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Short Communication

Linezolid interaction with serotonin reuptake inhibitors: report of two cases and incidence assessment

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Abstract

Background: Prompted by the advent of potentially life-threatening neuromuscular symptoms following initiation of linezolid therapy in two patients receiving treatment with a serotonin reuptake inhibitor antidepressant, an evaluation was conducted to determine the incidence and characteristics of symptomatic serotonin toxicity among hospitalized patients receiving combined treatment with these medications.
Methods: Patients admitted between January 1, 2006 and August 30, 2008 who received linezolid concurrently with citalopram or escitalopram were identified and their medical records were examined. Patients were judged to have serotonin toxicity if their records contained documentation of clinical evidence adequate to fulfill requisites of the Hunter Serotonin Toxicity Criteria. Severity of serotonin-related symptoms was graded according to previously established criteria.
Results: During the period of observation, 24 patients received concurrent treatment with linezolid and citalopram or escitalopram. Of these, one patient (4%) treated with citalopram met evidentiary requirements for diagnosis of serotonin toxicity. The severity of symptoms in this patient was graded as mild. No evidence of serious harm related to a possible drug interaction was identified.
Conclusions: Severe symptoms associated with serotonin toxicity were shown to be uncommon in patients receiving linezolid and selected serotonin reuptake inhibitors. Nonetheless, serious interaction-related toxicity has been observed at our institution and reported in detail by others. Accordingly, concurrent use of these medications is categorized as contraindicated. Alternative antimicrobial therapy should be instituted in most cases. If no suitable alternative is available, recipient patients should be hospitalized for expectant observation and rigorous monitoring.

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Introduction

Owing to often favorable clinical pharmacological actions (1, 2), pharmacokinetics (3, 4), relative safety (5, 6) and, for selected patients, pharmacoeconomics (7, 8), linezolid is increasingly used for treatment of serious Gram-positive bacterial infections, including those suspected or proven to involve resistant strains. In addition to inciting antibacterial effects mediated by inhibition of protein synthesis, this oxazolidinone antimicrobial agent selectively and competitively binds to monoamine oxidase (MAO)-A receptors in serotonergic and noradrenerinergic neurons. This binding inhibits enzymatic degradation of monoamine neurotransmitters such that in susceptible but presently unidentifiable individuals concurrently receiving serotonergic drugs, these substances can accumulate to levels that result in a triad of symptoms that include mental status changes, autonomic instability, and neuromuscular irregularities ranging in severity from barely perceptible to lethal (9).

Possible sympathomimetic effects associated with linezolid-induced inhibition of MAO-A have been evaluated in considerable detail. In rodents, intravenous (IV) and oral challenges with tyramine, a common dietary MAO substrate, produced minimal pressor responses when administered with either acute or chronic doses of linezolid (30 mg/kg) near those that might be used clinically in humans, whereas higher doses (100 mg/kg) produced a moderate pressor response (10). In this study, potentiation of tyramine by linezolid was reversible, attenuated by food, and devoid of potential interaction effects associated with concomitant administration of pseudoephedrine, phenylephrine, and dextromethorphan (10).

Similar studies in healthy volunteers evaluated whether linezolid interacts with tyramine. Although pressor responses elicited by administration of very high-dose oral tyramine were potentiated by linezolid, investigations in subjects given usual doses of linezolid demonstrated that this antimicrobial exerted no intrinsic hypertensive actions and displayed little or no potential to elicit noticeable or measureable effects from either tyramine in amounts found in a normal diet or common oral decongestants. These findings led to conclusions that possible drug interactions leading to potentiation of cardio-

vascular effects produced by tyramine in amounts contained in foods or concurrent use of over-the-counter cold remedies are not clinically significant (11, 12).

In controlled clinical trials comprising assessment of linezolid-based antimicrobial treatment of 2046 patients, of whom nearly one-third were receiving analgesic, vasopressor, indirectly acting sympathomimetic, cyclic antidepressant, or serotonin reuptake inhibitor (SRI) medications that potentially could interact with an MAO inhibitor, evidence of a possible drug interaction was limited to a single episode of transient, asymptomatic hypertension in a patient with a history of high blood pressure who was receiving concomitant treatment with fluoxetine (13).

Despite these reassuring safety data, symptomatic adverse events temporally related to combined use of linezolid and serotonergic drugs continue to occur in a seemingly sporadic manner. We wish to report the occurrence of two such events as well as findings of a consequent study of exposed patients conducted for the purpose of determining the incidence with which these symptomatic events arise.

