall response rate

- 460/1079 (42.6%) physicians responded
- 19 members never prescribed linezolid; these members were excluded from analyses

2. Frequency with which linezolid is prescribed

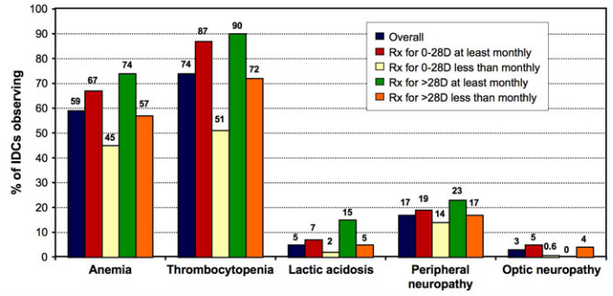


3. Frequency with which blood counts are obtained for patients prescribed linezolid



Only 22 (5%) of responding IDCs did not check blood counts on a routine basis

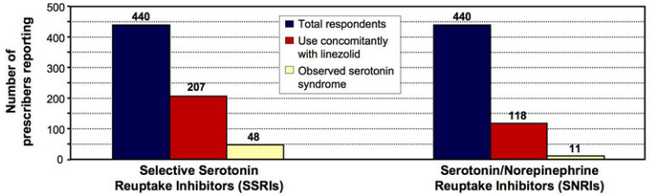
4. Occurrence of adverse events stratified by frequency of linezolid use



5. Serious adverse events

- Of patients who developed thrombocytopenia, a mean of 42% (s.d. 36, range 0-100%) required discontinuation of therapy.
- Of patients who developed anemia/neutropenia, a mean of 35% (s.d. 36, range 0-100%) required discontinuation of therapy.
- A total of 29 cases of lactic acidosis were reported by 23 member physicians. Two-thirds of these cases developed within 4 weeks of starting therapy, and almost one in three cases developed within 14 days.
- 64 cases of peripheral neuropathy were reported by 70 IDCs (range 1-4 cases/member).
- 15 IDCs reported seeing optic neuropathy at least once, and 2 members had seen 2 cases each.
- 56 (14%) of IDCs reported other serious adverse events, including GI intolerance/nausea and vomiting (N=21), hematologic side effects (N=10), rash/drug eruption (N=6), neuropathies (N=4), other neurological/psychiatric (N=3), and 1 each of sore mouth, confusion with SSRI etc, severe headaches, myositis with symptoms and elevated CPK after 3 month course, reversible posterior leukoencephalopathy, SBO requiring surgery (? Relationship to IV linezolid, no underlying pathology), severe pancreatitis, uncontrollable tremors (not on SSRI), DRESS (hypersensitivity) syndrome, black tongue in teenager, *C. difficile* colitis.

6. Serotonin syndrome and linezolid use



7. Completion rates for extended courses of linezolid

- Overall, of members who ever use linezolid for more than 4 weeks, 73% of their patients were able to complete the entire course of therapy. Nine members reported that none of their patients had completed an entire extended course, while 40 members reported that 100% of their patients completed extended courses.
- The 36 members who prescribed extended course linezolid more frequently reported that 81% of their patients completed these courses (range 30%-100%), while the 187 members who rarely prescribed extended courses reported a mean of 72% completion (range 0-100%).

Summary

- Short-course linezolid (<14 days) is given relatively commonly. However, the majority of members prescribe linezolid courses of more than 14 days on a less-than-monthly basis, and more than two-thirds never use linezolid for more than 90 days.
- New thrombocytopenia or anemia/neutropenia was reported by the majority of members, and more often by those who prescribe linezolid more frequently and for longer periods of time.
- Lactic acidosis was uncommon (reported by 5% of members) and was seen more often by those who prescribe linezolid more frequently for a longer duration (15%).
- Peripheral neuropathy was observed by 17% of members, while optic neuropathy was observed by 3%.
- Approximately half of respondents reported concomitant use of SSRIs with linezolid, and, of those, a quarter had observed serotonin syndrome. Physicians who use linezolid more often are more likely to co-administer SSRIs, but were not more likely to observe serotonin syndrome.
- Of respondents who ever use linezolid for >4 week durations, 74% of their patients were able to complete the entire course. Physicians who more routinely used linezolid used linezolid for >4 weeks reported a somewhat higher completion rate.