MAJOR ARTICLE

Serotonin Toxicity Associated with the Use of Linezolid: A Review of Postmarketing Data

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Background. Linezolid is the first oxazolidinone antimicrobial marketed in the United States. It exhibits monoamine oxidase (MAO) type A and MAO type B inhibitory effects. The concomitant administration of nonselective MAO inhibitors or MAO-A inhibitors with drugs that increase serotonin concentrations is associated with serotonin toxicity.

Methods. We requested from the US Food and Drug Administration all postmarketing adverse event reports regarding linezolid that included serotonin toxicity or any report describing cognitive or behavioral symptoms and autonomic and neuromuscular excitability. We assessed the case summaries obtained from the Adverse Event Reporting System database for serotonin toxicity. A case of serotonin toxicity was defined as having the following: (1) linezolid as the primary suspect drug; (2) concurrent administration of $\geqslant$1 secondary suspect drug known to increase serotonin concentrations in the central nervous system; and (3) serotonin toxicity, as defined by the modified Hunter Serotonin Toxicity Criteria or by the reporter.

Results. Twenty-nine cases were classified as serotonin toxicity. Patients' ages ranged from 17–83 years, and the ratio of females to males was 1:1. The most common class of drugs received concurrently with linezolid was selective serotonin reuptake inhibitors (26 of 43 patients). Thirteen patients required an intervention to prevent permanent impairment or required hospitalization for the adverse event.

Conclusion. The use of linezolid with medications that increase concentrations of serotonin in the central nervous system may result in serotonin toxicity. Prescribers must weigh risks and benefits of this combination. Patients and prescribers should be cognizant of signs and symptoms of serotonin toxicity and should initiate appropriate measures if such symptoms develop.

Linezolid was the first agent in the oxazolidinone class of antimicrobials to be approved by the US Food and Drug Administration (FDA). Linezolid was approved by the FDA for oral and intravenous use in 2000 [1]. It has in vitro activity against aerobic and anaerobic gram-positive organisms, including multidrug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus faecium, Enterococcus faecalis,* and *Streptococcus pneumoniae* [2, 3]. To date, its unique mechanism of action has resulted in a limited number of cases of bacterial resistance and no cross-resistance with other classes of antimicrobial agents [1, 3]. Linezolid's high oral bioavailability and in vitro spectrum have made it an appealing agent for use in both inpatients and outpatients [2].

The oxazolidinones are similar in structure to toloxatone, a known inhibitor of monoamine oxidase (MAO) [4]. In humans, there are 2 different forms of MAO enzymes, types A and B [4]. These enzymes are responsible for metabolism of the monoamine neurotransmitters epinephrine, norepinephrine, serotonin, and dopamine. MAO-A is preferentially responsible for the metabolism of epinephrine, norepinephrine, and serotonin [4]. Linezolid exhibits weak reversible MAO-A and MAO-B inhibitory effects [5]. Comparison of inhibitory effects for linezolid demonstrates inhibitory binding affinity constant (K_i) values of 56 μM and 0.71 μM, respectively, for MAO-A and MAO-B. The average maximal plasma concentration after a single 600-mg dose of linezolid is ~18 μg/mL (53.4 μM), which is close to its K_i for MAO-A inhibition and much greater than its K_i for MAO-B inhibition, indicating that an

Received 31 October 2005; accepted 1 February 2006; electronically published 27 April 2006.

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Clinical Infectious Diseases 2006; 42:1578–83

1058-4838/2006/4211-0010$15.00

interaction with sympathomimetic agents would be likely [5].

The concomitant administration of a nonselective MAO inhibitor (e.g., phenelzine) and a serotonin reuptake inhibitor (SSRI) is a well-documented cause of serotonin syndrome [6]. However, some drugs not widely known for affecting serotonin concentrations (eg, linezolid, meperidine, and tramadol) when combined with a SSRI or nonselective MAO inhibitor may also cause serotonin syndrome [6]. Many of the lesser known reversible inhibitors of MAO-A, such as linezolid and moclobemide, are weak inhibitors and cannot produce serotonin syndrome when taken alone, even as an overdose.

