Title
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Journal
The Journal of Pediatric Pharmacology and Therapeutics, 27(6)

ISSN
1551-6776

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Publication Date
2022-07-01

DOI
10.5863/1551-6776-27.6.564

Peer reviewed

JPPT | Case Report

Serotonin Syndrome in an Infant Associated With Linezolid and Opioid Use

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Most reported cases of serotonin syndrome involve either a selective serotonin reuptake inhibitor (SSRI) or monoamine oxidase inhibitors (MAOI) and at least 1 other serotonergic medication or exposure to a single serotonin-augmenting drug. This case report describes serotonin syndrome occurring in association with the concomitant use of the antibiotic linezolid and opioids, specifically methadone, in a pediatric intensive care unit patient. The patient developed hyperpyrexia, muscle rigidity, clonus, and multiorgan dysfunction within 48 hours of receiving linezolid while concurrently on methadone. This drug-drug interaction is a rare cause of serotonin syndrome that has only been described 1 other time in the adult literature. This report raises awareness of this rare but serious and potentially lethal complication of serotonin syndrome associated with concomitant linezolid and opioid use. Timely consideration of the diagnosis in the setting of hyperpyrexia can facilitate prompt initiation of targeted therapies to prevent sequela.

ABBREVIATIONS MAOI, monoamine oxidase inhibitor; SS, serotonin syndrome; SSRI, selective serotonin reuptake inhibitor

KEYWORDS hyperpyrexia; linezolid; nosocomial pneumonia; opioids; pediatrics; serotonin syndrome

J Pediatr Pharmacol Ther 2022;27(6):564–568

DOI: 10.5863/1551-6776-27.6.564

Introduction

The increasing use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors to treat depression and mood disorders in the pediatric population presents an exposure risk of developing serotonin syndrome (SS), a rare but serious complication. This potentially life-threatening condition, caused by excessive serotonergic activity in the nervous systems, results in hyperpyrexia, mental status changes, autonomic instability, and neuromuscular hyperactivity. Most cases of SS are managed by withdrawal of the offending agent and supportive care.[1]

Most documented cases of SS are in patients taking multiple serotonergic drugs or who have had considerable exposure to a single serotonin-augmenting drug.[2] The diagnosis can be challenging when non-traditional serotonergic medications are used. Linezolid, an oxazolidinone antibiotic used for the treatment of resistant Gram-positive cocci infections, is a non-selective monoamine oxidase inhibitor (MAOI).[3] Common side effects include nausea, vomiting, dizziness, rash, and thrombocytopenia with the rare side effect of SS.[4] This report describes the drug-drug interaction of non-traditional serotonergic agents; an opioid agonist, methadone, and linezolid that caused SS in a pediatric patient in an inpatient setting.

Case Description

An 8-month-old term male born with complex congenital anomalies underwent surgical repair for his atrial and ventricular septal defects as well as tracheoplasty at 6 weeks of life. He experienced numerous complications post-operatively leading to chronic respiratory failure.

Despite successful extubation at 7 months of age, he required reintubation for acute respiratory failure due to presumed bacterial pneumonia. Bronchoscopy and bronchoalveolar lavage were performed to assess for post-surgical airway stenosis and to evaluate other potential etiologies of his acute on chronic respiratory failure. Findings were notable for significant laryngeal edema, bronchospasm, and secretions consistent with an infectious etiology. Bronchoalveolar lavage cultures grew methicillin-resistant *Staphylococcus aureus* and *Coryneform* species. In addition, a chest computed tomography scan revealed a persistent focal right lower lobe infiltrate. The patient continued to have recurrent intermittent fevers and leukocytosis despite completing appropriate antimicrobial courses, which included vancomycin, cefepime, azithromycin, fluconazole, and nafcillin for lower respiratory tract and suspected systemic infections. The last regimen completed prior to the bronchoalveolar lavage consisted of a 7-day course of vancomycin and a 48-hour course of cefepime. The pediatric infectious disease service was consulted and recommended linezolid (10 mg/kg/dose enterally, every 8 hours).

At the time linezolid was started, the patient was

Table 1. Blood Laboratory Results Obtained Over 72 Hours From Initiation of Linezolid

	Laboratory Values		
	24 hr	**48 hr**	**72 hr**
WBC count (nl 5.5–17.5 × 10^9/L)	36,000	29,300	18,000
CRP (nl < 7.5 mg/L)	0.3	4.3	20.8
Procalcitonin (nl < 0.26 μg/L)	0.06 μg/L	12.32	171.48
CK (nl 41–277 U/L),	—	1129	22,100
Creatinine (nl 0.1–0.3 mg/dl)	0.24	0.72	0.41
INR (nl 0.9–1.2)	—	3.3	4.0
PTT (nl 21.9–32.3 secs)	—	39.6	49.9
AST (nl 13–65 U/L)	—	2108	4730
ALT (nl 20–60 U/L)	—	2108	3310
Lactate (nl 0.5–2.0 mmol/L)	1.9	3.9	5.7

ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; CRP, C-reactive protein; INR, international normalized ratio; nl, normal; PTT, prothrombin time; WBC, white blood cell

concurrently receiving the following: bosentan, chlorothiazide, cholecalciferol, furosemide, lansoprazole, lorazepam, melatonin, methadone, spironolactone, as well as iron and zinc supplements. He was also receiving continuous infusions of morphine 50 mcg/kg/hr and dexmedetomidine at 1.2 mcg/kg/hr.

