Case Report

Linezolid-Induced Near-Fatal Serotonin Syndrome During Escitalopram Therapy: Case Report and Review of Literature

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ABSTRACT

Linezolid is a synthetic antimicrobial agent of the oxazolidinone class with weak, nonspecific inhibitor of monoamine oxidase enzymes. Concomitant therapy with an adrenergic or serotonergic agent or consuming tyramine (>100 mg/day) may induce serotonin syndrome (SS). We present a case report of near-fatal adverse interaction between linezolid and escitalopram inducing SS in a 65-year-old woman with sepsis, under empirical antibiotic treatment. This report also summarizes the current relevant literature as identified via PubMed, EMBASE, and PsycINFO, supplemented with a manual search of cross references.

Key words: *Adverse event, escitalopram, linezolid, serotonin syndrome*

INTRODUCTION

Monoamine oxidases (MAO) are mitochondrial enzymes responsible for the metabolic breakdown of monoamines (serotonin, norepinephrine, and dopamine) in neuronal tissues causing depletion of monoamines and clinical depression; while MAO inhibitors (MAOIs) result in the clinical improvement of mood states. Interestingly, drugs that possess MAOI properties but are used for purposes unrelated to antidepressant activity are furazolidone (an antiinfective); procarbazine (drug used for Hodgkin's disease); and linezolid (an antibiotic used for serious infections).[1] We report a case of serious adverse drug interactions between escitalopram and linezolid precipitating near-fatal serotonin syndrome (SS) in an elderly female. Relevant literature was retrieved via PubMed, EMBASE, and PsycINFO using the keywords; ''linezolid'', ''escitalopram'', ''serotonin syndrome" supplemented with a manual search of cross references.

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CASE REPORT

A 65-year-old elderly female, from urban and middle socioeconomic background, presented with history suggestive of depressed mood, middle and late insomnia, anorexia, lethargy, reduced interest in pleasurable activities since 1 year. She was diagnosed as depressive disorder as per ICD-10 diagnostic criteria.[2] She had no prior medical history of hypertension, diabetes, or any drug intake. Escitalopram (5 mg/day) and clonazepam (0.25 mg/day) therapy showed partial improvement, fortnight later. Escitalopram was increased to 10 mg/day, while clonazepam was discontinued due to drowsiness, a month later. Patient

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had full remission of depressive symptoms with escitalopram (10 mg/day), 2 months later. Compliance with medications was ensured and supervised by her apprehensive spouse.

Patient presented with acute onset high-grade fever, cough with greenish-yellow expectoration, breathlessness, and asthenia of a week's duration following recent travel. She had received antipyretics, mucolytics, expectorants, antibiotics (amoxicillin and clavulanate) for 5 days from medical practitioner but found no respite. Later, she was referred to physician and hospitalized. On admission, she had 101°F temperature, pulse rate of 126/min, and blood pressure (BP) of 136/88 mm Hg. Her general physical and systemic examination revealed no other abnormal findings, except for bilateral scattered fine crepitations and reduced bilateral air entry in lower respiratory areas. A complete blood count revealed leukocytosis (15640/cmm) and neutrophilia (80%). Her blood glucose (105 mg/dL), blood urea (25 mg/dL), and serum creatinine (1.0 mg/dL) were within normal limits. Electrocardiograph revealed no abnormalities. Her chest roentgenogram showed bilateral patchy consolidation suggestive of pneumonitis. Patient was treated with intravenous linezolid (600 mg twice daily), antipyretics, bronchodilators (etophylline), expectorants (guaiphenesin), mucolytics (ambroxol), and chest physiotherapy.

Within the first 24 hours of antibiotic treatment, the patient had a rapid clinical deterioration with restlessness, diaphoresis, tremor, shivering, myoclonus, diarrhoea, exaggerated deep tendon reflexes, hypoxia (SPO_2-80% with 6-8 L of oxygen) and high fever (103°F), along with mental status changes such as disorientation, confusion, and hallucinatory behavior. However, in view of neurological symptoms, cranial computerized tomography and lumbar puncture for the exclusion of central nervous system (CNS) infection were performed but were unremarkable. The patient was intubated due to severe respiratory difficulties and transferred to the intensive care unit. Psychiatrist consultation was sought for delirium. Detailed history and sequence of emergence of events (including history of depression and escitalopram treatment from caregivers) were observed and SS was suspected. Linezolid and escitalopram were discontinued, and cyproheptadine (4 mg thrice daily) via the nasogastric tube was initiated. Pneumonitis was treated with intravenous cephalosporin (cefotaxime; 2 g twice daily) and aminoglycoside (amikacin; 500 mg twice daily) antibiotics. Patient showed the first signs of improvement few hours later. Withdrawal of sedation and ventilator weaning took place 48 hours later. Patient gradually regained consciousness and orientation to person, location, and time. At discharge, vital parameters were stable with pulse of 86 bpm and BP of 130/80 mm Hg. Patient was discharged with escitalopram 10 mg/day.