Serotonin syndrome is mediated by a drug-induced excess of serotonin in the CNS [7, 8]. It is a predictable and preventable reaction leading some authors to recommend the use of "serotonin toxicity" as a more accurate description of this toxidrome [7, 8]. The degree of increase in serotonin caused by the administered medications determines the severity of the toxidrome, which occurs on a spectrum which may progress from mild adverse effects to life-threatening toxicity [6, 8].

The clinical presentation of serotonin toxicity is marked by a triad of cognitive or behavioral changes, autonomic instability, and neuromuscular excitability [6, 8]. The most reliable sign of serotonin toxicity is the presence of spontaneous clonus [8]. Serotonin toxicity has caused fatalities. The most widely recognized case is that of Libby Zion, an 18-year-old patient who died as a result of a preventable interaction between meperidine, an unsuspected inhibitor of serotonin reuptake, and phenelzine, an irreversible MAO inhibitor [6]. Serotonin toxicity is self-limiting if it is recognized early, if the suspected serotonergic agent(s) is discontinued, and if appropriate supportive therapy is initiated [6, 8].

The purpose of our study is to delineate the quantity and outcomes of patients who have developed serotonin toxicity while undergoing concurrent therapy with linezolid and medications that increase CNS serotonin concentrations. Postmarketing voluntary adverse event reports are the source of our data.

METHODS

FDA request. On 17 September 2003, under the Freedom of Information Act, we requested from the FDA all postmarketing voluntary adverse event reports of linezolid that included serotonin syndrome. Specifically, we requested all reports of serotonin syndrome or any report of cognitive or behavioral symptoms (confusion, visual hallucinations, delusions, elevated mood, agitation, insomnia, nervousness, delirium, or coma), autonomic instability (fever, hyperhidrosis, hypertension, palpitations, or tachycardia), and neuromuscular excitability (myoclonus, tremors, chills, rigidity, hyperreflexia, or akathisia).

Because serotonin toxicity with linezolid has only been reported in patients receiving concurrent therapy with medications known to potentiate central serotonergic activity [9–17], we requested that the FDA provide a complete list of concurrent medications received by patients.

In response to our request, the FDA searched the Adverse Event Reporting System (AERS) database. The database contains spontaneous reports generated by health professionals, consumers, and manufacturers from both the United States and countries overseas [18].

Case definition. A case of serotonin toxicity was defined as having the following 3 components: (1) linezolid as the primary suspect drug; (2) concurrent administration of $\geqslant 1$ secondary suspect drug known to increase serotonin concentrations in the CNS (table 1) [19, 20]; and (3) serotonin toxicity, as defined by the modified Hunter Serotonin Toxicity Criteria (HSTC) or by the reporter.

Two of us (K.R.L. and P.K.G.) agreed on a list of surrogate terms that would be used to develop the modified HSTC (table 2). Modification of the original HSTC was necessary, because in its summary of the adverse event, the FDA uses the *Medical Dictionary for Regulatory Activities* to code reported reactions. Because the summary may not contain the medical terminology used in the original HSTC, alteration of the original criteria was necessary. Using this case definition, all reports were reviewed and assessed for the presence of serotonin toxicity. Any duplicate events were eliminated.

Data collection. For each report that met the case definition, the following information was retrieved and entered into a database created with Microsoft Access software (Microsoft): age, sex, concomitant medications known to increase concentrations of serotonin in the CNS, description of serotonin toxicity, and outcome. The patient's outcome was classified as $\geqslant 1$ of the following: death, life-threatening illness, hospitalization (initial or prolonged), disability, congenital anomaly, intervention to prevent permanent impairment and/or damage, and/or other [18].

RESULTS

The FDA searched the AERS database for records from 1 November 1997 to 25 September 2003. Twenty-nine cases were classified as serotonin toxicity due to treatment with linezolid (table 3). Twenty-six cases were described by the reporter as serotonin toxicity, and 3 cases met the modified HSTC.

Ages of patients ranged from 17–83 years, and the ratio of females to males was 1:1. A total of 43 drugs with serotonergic properties were reported. Twenty cases involved the use of only 1 concomitant drug, 6 cases involved the use of 2 concomitant drugs, and 3 cases involved the use of $\geqslant 3$ concomitant drugs.

