CASE REPORT

Linezolid-induced serotonin syndrome

Anish Shouan, Rajeet Kumar, Vivek Lal, Sandeep Grover
Departments of Psychiatry and Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence:
Dr. Sandeep Grover,
Department of Psychiatry,
Postgraduate Institute of Medical Education and Research,
Chandigarh - 160 012, India.
E-mail: drsandeepg2002@yahoo.com

Received: 04 May 2019
Revised: 17 November 2019
Accepted: 11 December 2020
Published: 15 March 2021

Abstract
Linezolid is an oxazolidinone antibiotic, which is a weak, reversible, nonselective monoamine oxidase A and B inhibitor; is known to increase serotonin levels, and has been implicated in the development of serotonin syndrome (SS). There is limited literature on the development of SS with linezolid, when used alone. In this report, we present the case of a 70-year-old female who developed features of SS while being treated with linezolid 600 mg twice daily for pneumonia. The SS in her case was managed with stoppage of linezolid, administration of cyproheptadine, and supportive measures.

Keywords: Delirium, linezolid, serotonin syndrome

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How to cite this article: Shouan A, Kumar R, Lal V, Grover S. Linezolid-induced serotonin syndrome. Ind Psychiatry J 2020;29:345-8.

Serotonin syndrome (SS) is a potentially life-threatening adverse drug reaction which occurs due to serotonergic drug administration. The diagnosis may be easily missed due to initial subtle manifestation which may be thought to be unrelated or inconsequential or misattributed to other conditions such as anxiety. Usually, the diagnosis is considered when the patient is receiving a psychotropic, especially antidepressants. However, many other drugs, such as meperidine, fentanyl, ondansetron, sumatriptan, and ritonavir, dextromethorphan, and herbal products such as St. John’s wart and ginseng, can also precipitate SS. However, clinicians are often unaware of SS with many of these agents, and resultanty SS is often missed.

Linezolid is an antibiotic, which has been linked with SS. However, the literature on this association is limited. In this report, we present a case who developed SS with linezolid and review the existing literature on this association.

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A 70-year-old female presented with acute-onset illness of 2 days’ duration characterized by sudden loss of consciousness followed by hemiparesis of the right side of the body. On evaluation, she was detected to have high blood pressure (BP: 150/90 mmHg) and raised blood glucose levels (201 mg/dL), although she was not diagnosed with hypertension and diabetes mellitus earlier. Her magnetic resonance imaging of the brain revealed evidence of intracranial hemorrhage (left basal ganglia bleed). Her investigations in the form of hemogram, renal function test, liver function test, serum electrolytes (i.e., serum sodium, potassium, and calcium), electrocardiogram, X-ray chest (posteroanterior view), and cerebrospinal fluid analysis did not reveal any abnormality. Her intracranial pressure was normal, and physical examination did not reveal evidence of any
abnormality in the cardiovascular, gastrointestinal, and respiratory systems. Neurological examination was also unremarkable apart from decreased power in all the four limbs (power – 4/5).

Intracranial hemorrhage was managed conservatively as there were no signs of raised intracranial pressure and there were no neurological deficits. During the course of her illness, she developed pneumonia, which was initially managed with vancomycin for 2 weeks, but the pneumonia did not resolve. However, at this time, the patient was responsive and would answer to questions asked by her family members, but with difficulty. In view of culture sensitivity showing sensitivity toward linezolid and nonresponsiveness toward vancomycin, she was started on injection linezolid 600 mg twice a day. After about 6–7 h of starting of injection linezolid, she developed symptoms characterized by shivering, diaphoresis, fluctuations in BP (ranging from 90/60 to 170/100 mmHg), tachycardia (pulse rate – 110/min), fever, and altered sensorium. Her neurological examination revealed evidence of muscle rigidity. On investigations, she was found to have raised creatinine kinase (7914 U/L) levels along with leukocytosis (total leukocyte count: 16,000).

In view of these findings, a diagnosis of neuroleptic malignant syndrome (NMS) was considered, and she was started on tablet bromocriptine 5 mg TDS by the primary treating team. However, the altered sensorium and rigidity did not improve and in view of the same, a liaison psychiatry team was consulted. At the initial psychiatric evaluation, history did not reveal evidence of any primary psychiatric illness anytime in lifetime and there was no history of receiving any antipsychotic, antidepressant, and antiemetic medications. Neurological examination, in addition to the rigidity, revealed evidence of hyperreflexia and ankle clonus. Mental status examination was suggestive of delirium, with Delirium Rating Scale-Revised 98 version total score of 19. A review of medication chart revealed use of no other serotonergic agent in the recent times and lack of introduction of any other medications while the new set of symptoms developed, except for linezolid. In view of a temporal correlation between starting of symptoms with the use of injection linezolid, a diagnosis of linezolid-induced SS was considered and in liaison with the neurologist, injection linezolid was stopped and the patient was started on tablet cyproheptadine 1 mg qid and supportive care was started. Over the next 48 h, all the symptoms of SS resolved and her sensorium improved. She was managed with piperacillin-tazobactam 4.5 g IV every 6 hourly for pneumonia. She started to improve over the next 2 days and was discharged from the hospital on the same antibiotics, antihypertensives, and hypoglycemic agents.