Case report number 1

Seven days after discharge following orthotopic liver transplantation, a 54-year-old male presented to the emergency department with complaints of tremor in his hands. Examination revealed bilateral hand tremors as well as fasciculations of the tongue but no focal motor deficits, focal sensory deficits, or cerebellar deficits. Hepatic transaminase levels were within normal limits but total bilirubin was 2.0 mg/dL (34.2 μmol/L). The serum tacrolimus concentration was 5.9 ng/mL. He was admitted to the hospital for determination of the cause of his tremor and dose adjustment of immunosuppressant medications. His usual maintenance medications, including sertraline, metoprolol, esomeprazole, docusate, and co-trimoxazole were continued upon admission.

An increasing intra-abdominal fluid collection prompted surgical exploration that revealed biliary stricture and a bile leak that was treated with drainage and stent placement. The peritoneal fluid was cultured and found to contain *Candida albicans*, *Enterobacter cloacae*, and vancomycin-resistant *Enterococcus faecium*. IV antimicrobial therapy was initiated with caspofungin, imipenem-cilastatin, and linezolid.

At the time of initiation of linezolid, managing physicians were contacted and warned of the potential for an adverse drug interaction in this patient who was maintained on selective SRI therapy. A cursory risk-benefit assessment was performed and, based largely upon the potential severity of infection in this patient with compromised immunity, a subsequent decision was made that favored selection and continued use of linezolid.

Two days after antibiotic initiation, he lost balance and fell amid increasing restlessness and confusion. He experienced visual hallucinations and was agitated, combative, and pulling at IV access and nasogastric tubes such that physical restraints were required. To evaluate possible causes of his acute mental status changes, a cerebral computed tomographic (CT)-scan was requested. Uncontrollable agitation precluded this investigation. Endotracheal intubation, sedation, and administration of neuromuscular blocking agents were required to facilitate scan completion and mechanical ventilation was maintained overnight in the intensive care unit (ICU). Subsequent CT-scan results were essentially normal.

Concern for possible adverse effects related to medications led to discontinuation of sertraline and his immunosuppressant regimen was changed from tacrolimus to mycophenolate sodium and sirolimus. Within 24 h, the patient's mental status began to improve. He was extubated and, with no further eventualities, was asymptomatically discharged from the hospital 48 h later.

Case report number 2

A 52-year-old female presented to the hospital with complaints of right-sided back pain. Her medical history within the preceding 6 months included prolonged hospitalizations for necrotizing fasciitis of the face and subsequently respiratory and blood stream infections associated with it.

At the time of presentation, diagnostic imaging revealed a T11-L1 spinal compression fracture with paraspinous fluid accumulation associated with osteomyelitis. Cultures of this fluid demonstrated methicillin-resistant *Staphylococcus aureus* (MRSA) with minimum inhibitory concentrations to both vancomycin and daptomycin of 2 mg/L. Spinal decompressive surgery was performed, antibiotic monotherapy was initiated with IV linezolid, and comprehensive postoperative care including mechanical ventilation was provided in the ICU. Maintenance medications including duloxetine and escitalopram for depressive disorder were continued.

Nine days after initiation of linezolid, examination disclosed 6 beats of inducible clonus bilaterally in the lower extremities and 5 beats of inducible clonus in the upper extremities. At this time, reflexes were normal but the patient was tachycardic with bilaterally dilated pupils and a dry oral mucosa. Suspicion for serotonin toxicity prompted discontinuation of linezolid and substitution with IV vancomycin and doxycycline. Examination approximately 24 h later revealed resolution of clonus. The patient underwent a prolonged but uneventful recovery and eventually was discharged home.

Materials and methods

This study was performed with oversight by the Colorado Multiple Institutional Review Board. Adults admitted to University of Colorado Hospital between January 1, 2006 and August 30, 2008 who received oral or IV linezolid and the SRIs citalopram or escitalopram during the time of their admission were identified from inpatient prescription medication records. Patients were included in this study if they received linezolid and escitalopram or citalopram concurrently. These medications were selected for study on the basis of their mutual comparatively high SRI potencies (14–17) and because prior usage records indicated that, among all available antidepressants, these are prescribed most frequently at our hospital.

The medical records of patients who received concurrent treatment with linezolid and SRIs were examined for signs of symptomatic serotonin (5-hydroxytryptamine, 5-HT) toxicity. Patients were judged to have serotonin toxicity if their records contained documentation of clinical evidence sufficient to fulfill diagnostic requisites of the Hunter Serotonin Toxicity Criteria (myoclonus, agitation, diaphoresis, tremor, and/or hyperreflexia) (18). Based upon recorded clinical descriptions, the severity of serotonin toxicity was graded according to criteria proposed by Boyer and Shannon in their authoritative review in 2005 (19).