The most common class of drugs received concurrently with linezolid was SSRIs (26 of 43 patients), followed by tricyclic antidepressants (6 of 43 patients) and atypical antidepressants (4 of 43 patients). Other concomitant medications were me-

Table 1. Drugs that increase CNS serotonin concentrations.

- Analgesics
  - Codeine
  - Dextropropoxyphene
  - Fentanyl
  - Meperidine
  - Pentazocine
  - Tramadol
- Anti-Parkinsonians
  - Amantadine
  - Bromocriptine
  - Levodopa
  - Selegiline
- Migraine therapy
  - Dihydroergotamine
  - 5-HT_1 agonists
    - Naratriptan
    - Rizatriptan
    - Sumatriptan
    - Zolmitriptan
- Antidepressants
  - Monoamine oxidase inhibitors
    - Isocarboxazide
    - Moclobemide
    - Phenelzine
    - Tranylcypromine
  - Selective serotonin reuptake inhibitors
    - Citalopram
    - Fluoxetine
    - Fluvoxamine
    - Paroxetine
    - Sertraline
  - Tricyclic antidepressants
    - Amitriptyline
    - Clomipramine
    - Desipramine
    - Doxepine
    - Imipramine
    - Nortriptyline
  - Others
    - Bupropion
    - Mirtazapine
    - Nefazodone
    - Trazodone
    - Venlafaxine
- Amphetamine and derivatives
  - Dextramphetamine
  - Metamphetamine
  - Fenfluramine
  - Dexfenfluramine
  - Phentermine
- Atypical antipsychotics
  - Clozapine
  - Olanzapine
  - Risperidone
  - Zisprasidone
- Antiemetics
  - 5-HT_3 antagonists
    - Dolasetron
    - Granisetron
    - Ondansetron
  - Droperidol
  - Metoclopramide
- Illicit drugs
  - Cocaine
  - Lysergic acid diethylamide (LSD)
  - 3,4-methylenedioxymethamphetamine (MDMA)
  - Mescaline
- Miscellaneous
  - Bromopheniramine
  - Buspirone
  - Carbamazepine
  - Dextromethorphan
  - Diphenhydramine
- L-tryptophan
  - Linezolid
  - Lithium
  - Moclobemide
  - Reserpine
  - Sibutramine
  - St. John's wort
  - Tetrabenazine

NOTE. Adapted from [19, 20].

toclopramide (1 patient), carbidopa-levodopa (2 patients), tramadol (1 patient), lithium (1 patient), dextromethorphan (1 patient), and risperidone (1 patient).

Patient outcomes consisted of death (3 patients), intervention to prevent permanent impairment or damage (6 patients), and initial or prolonged hospitalization (7 patients). Patient outcomes for the remaining 13 patients were not provided by the reporter.

DISCUSSION

Linezolid is a member of the oxazolidinone class of antibacterial agents, a class that is structurally similar to tolaxotone, a known MAO inhibitor. In addition, 2 of its metabolites are structurally related to moclobemide [4]. Moclobemide is a reversible MAO-A inhibitor and has been reported to cause serotonin toxicity when administered in combination with a SSRI or a nonselective MAO inhibitor [6, 8]. Therefore, under similar circumstances, a risk of serotonin toxicity would be anticipated with linezolid [6].

The use of the AERS database yielded 29 cases of serotonin toxicity associated with linezolid, of which 9 cases were previously published. Linezolid was most often concurrently administered with an SSRI.

Strengths. The strengths of this study include the use of the AERS database and the modified HSTC for assessing the presence of serotonin toxicity. Clinical trials are limited in type

Table 2. Original and modified Hunter Serotonin Toxicity Criteria (HSTC).

Original HSTC
Spontaneous clonus
Inducible clonus and agitation or diaphoresis
Ocular clonus and agitation or diaphoresis
Tremor and hyperreflexia
Hypertonia, a temperature of >38°C, and ocular clonus or inducible clonus
Modified HSTC
Clonus, seizure, myoclonus, ataxia, incoordination, jaw-trismus, rigidity, shivering, rigors, or nystagmus
Tremor or twitching and hyperreflexia

NOTE. Serotonin toxicity is defined as meeting ⩾1 of the criteria.

and number of patients. The types of patients range from healthy volunteers to a limited selection of patients who are candidates for the drug and who meet a list of inclusion and an endless list of exclusion criteria. Therefore, these trials are not capable of detecting serious adverse events that are rare. Postmarketing experience allows broader exposure to the drug in "real life" patients, thereby allowing more information regarding rare adverse effects to be gathered. The AERS database is the primary source of postmarketing reports of adverse effects. The use of the AERS database as a source of information has resulted in the withdrawal of >75 drugs from the US market, but the database is beleaugered by underreporting, with rates varying from <1% to 53% [22]. Frequency of reporting increases with severity of the adverse event [23].