DISCUSSION

In our case, addition of antibiotic linezolid (600 mg twice daily) for the treatment of acute onset pneumonia in a patient receiving serotonergic antidepressant, escitalopram (10 mg/day) for depressive disorder since 2 months, temporally led to the constellation of the neurological and mental state features in the absence of other CNS pathology led to the diagnosis of SS. We ruled out the possibility of other drug interactions, as none of them (paracetamol, etophylline, guaiphenesin, ambroxol) possess either adrenergic or serotonergic properties supplemented by literature search.

Linezolid is a totally synthetic compound that was initially synthesized as a reversible MAOI class antidepressant.[3] Due to its weak, nonspecific MAO inhibition, concomitant therapy with an adrenergic or serotonergic agent or consuming tyramine (>100 mg/day) may increase the risk of SS.[1] It is believed to act through early inhibition of protein synthesis via binding to the 23S portion of the 50S ribosomal bacterial rRNA subunit inducing conformational structural changes and preventing tRNA to enter and functionally bind to the ribosome therefore inhibiting mRNA translation. Its oral bioavailability is nearly equal to intravenous administration, with plasma half-life of 4-6 h. Peak serum concentrations attain about 20 mcg/mL on 600 mg twice daily dosing in adults. Linezolid is 30% protein-bound and distributed widely to well-perfused tissues.[1] Linezolid is metabolized via oxidation procedure in a way independent of cytochrome P450 (CYP-450); consequently there is no possible pharmacokinetic mechanism of interaction between linezolid and other medication metabolized through CYP450 pathways. Although 80% of the dose of linezolid appears in the urine, dose modification has not been currently recommended in renal insufficiency as serum concentrations and half-life of the drug are not appreciably affected. However, linezolid and its breakdown products are eliminated by dialysis; the drug should be administered after hemodialysis.[1] Linezolid is generally well-tolerated, with some minor side-effects like gastrointestinal disturbances, headache, and rashes. Rarely, myelosuppression including anaemia, leukopenia, thrombocytopenia, and peripheral as well as optic neuropathy have been reported on prolonged use (>8 weeks).[1]

Escitalopram is the S-enantiomer of racemic citalopram with antidepressant activity through selective serotonin reuptake inhibition (SSRI), a drug category that is believed to act through boosting of serotonin

neurotransmission via blockade of serotonin reuptake pump, therefore theoretically more prone to be involved in the development of SS. It is 56% plasma protein bound with plasma half-life of 27-32 h and reaches steady state plasma levels in 7 days. It is metabolized to S-demethylcitalopram and S-didemethylcitalopram. The primary CYP isoenzymes involved in its metabolism are CYP 3A4, CYP 2D6, and CYP 2C19. Escitalopram displays linear and dose-proportional pharmacokinetics for single and multiple doses in the dose range of 10-30 mg/day. Its clearance in elderly subjects (>65 years) in single-dose and multiple-doses showed approximate increase of 50% in half-life. Its recommended daily dose in the geriatric population is 10 mg.[4]

SS is a disorder typically caused by the combination of two or more medications with serotonergic properties due to increased serotonin release. It is characterized by restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, and mental status changes, such as confusion. It usually consists of a constellation of neurological and mental state symptoms and commonly diagnosed according to the widely accepted criteria,[5-8] as summarized in Table 1. The pathophysiological mechanism of SS does not include idiosyncratic, neither idiopathic nor pharmacokinetic drug reactions, but is considered to be a predictable and preventable pharmacodynamic consequence of the excess of serotonergic agonism in CNS and peripheral serotonergic receptors.[7] Symptoms usually improve with the withdrawal of the predisposing drug agents plus supportive care, as there is no specific evidence-based treatment of the SS.[9] Cyproheptadine is a H1 histamine receptor antagonist as well as a nonspecific serotonin receptor antagonist,[10] may have a role in the management of SS (4 mg thrice daily).