Patients were excluded if concurrent therapy was administered for <24 h, if signs or symptoms suggestive of serotonin toxicity were present prior to receiving concurrent therapy, or if their medical records contained incomplete, equivocal, or contradictory data.

Results and discussion

During the 32-month period of observation, 53 patients received linezolid and citalopram or escitalopram therapy during their hospitalization. Of these, 29 patients did not receive these medications concurrently and therefore were excluded. A total of 24 patients met inclusion criteria. The patients included in the study ranged from 22 to 93 years of age (mean 55.6 years). Twelve (50%) were male. Salient treatment details are shown in Table 1.

Patients received concurrent linezolid-SRI therapy for an average of 4.2 days, with a range of 2–12 days. Eighteen patients (75%) were taking an SRI prior to hospital admission, and this was continued during hospitalization. Four patients (17%) were discharged with instructions to take both linezolid and an SRI at home following discharge (Table 1).

Ten (42%) out of 24 patients included in this study had documented clinical signs consistent with serotonin toxicity. One patient (4%) fulfilled the evidentiary Hunter criteria required for diagnosis of serotonin toxicity based upon the presence of spontaneous clonus (18). This patient was continued on her routine pre-admission dosage of citalopram when IV linezolid 600 mg every 12 h was initiated for treatment of suspected sepsis. She began showing signs of mild serotonin toxicity, including trembling, shaking, and altered mental status approximately 20 h after conclusion of the course of linezolid therapy. These symptoms persisted for approximately 32 h and then resolved spontaneously.

In the case reports presented, clinical findings fulfill decision-rule criteria for diagnosis of serotonin toxicity (18). In the first case described above, we believe that the patient's initially mild symptoms of tremor and muscle fasciculations probably were incited by treatment with the selective SRI sertraline. Approximately 48 h after this therapy was combined with linezolid, adverse symptoms markedly increased in severity. Incoordination, confusion, and severe agitation eventually required IV sedation, mechanical ventilation, and admission to a critical care unit. Costly diagnostic interventions were required and hospitalization was prolonged. Causality association of these events with a drug interaction between linezolid and an SRI in this case was graded as probable (20).

In the second case report, we suspect that clonic symptoms were delayed results of the combination of linezolid with duloxetine and escitalopram. This patient was given combined linezolid-SRI treatment but experienced a reaction some 9 days after initiation of linezolid. Causality association with a drug interaction between linezolid and SRIs in this case likewise was graded as probable (20).

Our observational study of exposed patients revealed varying levels of discernment and understanding of the potential drug interaction between linezolid and SRIs. This study additionally disclosed prescriber actions to manage or avert this interaction that ranged from apparent inattention or discounting and disregard of warnings to rigid insistence upon complete avoidance of concomitant administration of these medications.

In total, this study identified 24 hospitalized adults that received concurrent treatment with linezolid and an SRI during the 32-month period of observation. Among these patients, symptoms fulfilling evidentiary requirements for diagnosis of serotonin toxicity were present in one patient (4%). This observed incidence of serotonin toxicity is consistent with that reported in other retrospective studies (Figure 1).

Among 72 patients in Minnesota, two (3%) were found to fulfill criteria for high probability of serotonin toxicity associated with concomitant treatment with linezolid and sertraline or venlafaxine manifest as restlessness, agitation, myoclonus, incoordination, and hyperreflexia (21). Of 53 patients

Table 1 Treatment medications in patients receiving concurrent linezolid-SRI therapy (n=24).

Medication	n	%
Medications prior to admission		
SRI	18	75
Linezolid	0	0
SRI used with linezolid		
Citalopram	8	33
Escitalopram	16	67
Discharge medications		
SRI	16	67
Linezolid	7	29
Both	4	17

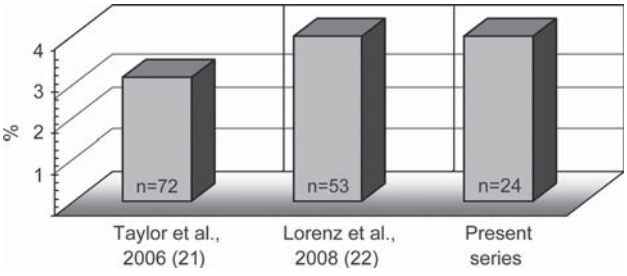

Figure 1 Incidence of serotonin toxicity associated with linezolid-SRI therapy.