**DISCUSSION**

Linezolid is an oxazolidinone antibiotic, which was originally developed as an antidepressant. It is a weak, reversible, nonselective monoamine oxidase (MAO) A and B inhibitor. It has also been found to have antibiotic potential, especially against drug-resistant Gram-positive cocci, such as methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* infection. In view of its MAO inhibitor potential, it is known to increase serotonin levels, and has been implicated in the development of SS. Data arising out of the Phase-3 and 4 randomized controlled trials (RCTs) suggest that the incidence of serotonin toxicity with linezolid is 0.54%, in contrast to 0.19% in the comparator group with no significant difference between the two groups. Another review of RCTs covering >5000 patients in each of the linezolid and the comparator group reported the incidence of linezolid-associated serotonin toxicity to be 0.24%, compared to 0.12% in the comparator group. In terms of the use of concomitant medications, both the reviews suggested slightly higher incidence of serotonin toxicity among the patients receiving two or more serotonergic agents in both the groups.

A large number of case reports in the literature have reported SS with the use of linezolid. In some of these reported cases, SS developed when linezolid was either used in combination with antidepressants or used alone. The index case developed SS in the absence of the use of concomitant antidepressants, and fulfilled the criteria of SS, as per both Sternbach’s and Boyer’s criteria for SS.

In the index case, the diagnosis was initially missed possibly because of lack of awareness about the association of linezolid with SS. Rather, a diagnosis of NMS was considered. The SS is often described as a clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities, but not all of these findings are consistently present in all patients with the disorder but were present in the index case. The difficulty for clinicians is that mild symptoms may be easily overlooked, and an inadvertent increase in the dose of the causative agent or the addition of a drug with pro-serotonergic effects may provoke a dramatic clinical deterioration, which also happened in the index case which was mislabeled as NMS and was started on bromocriptine. This finding suggests that there is a need to increase the awareness about SS among clinicians and about the signs and symptoms of SS among other specialists, along with the improvement in awareness about the precipitating events.

From a liaison psychiatrist’s perspective, the index case exemplifies that, whenever a patient with delirium is evaluated,
it is very important to carry out proper physical examination and review the treatment chart for the ongoing medications to understand the possible etiological cause of delirium. In the index case, focusing on hyperreflexia and clonus provided hints for the possibility of SS and a review of treatment chart provided supportive evidence for the same.

Two previous reviews have compiled the available case reports/series reporting the association of linezolid with SS. Various antidepressants which lead to SS when used along with linezolid include citalopram, escitalopram, fluoxetine, sertraline, venlafaxine, duloxetine, mirtazapine, paroxetine, and amitriptyline and also some opioids which could lead to SS when used along with linezolid include meperidine, fentanyl, and methadone. Among various case reports, SS has been most commonly reported with the use of combination of linezolid with citalopram and sertraline. Accordingly, in the liaison psychiatry setup, clinicians, while prescribing various antidepressants, should give due weightage to the ongoing medications, including antibiotics. Clinicians should inquire the use of prescription (analgesics, opioids, buspirone, stimulants, anti-migraine agents, and dopamine agonists) and over-the-counter drugs, illicit substances, and dietary supplements because all of these agents have been implicated in the development of SS.

A severe case may present with severe hypertension and tachycardia that may abruptly deteriorate into frank shock. Such patients may have agitated delirium as well as muscular rigidity and hypertonicity, which happened in the index patient.

Removal of the precipitating drugs is the most important step in the management of SS. Administration of 5-hydroxytryptamine antagonists such as cyproheptadine is recommended for the management of SS. Treatment of SS in adults may require 12–32 mg of the drug during a 24 h period, a dose that binds 85%–95% of serotonin receptors. Benzodiazepines may be used to control agitation. Control of autonomic instability and the control of hyperthermia with supportive care remain a mainstay of the therapy.