Twenty-four hours after linezolid initiation, the patient developed a new fever to 40.7°C. In consultation with the infectious disease team, linezolid was discontinued, and antimicrobial coverage was changed to vancomycin and cefepime. In total, he had received 3 doses of linezolid prior to discontinuation. Laboratory findings were significant for leukocytosis with normal inflammatory markers (Table 1). He remained intermittently febrile, tachycardic, and developed new agitation. During the first 24 hours with fever, he received multiple doses of morphine and midazolam, titrated up on a morphine infusion to 60 mcg/kg/hr, and continued his scheduled methadone (0.75 mg/kg/day). He had been on a continuous morphine infusion for the 30 days prior to this event with a peak infusion rate of 130 mcg/kg/hr, which had been weaned down slowly while transitioning to enteral methadone. The methadone had been initiated 3 weeks prior to this event as part of the weaning plan.

Twenty-four hours after linezolid discontinuation, fevers persisted, and the patient developed signs of decompensated shock with hypotension requiring volume resuscitation and the initiation of an epinephrine infusion at 0.05 mcg/kg/min. His mental status declined dramatically and progressed from agitation to lethargy, with a 3 on the Glasgow Coma Scale. He then developed bilateral upper extremity rhythmic jerking, classified on video electroencephalography as myoclonic seizures. Antipyretics were ineffective and the patient's core temperature reached a maximum of 42.5°C (108.5°F). Ice packs, fans, and a cooling blanket were used for management of his hyperpyrexia. His condition continued to deteriorate requiring escalation in inotropic support from 1 to 3 vasopressors (epinephrine infusion rates ranging from 0–0.1 mcg/kg/min, norepinephrine infusion rates ranging from 0–0.1 mcg/kg/min, and vasopressin infusion rates ranging from 0–0.0008 mcg/kg/min), and empiric initiation of stress dose hydrocortisone (100 mg/m^2 divided every 6 hours). Anti-infective therapy was further broadened to include vancomycin, meropenem, ciprofloxacin, caspofungin, and acyclovir, all at appropriate weight-based dosing. Laboratory findings demonstrated elevated inflammatory markers and end organ dysfunction (Table 1). Clinical findings included the following: cool and mottled extremities with thready distal pulses, oliguria, hypoactive bowel sounds, and bloody stools. His neurologic exam was significant for 1-mm pupils bilaterally and spontaneous clonus. He did not respond to central or peripheral noxious stimulus and had an absent cough and gag. He was hypotonic with absent reflexes. Clonus was noted in the left wrist.

Although sepsis was initially the leading diagnosis, all cultures from blood, urine, and respiratory tract were negative. With the constellation of extreme hyperpyrexia, diaphoresis, muscle rigidity, inducible clonus, agitation, and end organ dysfunction, a potential drug-drug interaction such as SS emerged as a likely cause. Morphine and methadone were discontinued given opioids' potential causative or potentiating role in SS.

Management for presumed SS was undertaken based on published guidelines,[3,5] which included the following: aggressive hydration with boluses of normal

saline (20 cc/kg) and maintenance fluids (32 mL/hr), active cooling through the use of cold packs, fans, and a cooling blanket, continuous infusion of neuromuscular blockade (vecuronium at 0.1 mg/kg/min) to prevent rigors or shivering, sedation with boluses of lorazepam (0.5 mg/kg) and continuous infusions of midazolam (0.02 mg/kg/hr) and dexmedetomidine (1 mcg/kg/hr). In consultation with toxicology, a morphine infusion at 30 mcg/kg/hr was initiated to help prevent withdrawal from the longstanding usage of opioids. Morphine was considered to be the safest opioid to administer in terms of serotonergic effects as opposed to fentanyl or methadone.[6]

Forty-eight hours after discontinuation of linezolid, the patient's hemodynamic status improved and the medical team was able to wean the patient off of all vasopressors. Clinical laboratory signs of organ dysfunction peaked at 48 to 72 hours after initiation of the linezolid, and then began to normalize (Table 1).