in South Carolina concomitantly treated with linezolid and a potentially interacting SRI antidepressant, one patient (2%) who was given escitalopram developed spontaneous clonus was judged to have symptoms possibly related to serotonin toxicity and one patient (2%) who was given citalopram exhibited mental status changes, agitation, tremor, and hyperreflexia that was judged as probably related to serotonin toxicity (22). In a 6-year overview of postmarketing linezolid-related adverse event data submitted to the US Food and Drug Administration, 29 cases classified as serotonin toxicity were identified in which linezolid was the primary suspect drug administered concurrently with ≥1 secondary suspect drugs known to increase serotonin concentrations in the central nervous system (23). Twenty-four patients (83%) in this series received an SRI antidepressant as the suspect interacting medication; 13 patients (45%) needed intervention to prevent permanent impairment or required hospitalization for the adverse event (23).

Thus, our experience and available published information suggests that symptomatic serotonin toxicity associated with combined use of linezolid and SRIs affects <1 in 20 exposed patients and that serious interaction-related toxicity is uncommon.

The range of severity of symptoms associated with these drug interactions is broad, with a spectrum that varies from imperceptible or barely noticeable to potentially fatal (9, 18, 19). Although infrequent, serotonin concentrations sufficient to cause life-threatening toxicity have been shown to occur more commonly from interactions between MAO inhibitors and serotonergic drugs than any cause other than massive overdoses with these antidepressants (24). To date, the interaction between linezolid and SRIs has been associated with at least four deaths (23, 25). For these reasons, the US professional product information for linezolid was strengthened in 2008 to include selective SRIs among drugs that are categorized as a contraindication for use in combination with this antimicrobial agent (26).

Serotonin toxicity arising from interaction with linezolid appears to be a potential complication associated with most antidepressants. Serotonin toxicity of varying severity has been reported in association with concomitant use of linezolid and fluoxetine (21, 23, 27–30), sertraline (9, 21, 31–33), amitriptyline (23, 34), paroxetine (21, 34–36), venlafaxine (37–40), mirtazepine (21, 41, 42), bupropion (23, 32), trazodone (31, 34), duloxetine (43), citalopram (21–23, 25, 33, 40, 42, 44), and escitalopram (22). Accordingly, the product information for linezolid currently lists not only SRIs but also tricyclic antidepressants as agents that potentially are capable of causing serotonergic interactions with linezolid, and combined therapy with tricyclics and linezolid therefore is contraindicated (26). However, no such interaction precautions or contraindications are included in this information concerning bupropion or trazodone, the other non-SRI selective antidepressants in the listing above.

In its recognition of this medication as a reversible, nonselective MAO inhibitor that should not be used in patients who are taking SRIs, the US product information for linezolid provisionally qualifies this statement that combined use of these medications is contraindicated "unless patients are carefully observed for signs and/or symptoms of serotonin syndrome" (26). In the precautions section, this information further suggests that when administration of linezolid and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination. Although we do not disagree with the perceived intent and most of the content of this recommendation, we believe that these warning statements are vague with poorly defined requisites for safe use of these medications in combination. In addition, these permissive statements could unnecessarily endanger patients and place providers in a position that is ethically problematic and potentially litigious. Our cases and others illustrate that not only failure to recognize and heed the contraindication to combined use but also decisions to override its ethical and legal implications can lead to serious unwanted consequences. Greater vigilance and concerted efforts by clinicians to carefully avoid these drug combinations and their interactions are needed.

Concomitant use of linezolid and SRIs should be avoided. The implication of this is that clinical decisions must be made such that patients maintained on SRI therapy are deliberately not initiated on linezolid and, conversely, patients receiving anti-infective treatment with linezolid are not initiated on SRI therapy. If a patient receiving SRI therapy develops an infection for which linezolid is indicated, providers must be fully informed of the levels of risk and the severity of possible adverse effects of combined use of these medications and, following this, an alternative antibiotic should be selected and used. Alternative antibiotics for multidrug-resistant Gram-positive infections potentially administered as part of a double- or triple-coverage combination antimicrobial regimen could include vancomycin, daptomycin, telavancin, quinupristin/dalfopristin, tigecycline, doxycycline, minocycline, trimethoprim/sulfamethoxazole, clindamycin, cefditoren, or ceftobiprole (44–48).