The first case of serotonin toxicity was reported by Oates and Sjostrand [24] in 1960. However, it was not until 1991 that Sternbach published the first diagnostic criteria for serotonin toxicity [25]. These criteria were developed after a review of selected case reports of patients with serotonin syndrome. Since then, several modifications to these criteria have been made. The HSTC were developed on the basis of clinical findings from 2222 consecutive cases of self-poisoning with serotonergic drugs [21]. The clinical features that were significantly associated with serotonin toxicity were analyzed and used to develop the decision rules. The final decision rules, defined as HSTC, were then compared against the gold standard, a diagnosis of serotonin toxicity made by a medical toxicologist, and against Sternbach's original criteria. Compared with a diagnosis determined by a clinical toxicologist, HSTC were found to be 84% sensitive and 97% specific, whereas Sternbach's original criteria were found to be 75% sensitive and 96% specific. Despite clear improvements, compared with older methods of diagnosis, the HSCT have not been validated in patients who developed serotonin toxicity while receiving therapeutic doses of serotonergic medications, either alone or in combination.

There are several barriers to diagnosing serotonin toxicity. A study published in 1999 reported that ~85% of physicians were unaware of serotonin toxicity as a clinical diagnosis [26]. Although more prescribers may presently be aware of serotonin toxicity, a number of signs and symptoms may be dismissed by both patient and clinician as inconsequential, unrelated to drug therapy, or misattributed to the patient's mental status. Signs of serotonin toxicity range in presentation from subtle and nonspecific—such as agitation, diarrhea, sweating, and tachycardia—to overtly severe or life-threatening, such as hyperthermia and rigidity. Milder forms may not be recognized. In addition, prescribers may not be aware of medication combinations that may precipitate serotonin toxicity. The use of a strict criteria for diagnosing serotonin toxicity and the frequently documented underreporting of adverse events suggests that we are not exaggerating the risk of serotonin toxicity with linezolid; we risk underestimating it.

Limitations. The AERS database is hampered by limitations in the overall quality and quantity of the reports. The summary reports lack detailed and pertinent information, such as patients' demographic characteristics (e.g., weight), medical conditions, duration of treatment, and dosages of concurrent drugs, as well as temporal associations and the medical management of serotonin toxicity. There are many limitations associated with the use of spontaneous adverse event reporting to establish causality or incidence; therefore, we have not attempted to establish either one.

Published data. Linezolid exhibits MAO inhibition affects that are similar to those exhibited by moclobemide, when such effects are measured by the pressor response to oral tyramine [27]. In healthy volunteers, the concurrent administration of linezolid with phenylpropanolamine or pseudoephedrine yielded an enhanced but reversible pressor response [28].

To date (2001–May 2005), 11 cases of serotonin toxicity with linezolid have been published [9–17]. Nine of the cases were associated with concomitant administration of a SSRI, and 2 cases were associated with concomitant administration of venlafaxine. The majority of patients had onset of serotonin toxicity within 1 week (range, 1–21 days) of intiation of treatment. Care of patients consisted of discontinuing linezolid or the concomitant agent or both. Three of the patients were also treated with cyproheptadine, an effective antidote for serotonin toxicity. Time to resolution of symptoms was within the first 48 h (range, 24 h–9 days) for 7 of 11 patients.

The pharmaceutical manufacturers of 2 SSRIs took steps to include new warnings about the risk of serotonin toxicity during concurrent administration of linezolid [29, 30]. The manufacturer of linezolid has recently changed the precaution section of the product label to include additional warnings about the risk of serotonin toxicity during concurrent administration of a SSRI or an antidepressant [31].

Data from phase III clinical trials demonstrated that 52 of

Table 3. Summary of patients with serotonin toxicity identified in the Adverse Event Reporting System database.