Despite improvement in his multiorgan dysfunction, unfortunately, the patient's abnormal neurologic exam persisted. Magnetic resonance imaging performed 10 days after onset of symptoms showed irreversible profound brain injury, which was most consistent with acute and likely superimposed chronic, degenerative brain injury. After discussing findings with the family, the decision was made to discontinue life-sustaining support, and the patient was compassionately extubated. Within 20 minutes of extubation, the patient developed desaturations, bradycardia, and ultimately died of cardiac arrest.

Discussion

Linezolid. Linezolid, originally developed as a psychotropic agent with antidepressant effects as it functions as a non-selective MAOI, is now clinically used as an oxazolidinone antibiotic with efficacy against drug-resistant Gram-positive cocci, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. The drug has been shown to be an effective and well-tolerated antimicrobial for patients with *S aureus* infections including those who have failed to respond or who were intolerant to previous treatments.[7,8]

Serotonin Syndrome. Serotonin syndrome is a potentially life-threatening toxidrome associated with increased serotonergic activity in the body resulting in overactivation of the central nervous system. Serotonin syndrome is a diagnosis of exclusion. With no single diagnostic test available for confirmation, having a high index of suspicion based on recent use of associated medications and recognizing the clinical signs and symptoms are of paramount importance in making a timely diagnosis.[1]

Most reported cases of SS involve either an SSRI or MAOIs and at least 1 other serotonergic medication or exposure to a single serotonin-augmenting drug (Table 2). The mechanism is thought to be related to excess agonism of serotonin receptors in the central nervous system and peripheral tissues via elevated synaptic concentrations of serotonin. Linezolid, a weak MAOI, can prevent breakdown of serotonin, as well as other biogenic amines such as dopamine and norepinephrine. There have been no randomized controlled trials or prospective cohort studies to date that assess the incidence of serotonin toxicity in patients receiving linezolid and serotonergic agents. In a retrospective chart review of 17 cases, authors found an incidence of serotonin toxicity in 3.0% of both adult and pediatric patients who were on SSRIs and taking linezolid concurrently.[9,10]

Symptoms of SS include hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes. In cases classified as severe, signs of multiorgan failure such as rhabdomyolysis, metabolic acidosis, disseminated intravascular coagulation, renal failure, and acute respiratory distress can be seen.[11] The constellation of symptoms—extreme autonomic dysfunction, spontaneous clonus, inducible clonus plus agitation and dia-

Table 2. Examples of Drugs That Might Interact With Linezolid, Resulting in Increased Serotonin Concentrations

Category	Example
SSRIs*	Paroxetine Sertraline Fluoxetine Citalopram Escitalopram
SNRIs*	Venlafaxine Duloxetine Mirtazapine
MAOIs*	Linezolid
TCAs	Imipramine Amitriptylinee
Analgesics	Tramadol Meperidine Methadone Dextromethorphan Pentazocine
Antituberculosis	Isoniazid
Anxiolytics	Buspirone
Migraine	Triptan drug class
Stimulants	Amphetamines
Dopamine agonists	Bromocriptine
Illicit drugs	Cocaine

MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SS, serotonin syndrome; SSRI, selective serotonin receptor inhibitor; TCA, tricyclic antidepressant

* Indicate more common causative agent of SS.

Table 3. Criteria for Hunter Serotonin Toxicity[15]

Criteria
Use of a serotonergic agent + at least 1 of 5 examination findings: • Spontaneous clonus • Inducible clonus plus agitation or diaphoresis • Ocular clonus plus agitation or diaphoresis • Tremor and hyperreflexia • Hypertonia and a temperature above 38°C plus ocular or inducible clonus

phoresis within 24 hours of initiation of linezolid while concurrently receiving serotonergic agents morphine and methadone—made SS the most likely diagnosis. His clinical presentation fulfilled the required criteria of being on a serotonergic agent and having inducible clonus and diaphoresis. 1 major and 2 minor of the Hunter Serotonin Toxicity Criteria (Table 3).

When the patient was started on linezolid, he was not receiving any other SSRIs or MAOIs. However, the patient had been on chronic enteral methadone (0.75 mg/kg/day) for 3 weeks. Although not an SSRI or MAOI, it has been shown that some opioid analgesics, including methadone, are weak serotonin reuptake inhibitors. *In vitro* studies have shown that methadone has a greater tendency toward serotonin reuptake inhibition compared with other opiates.[12] The additional intermittent morphine doses given during this time period potentially contributed to the interaction of the opioids and linezolid. In the 24 hours after initiating linezolid, the patient had received the equivalent of 28 mg of intravenous morphine. This included ten 60 mcg/kg/doses of intravenous morphine boluses, a continuous morphine infusing at 60 mcg/kg/hr, and 4 doses of 1.5 mg of enteral methadone for treatment of pain and agitation. We found it interesting that the patient's symptoms peaked after discontinuation of linezolid. The drug is metabolized by the liver with an average half-life of ~3.9 hours and would have been expected to be eliminated in 12 hours. However, it was evident that his liver suffered significant injury as a result of his vasopressor-dependent shock, and one hypothesis is that there was accumulation of linezolid during this time period, further prolonging elimination and contributing to the presentation of SS.