In the perhaps unusual situation in which no suitable alternative for linezolid is available for a patient with a serious suspected or proven infection who is also receiving an SRI, three options are available: administer linezolid and 1) continue the SRI without change; 2) alter the dose of the SRI; or 3) discontinue the SRI.

If no acceptable substitute for linezolid is available and the decision is made to follow the alternative strategy of continuing both linezolid and an SRI, the probable severity of infections involved and risks for symptomatic drug interactions and/or antidepressant discontinuation strongly argue in favor of hospitalization of these patients. Hospitalized patients receiving linezolid and an SRI should be expectantly and preferably continuously observed for signs and symptoms of a possible MAO-related drug interaction, as described above. These patients should be rigorously monitored, including at least twice-weekly hematological (hemoglobin, leukocytes, and platelets) and liver function assessments during therapy and, for those expected to receive linezolid for more than 28 days, routine ophthalmologic and neurological evalu-

ations (49). Concomitant use of other drugs that increase serotonin concentrations within the central nervous system and consequently increase risk for serotonin toxicity generally should be avoided. These medications include antidepressants, migraine therapy, anti-Parkinsonian medications, 5-HT_3-receptor antagonist antiemetics such as ondansetron, and certain opioid analgesics such as meperidine and tramadol (9, 23, 49).

For patients receiving linezolid and concurrent serotonergic agents, duration of hospitalization should be determined first by infection response and secondly by the period of vulnerability to symptomatic linezolid-related drug interactions. For most SRIs, this period of time correlates with their elimination half-life and the approximate time required for resolution of symptoms in documented interaction-related cases of serotonin toxicity. With the exception of drugs with an extended duration of serotonergic actions such as citalopram in which vulnerability can be extended to 5–9 days or more, this period of greatest concern usually is limited to approximately 48 h (50).

If a linezolid-treated patient develops symptoms believed to be associated with serotonin toxicity, precipitating serotonergic medications, if not already stopped, should be discontinued. Treatment is primarily symptomatic and supportive, including administration of benzodiazepines for management of agitation (15). The serotonin- and histamine H1-antagonist cyproheptadine has been administered in a small number of patients with severe symptoms of serotonin toxicity, but its efficacy has not been sufficiently established (19, 50).

To date, SRI dosage decreases have been tentatively associated with improvement in symptoms related to serotonin toxicity in just two patients with severe linezolid-related drug interactions (40, 41). The level of symptomatic advantage, if any, to be gained with SRI dose tapering is therefore uncertain (51). For these reasons and because of patient risk associated with the potentially adverse drug interaction described above, we believe that in most cases the best course of action is to discontinue the SRI during the period of administration of linezolid and, to allow regeneration of new MAO-A, throughout 14 days afterward (9, 49).

Recipient patients in whom SRIs are discontinued additionally should be carefully observed for possible symptoms associated with antidepressant withdrawal. A so-called discontinuation syndrome could affect as many as 50% of patients given extended treatment with SRIs. This often manifests as transient but troublesome problems of disequilibrium, gastrointestinal upset, influenza-like symptoms including fatigue, lethargy, myalgia, and chills, sleep disorders such as insomnia or vivid dreams, and sensory disturbances including paresthesias and sensations of electric shock (52, 53). Patients developing symptoms associated with SRI discontinuation should be managed symptomatically, with reassurance provided that any noticeable effects are likely to disappear within a few days. In extreme cases, cautious reinstitution of the discontinued SRI could be attempted (54).

As with similar incidence surveys (21, 22), this study has several important limitations. It was performed with a retrospective, uncontrolled design, and an assessment of care provided at the discretion of autonomous physicians. There was no institutional mandate for recording of specific clinical findings of interest. The medical records used to identify signs and symptoms of serotonin toxicity did not specifically or consistently address clinical criteria required for patient evaluation using the Hunter Toxicity assessment tool (18). Despite the potential for a drug interaction to occur during the recommended washout period for citalopram and escitalopram, only patients that received concurrent linezolid-SRI therapy were included in the evaluation. Nonetheless, this assessment of case findings and interaction prevalence offers a clinical perspective taken from typical contemporary acute patient care.

In conclusion, severe symptoms associated with serotonin toxicity were shown to be uncommon in patients receiving linezolid and selected SRIs. However, potentially serious interaction-related toxicity remains a major concern. Accordingly, use of these medications in combination is categorized as contraindicated. If combined use of these medications is being considered, individual providers should be fully informed and alternative antimicrobial therapy should be instituted. If no suitable alternative is available, recipient patients should be hospitalized, expectantly observed, and rigorously monitored.

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