All the above-mentioned measures were done in the index case, leading to improvement over a period of 48 h.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-20.
2. Butterfield JM, Lawrence KR, Reisman A, Huang DB, Thompson CA, Lodise TP. Comparison of serotonin toxicity with concomitant use of either linezolid or comparators and serotonergic agents: an analysis of Phase III and IV randomized clinical trial data. J Antimicrob Chemother 2012;67:494-502.
3. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin Syndrome. Ochsner J 2013;13:533-40.
4. Kulkarni RR, Kulkarni PR. Linezolid-induced near-fatal serotonin syndrome during escitalopram therapy: Case report and review of literature. Indian J Psychol Med 2013;35:413-6.
5. Frykberg RG, Gordon S, Tierney E, Banks J. Linezolid-associated serotonin syndrome. A Report of two cases. J Am Podiatr Med Assoc 2015;105:244-9.
6. Khoury A, Runnstrom M, Ebied A, Penny ES. Linezolid-associated serotonin toxicity after escitalopram discontinuation: Concomitant drug considerations. BMJ Case Rep 2018;2018:bcr2018226597.
7. Hasani R, Sarma J, Kansal S. Serotonin syndrome induced by combined use of sertraline and linezolid. Anesth Essays Res 2019;13:188-90.
8. Ma J, Zhu P, Tu G, Li X. Serotonin syndrome under combination of linezolid and low-dose citalopram with amiodarone. Psychiatry Clin Neurosci 2013;67:457.
9. Bernard L, Stern R, Lew D, Hoffmeyer P. Serotonin syndrome after concomitant treatment with linezolid and citalopram. Clin Infect Dis 2003;36:1197.
10. 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.
11. Tahir N. Serotonin syndrome as a consequence of drug-resistant infections: An interaction between linezolid and citalopram. J Am Med Dir Assoc 2004;5:111-3.
12. Morales N, Vermette H. Serotonin syndrome associated with linezolid treatment after discontinuation of fluoxetine. Psychosomatics 2005;46:274-5.
13. Thomas CR, Rosenberg M, Blythe V, Meyer WJ 3rd. Serotonin syndrome and linezolid. J Am Acad Child Adolesc Psychiatry 2004;43:790.
14. 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.
15. Jones SL, Athan E, O’Brien D. Serotonin syndrome due to co-administration of linezolid and venlafaxine. J Antimicrob Chemother 2004;54:289-90.
16. Bergeron L, Boulé M, Perreault S. Serotonin toxicity associated with concomitant use of linezolid. Ann Pharmacother 2005;39:956-61.
17. Marcuccio C, Sandson NB, Dunlap JA. Linezolid-bupropion interaction as possible etiology of severe intermittent intraoperative hypertension? Anesthesiology 2004;101:1487-8.
18. Strouse TB, Kerrihard TN, Forscher CA, Zakowski P. Serotonin syndrome...
18. Wigen CL, Goetz MB. Serotonin syndrome and linezolid. Clin Infect Dis 2002;34:1651-2.
19. Samartzis L, Savvari P, Kontogiannis S, Dimopoulos S. Linezolid Is Associated with Serotonin Syndrome in a Patient Receiving Amitriptyline, and Fentanyl: A Case Report and Review of the Literature. Case Reports in Psychiatry; 2013. Available from: https://www.hindawi.com/journals/crips/2013/617251/. [Last accessed on 2019 Apr 20].
20. Manappallil RG, Kakkattil A. Linezolid induced Serotonin Syndrome in the absence of serotonergic agent. Asian J Med Sci 2018;9:65-6.
21. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991;148:705-13.
22. Sampson E, Warner JP. Serotonin syndrome: Potentially fatal but difficult to recognize. Br J Gen Pract 1999;49:867-8.
23. Martin TG. Serotonin syndrome. Ann Emerg Med 1996;28:520-6.
24. Ramsey TD, Lau TT, Ensom MH. Serotonergic and adrenergic drug interactions associated with linezolid: A critical review and practical management approach. Ann Pharmacother 2013;47:543-60.
25. Woytowish MR, Maynor LM. Clinical relevance of linezolid-associated serotonin toxicity. Ann Pharmacother 2013;47:388-97.
26. Das PK, Warkentin DI, Hewko R, Forrest DL. Serotonin syndrome after concomitant treatment with linezolid and meperidine. Clin Infect Dis 2008;46:264-5.
27. Steinberg M, Morin AK. Mild serotonin syndrome associated with concurrent linezolid and fluoxetine. Am J Health Syst Pharm 2007;64:59-62.
28. Mastroianni A, Ravaglia G. Serotonin syndrome due to co-administration of linezolid and methadone. Infez Med 2017;25:263-6.