Table 1: Widely accepted diagnostic criteria for serotonin syndrome

Sternbach's criteria for serotonin syndrome (1991)[5,6]
Presence of all of the following:
Recent addition or increase in a known serotonergic agent
Absence of other possible aetiologies (infection, substance abuse/ withdrawal, and so on.)
No recent addition or increase of a neuroleptic agent
At least 3 of the following 10
Mental changes (confusion, hypomania)
Agitation
Myoclonus
Hyperreflexia
Diaphoresis
Shivering
Tremor
Diarrhea
Incoordination
Fever
Hunter's criteria for serotonin syndrome (2003)[7,8]
Presence of a serotonergic agent and at least one of following five:
Spontaneous clonus
Inducible clonus and agitation or diaphoresis
Ocular clonus and agitation or diaphoresis
Tremor and hyperreflexia, or
Hypertonia and temperature >38°C and ocular clonus or inducible clonus

Concomitant use of MAOIs (including linezolid, furazolidone, and procarbazine) along with adrenergic/ serotonergic antidepressants, St. John's wort, sibutramine, or opiate drugs that have SSRI-like properties (meperidine, tramadol, methadone, dextromethorphan, propoxyphene, and fentanyl) have been reported to precipitate dangerous SS.[1,11-16] Rarely, SS may also be precipitated by concomitant use of SSRIs with metoclopramide,[17-19] sibutramine, fenfluramine or dexfenfluramine, lithium, dihydroergotamine, sumatriptan; but risk is severe when SSRIs and MAOIs are combined.[4] Linezolid has been reported to induce SS as an interaction with almost every category of antidepressant medications like imipramine,[20] amitriptyline,[21,22] fluoxetine,[23,24] citalopram,[3,25,26] escitalopram,[25] paroxetine,[27] sertraline,[28] L-tryptophan (precursor of serotonin),[17] mirtazapine,[3] trazodone,[26] buspirone,[29] venlafaxine,[26,30,31] and duloxetine.[32]

Psychiatrists need to be aware that all SSRIs (except fluoxetine) should not be co-administered with MAOIs within 2 weeks of discontinuing either drug, lest may precipitate SS. Fluoxetine due to its long half-life is recommended to be stopped at least 5 weeks prior to initiation of MAOIs and conversely, MAOIs are to be discontinued at least 3 weeks prior to initiation of fluoxetine.[4] However, in patients receiving SSRIs who acutely require linezolid therapy for short-term (10-14 days) therapy, coadministration with careful monitoring is reasonable because SSRIs generally require tapering to avoid discontinuation symptoms.[1] Physicians utilizing these drugs (linezolid, furazolidone, procarbazine) need to be sensitized about potentially fatal SS when coadministered with antidepressant therapy. Clinicians need to exercise reasonable degree of care and skills to prevent such interactions primarily and also be competent to detect early and manage such adverse events, lest may amount to medical negligence.[33]

REFERENCES

1. MacDougall C, Chambers HF. Protein synthesis inhibitors and miscellaneous antibacterial agents. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw Hill; 2011. p. 1537-8.
2. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions

and Diagnostic Guidelines. 10th ed. Geneva: World Health Organization; 1992.
3. DeBellis RJ, Schaefer OP, Liquori M, Volturo GA. Linezolid-associated serotonin syndrome after concomitant treatment with citalopram and mirtazapine in a critically ill bone marrow transplant recipient. J Intensive Care Med 2005;20:351-3.
4. Sussman N. Selective serotonin reuptake inhibitors. In: Sadock BJ, Sadock VA, editors. Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 3191-205.
5. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991;148:705-13.
6. Taylor JJ, Wilson JW, Estes LL. Linezolid and serotonergic drug interactions: A retrospective survey. Clin Infect Dis 2006;43:180-7.
7. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-20.
8. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003;96:635-42.
9. Perry PJ, Wilborn CA. Serotonin syndrome vs neuroleptic malignant syndrome: A contrast of causes, diagnoses, and management. Ann Clin Psychiatry 2012;24:155-62.
10. Graudins A, Stearman A, Chan B. Treatment of the serotonin syndrome with cyproheptadine. J Emerg Med 1998;16:615-9.
11. Blumenfield M, Gamboa MC, Suojanen JK. Psychiatric care of the burned patient. In: Sadock BJ, Sadock VA, editors. Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 2456-68.
12. Ailawadhi S, Sung KW, Carlson LA, Baer MR. Serotonin syndrome caused by interaction between citalopram and fentanyl. J Clin Pharm Ther 2007;32:199-202.
13. Gollapudy S, Kumar V, Dhamee MS. A case of serotonin syndrome precipitated by fentanyl and ondansetron in a patient receiving paroxetine, duloxetine, and bupropion. J Clin Anesth 2012;24:251-2.
14. KirschnerR, Donovan JW. Serotonin syndrome precipitated by fentanyl during procedural sedation. J Emerg Med 2010;38:477-80.
15. Reich M, Lefebvre-Kuntz D. Serotoninergic antidepressants and opiate analgesics: A sometimespainful association. A case report. Encephale 2010;36:D119-23.
16. Rastogi R, Swarm RA, Patel TA. Case scenario: Opioid association with serotonin syndrome: Implications to the practitioners. Anesthesiology 2011;115:1291-8.
17. ColomarFerrá A, VentayolBosch P, Raurich JM. Serotonin syndrome due to interaction between linezolid, tryptophan, and metoclopramide. Med Intensiva 2009;33:360-1.
18. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors-metoclopramide interaction. Ann Pharmacother 2002;36:67-71.
19. Vandemergel X, Beukinga I, Neve P. Serotonin syndrome secondary to the use of sertraline and metoclopramide. Rev Med Brux 2000;21:161-3.
20. Miller DG, Lovell EO. Antibiotic-induced serotonin syndrome. J Emerg Med2011;40:25-7.
21. Nisijima K, Shimizu M, Abe T, Ishiguro T. A case of serotonin syndrome induced by concomitant treatment with low-dose trazodone and amitriptyline and lithium. Int Clin Psychopharmacol 1996;11:289-90.
22. Perry NK. Venlafaxine-induced serotonin syndrome with relapse following amitriptyline. Postgrad Med J 2000;76:254-6.
23. Steinberg M, Morin AK. Mild serotonin syndrome associated with concurrent linezolid and fluoxetine. Am J Health Syst Pharm 2007;64:59-62.
24. Thomas CR, Rosenberg M, Blythe V, Meyer WJ 3rd. Serotonin syndrome and linezolid. J Am Acad Child Adolesc Psychiatry 2004;43:790.
25. Lorenz RA, Vandenberg AM, Canepa EA. Serotonergic antidepressants and linezolid: A retrospective chart review and presentation of cases. Int J Psychiatry Med 2008;38:81-90.
26. Bergeron L, Boulé M, Perreault S. Serotonin toxicity associated with concomitant use of linezolid. Ann Pharmacother 2005;39:956-61.
27. WigenCL, Goetz MB. Serotonin syndrome and linezolid. Clin Infect Dis 2002;34:1651-2.
28. Clark DB, Andrus MR, Byrd DC. Drug interactions between linezolid and selective serotonin reuptake inhibitors: Case report involving sertraline and review of the literature. Pharmacotherapy 2006;26:269-76.
29. Morrison EK, Rowe AS. Probable drug-drug interaction leading to serotonin syndrome in a patient treated with concomitant buspirone and linezolid in the setting of therapeutic hypothermia. J Clin Pharm Ther 2012;37:610-3.
30. Mason LW, Randhawa KS, Carpenter EC. Serotonin toxicity as a consequence of linezolid use in revision hip arthroplasty. Orthopedics 2008;31:1140.
31. Packer S, Berman SA. Serotonin syndrome precipitated by the monoamine oxidase inhibitor linezolid. Am J Psychiatry 2007;164:346-7.
32. Strouse TB, Kerrihard TN, Forscher CA, Zakowski P. Serotonin syndrome precipitated by linezolid in a medically ill patient on duloxetine. J Clin Psychopharmacol 2006;26:681-3.
33. Modi JP. Medical negligence and consumer protection act. In: Kannan K, Mathiharan K, editors. Modi's A Textbook of Medical Jurisprudence and Toxicology. 24th ed. Nagpur: Lexis Nexis; 2012. p. 119-68.

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