Potentially, this child's fulminant brain injury may have been related to young age and age-related developmental characteristics, such as an immature blood brain barrier or unique sensitivity to excitotoxic neurotransmitters. However, despite the widely held concept that the developing blood brain barrier is immature and leaky, recent investigations have shown this not to be the case.[13] Alternatively, inflammation or hypoxic ischemic brain injury may compromise barrier integrity. In combination with high fever and a compromised blood brain barrier, these neurotoxins may have contributed to the profound brain injury.

To our knowledge, this is the first reported case of linezolid and methadone resulting in SS in a pediatric patient. Although not a typical known trigger, the patient's prolonged use of methadone as well as its long half-life likely precipitated SS with initiation of linezolid. One other report describes a 39-year-old male with substance use disorder who developed SS after initiation of linezolid while taking methadone for opioid dependence.[14] In this case report, the patient became hemodynamically unstable, febrile, agitated, hypertonic, hyperreflexia, and had clonus in all extremities 3 days after initiating linezolid (600 mg twice a day) while on methadone (40 mg/day for a year). His autonomic and neuromuscular symptoms all resolved promptly after discontinuation of linezolid concurrently with the administration of benzodiazepines and fluid administration.

Given the increasing use of serotonergic medications, including prolonged use of opioids as well as linezolid as an antimicrobial in the pediatric population, this care report demonstrates the importance of maintaining a high clinical suspicion for the possibility of SS in this age group, highlighting the importance of recognizing the potentiating effect of high doses and prolonged use of triggering agents, specifically methadone. Early recognition and treatment of the signs and symptoms of SS are crucial to preventing significant morbidity and mortality.

Article Information

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Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review and informed consent were not required.

Acknowledgments. The authors thank pediatric physicians, pharmacists, medical teams, and nurses at Benioff Children's Hospital at University of California, San Francisco for their assistance. This manuscript has not been presented at a meeting.

Submitted. February 11, 2021

Accepted. December 10, 2021

References

1. Simon LV, Keenaghan M. Serotonin syndrome. Updated February 4, 2022. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; June 08, 2022. https://www.ncbi.nlm.nih.gov/books/NBK482377/
2. Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. *Am Fam Physician*. 2010;81(9):1139–1142.
3. Sutton J, Stroup J, Som M. Linezolid-induced serotonin toxicity in a patient not taking monoamine oxidase inhibitors or serotonin receptor antagonists. *Proc (Bayl Univ Med Cent)*. 2016;29(2):214–215.
4. Cunha JP. Zyvox (linezolid): uses, dosage, side effects, interactions, warning. Accessed November 4, 2021. https://www.rxlist.com/zyvox-drug.htm
5. Scotton WJ, Hill LJ, Williams AC, Barnes NM. Serotonin syndrome: pathophysiology, clinical features, management, and potential future directions. *Int J Tryptophan Res*. 2019;12.
6. Schenk M, Wirz S. Serotoninsyndrom und medikamentöse Schmerztherapie : Was ist für die Praxis relevant? [Serotonin syndrome and pain medication: What is relevant for practice?]. Schmerz. 2015;29(2):229–251. German.
7. Watkins RR, Lemonovich TL, File TM. An evidence-based review of linezolid for the treatment of methicillin-resistant Staphylococcus aureus (MRSA): place in therapy. *Core Evid*. 2012;7:131–143.
8. Moise PA, Forrest A, Birmingham MC, Schentag JJ. The efficacy and safety of linezolid as treatment for Staphylococcus aureus infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin. *J Antimicrob Chemother*. 2002;50(6):1017–1026.
9. Taylor JJ, Wilson JW, Estes LL. Linezolid and serotonergic drug interactions: a retrospective survey. *Clin Infect Dis*. 2006;43(2):180–187.
10. Quinn DK, Stern TA. Linezolid and serotonin syndrome. *Prim Care Companion J Clin Psychiatry*. 2009;11(6):353–356. 10.4088/PCC.09r00853
11. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. *Ochsner J*. 2013;13(4):533–540.
12. Rastogi R, Swarm RA, Patel TA. Case scenario: opioid association with serotonin syndrome: implications to the practitioners. *Anesthesiology*. 2011;115(6):1291–1298.
13. Mallard C, Ek CJ, Vexler ZS. The myth of the immature barrier systems in the developing brain: role in perinatal brain injury. *J Physiol*. 2018;596:5655–5664.
14. Mastroianni A, Ravaglia G. Serotonin syndrome due to co-administration of linezolid and methadone. *Infez Med*. 2017;25(3):263–266.
15. Dunkley EJC, 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(9):635–642.