Age, years	Sex	Drug(s) received	Symptom(s)	Outcome
39	F	Amitriptyline	ST	Hospitalization
NA	M	Amitriptyline, metoclopromide	Tremor, fever, seizure	Other
45	M	Bupropion, risperidone, sertraline, trazodone	ST, tremor, clonus	Required intervention
45	M	Buproprion, lithium, sertraline, trazodone	ST	Other
17	M	Citalopram	Muscle rigidity	NA
81	M	Citalopram	ST	Death
NA	NA	Citalopram	ST	NA
NA	M	Citalopram	ST, fever	Death
NA	M	Citalopram	ST, seizure	Required intervention
NA	F	Citalopram	ST, seizure	Hospitalization
56	F	Citalopram	ST, tremor	Death
NA	F	Citalopram, paroxetine	ST	Other
NA	F	Citalopram, paroxetine	ST, sweating	Other
NA	NA	Dextromethorphan	ST	NA
71	F	Carbidopa-levodopa	ST, agitation	Hospitalization
83	F	Fluoxetine	ST	Other
NA	NA	Fluoxetine	ST	Other
22	F	Mirtazapine	ST, seizure	Hospitalization
39	M	Mirtazapine, paroxetine	ST, seizure, twitching	Required intervention
56	F	Paroxetine	ST	Other
69	F	Paroxetine	ST	Life-threatening illness, hospitalization
56	F	Paroxetine	ST, fever	Other
NA	M	Paroxetine, trazadone, amitriptyline	ST	Other
71	F	Sinemet	ST, agitation	Hospitalization
36	M	Sertraline	ST, agitation	Required intervention
36	M	Sertraline	ST, agitation, akathesia, fever	Required intervention
NA	NA	SSRI	ST	NA
36	M	SSRI, sertraline	ST, agitation	Required intervention
81	M	Tramadol, paroxetine	Rigors	Hospitalization

NOTE. F, female; M, male; NA, not available; SSRI, selective serotonin reuptake inhibitor; ST, serotonin toxicity.

2046 patients randomized to receive linezolid were taking a SSRI, yet no cases of serotonin toxicity were identified [32]. However, because of the inadequacy of reporting of adverse drug effects in clinical trials, the upper limit of the 95% CI for this syndrome ranged from 0% to ~6% [33]. Our review of the AERS database suggests that there is a risk of serotonin toxicity during therapy with linezolid and drugs that increase serotonin concentration. Prescribers of linezolid must familiarize themselves with symptoms of serotonin toxicity and the medications that, if taken with linezolid, may precipitate this toxidrome. When confronted with a patient receiving a serotonergic medication, physicians must weigh the risks and benefits of initiating therapy with linezolid.

The management of this potential interaction may include the use of alternative antimicrobial agents, such as clindamycin, daptomycin, doxycycline, minocycline, trimethoprim-sulfamethoxazole, or vancomycin. Although some of the published case reports regarding linezolid and serotonin toxicity recommend the discontinuation of a SSRI, we do not consider this to be appropriate. Rapid discontinuation of a SSRI is associated with potentially severe withdrawal symptoms [34]. In addition, the parent drug and active metabolites of SSRIs have long elimination half-lives that require, in some cases, a washout period of several weeks before linezolid can be safely initiated. Such a delay in initiating antimicrobial therapy poses health risks to the patient. If serotoinin toxicity develops in a patient receiving linezolid, further treatment with linezolid should immediately be discontinued, and supportive therapy should be instituted.

CONCLUSION

Using the FDA's AERS database, we identified 29 patients who met our case definition of serotonin toxicity. Because of the risk of serotonin toxicity, prescribers must weigh the risks and benefits of therapy with this antimicrobial agent when patients are receiving medications that increase concentrations of serotonin in the CNS. Patients and prescribers should be cog-

nizant of signs and symptoms of serotonin toxicity and should immediately institute appropriate measures if they develop.

Acknowledgments

We thank Adah Lau, for her assistance in reviewing summary data provided by the FDA.

Potential conflict of interest. K.R.L. is a member of the speakers' bureaus for and has served as a consultant to Pfizer, Cubist, and Wyeth. M.A. is a shareholder in Pfizer. P. K. G: no conflicts.

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