

Serotonin Syndrome Associated with Linezolid Use: A Case Report

Volkan ŞAHİNER¹, Özlem Erden AKİ²

Abstract

The serotonin syndrome is a toxic state largely attributable to changes in sensitivity of serotonin receptor system in the brainstem and spinal cord resulting from increased serotonergic activity in central neurologic system, due to use of serotonergic agents either in overdose or in combination. Serotonin syndrome may present with neuromuscular (clonus, myoclonus, tremor, hyperreflexia) and autonomic (fever, mydriasis, tachycardia, tachypnea) symptoms and mental status changes (confusion, agitation) and may result in death in severe cases. The risk for the development of serotonin syndrome is increased with the combined use of agents from different groups such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). The growing use of SSRIs for depression and the introduction of pharmacological agents newly developed for the treatment of various medical disorders increases the risk of drug-drug interactions and toxic states like serotonin syndrome. In the presented case clinical presentation and outcome of the serotonin syndrome which has developed as a consequence of concomitant linezolid use in a young patient who was already on an SSRI antidepressant is discussed. Linezolid is an oxazolidinone antibiotic which has MAOI-like properties. This case is presented to inform psychiatrists especially working in consultation-liaison settings about the risk of drug-drug interactions and possible prevention of these.

Key Words: Serotonin syndrome, linezolid, antidepressant drugs

INTRODUCTION

Serotonin syndrome is a toxic condition central nervous system due to increased serotonergic activity in the spinal cord because of increased sensitivity of serotonin receptors (Boyer and Shannon, 2005). Serotonin syndrome is induced by the use of pharmacologic agents that increase serotonergic activity—either alone or with concomitant use of other agents. Serotonergic agents include medications that inhibit serotonin reuptake (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants, trazodone, meperidine, dextromethorphan, and tramadol), medications that increase serotonin release (amphetamines, opioid analgesics, and levodopa), agents that inhibit serotonin metabolism (monoamine oxidase inhibitors [MAOIs], linezolid, and selegiline), and post-synaptic serotonin receptor agonists (buspi-

rone, triptans, and carbamazepine) (Table). In particular, concomitant use of MAOIs and SSRIs comprise the greatest risk for serotonin syndrome (Gillman, 2005)

Diagnosis is made based on clinical symptoms; no radiologic or laboratory method exists for diagnosis. Neuromuscular excitation (clonus, myoclonus, tremor, and hyperreflexia), autonomic excitation (fever, mydriasis, tachycardia, and tachypnea), changes in mental status (agitation and confusion), and changes in vital signs (fever, tachycardia, and hypertension) are the most important clinical symptoms. Leukocytosis, increased serum creatinine, elevated liver enzymes, and acidosis can be observed in some patients. The spectrum of serotonin toxicity may include symptoms evaluated as mild side effects, as well as severe coma that can result in death (Dunkley et al., 2003; Isbister et al., 2005).

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¹MD., ²MD., Baskent University Faculty of Medicine, Department of Psychiatry, Ankara,
Volkan Şahiner, MD., e-mail: volkansahiner@gmail.com

Linezolid is the first oxazolidinone antibiotic. It has been approved by FDA and used since 2000 in United States. Linezolid is used primarily to treat multidrug-resistant streptococcus pneumonia infections, vancomycin-resistant enterococcus, and resistant gram-positive bacterial infections (Pfizer Zyvox prescribing information, Vardakas et al., 2007; Lentino et al., 2008). The most serious side effects of linezolid use are bone marrow suppression and thrombocytopenia due to long-term and high dose use of the drug (Hachem et al., 2003; Narita et al., 2007). Linezolid is also a well-known monoamine oxidase inhibitor. Although phase 1, 2, and 3 trials have not reported any cases of serotonin syndrome and there are no warnings in drug prospectuses, cases of serotonin syndrome due to concomitant use of linezolid with other serotonergic agents have been reported (Morales-Molina et al., 2005; Lawrence et al., 2006).

Herein we present a case of serotonin syndrome that was induced by concomitant use of linezolid and an SSRI antidepressant.

CASE

Psychiatric consultation was ordered for a 28-year-old woman diagnosed with bilateral metastatic ovary carcinoma that was followed-up at the inpatient medical unit. According to her medical history, the patient had undergone surgery for bilateral ovarian cancer and the pathology department reported that it had a yolk sac component, including a malignant mixed germ cell tumor. Four courses of cisplatin, etoposide, and bleomycin chemotherapy were administered between May and July 2007. She underwent emergency surgery for ileus perforation due to liver metastases in January 2008. Since then, she was hospitalized at the inpatient unit and was first referred to the psychiatry department on 26 February 2008.

The patient reported having anxiety attacks and trouble falling asleep for 2 months. She reported such somatic symptoms as irritability, nervousness, diaphoresis, palpitations and flushing, and depressive mood, hopelessness, and anhedonia were detected during her psychiatric evaluation. She was diagnosed with depression and anxiety; sertraline 25 mg d⁻¹, and alprazolam 0.75 mg d⁻¹ 3 times daily was started; sertraline was increased to 50 mg d⁻¹ after 1 week. Alprazolam was decreased and discontinued within 2 weeks. Reevaluation 2 weeks later revealed that the patient benefited from the treatment and her anxiety attacks stopped. Continuation of sertraline 50 mg d⁻¹ was recommended. Reconsultation

was requested to evaluate insomnia, disorientation to time and place, and the development of visual hallucinations on 17 March 2008. Antibiotic therapy was started (tienem 4 × 500 mg d⁻¹ and amoxicillin-clavulanic acid 3 × 1000 mg d⁻¹) for severe systemic enterococcus infection on 27 February 2008 due to inadequate response. It was replaced by linezolid therapy 1200 mg d⁻¹ 2 times a day on 4 March 2008. On the sixth day of linezolid therapy the unexpected emergence of diaphoresis and tremor was considered as relapse of the infection and linezolid therapy was continued. Sertraline was increased to 50 mg d⁻¹ on 9 March 2008. On the 12th day of linezolid therapy, despite the fact that an infection scan was negative, development of severe diaphoresis, hypnagogic and hypnopompic hallucinations, insomnia, and a gradual increase in the symptom severity prompted another request for psychiatric consultation.

The patient's pulse was 116 min⁻¹, blood pressure 110/70 mmHg, breath 22 min⁻¹, and body temperature 36.5 °C. She was oriented to place and person, but was disoriented to time diaphoretic, and had tremor and severe anxiety during the interview. She complained of visual and auditory hallucinations. In neurologic examination spontaneous widespread myoclonus and hyperreflexia were detected; no lateralizing neurological signs were observed. Leukocyte count, thrombocyte count, hemoglobin, liver and kidney function tests, and serum electrolyte values were all within normal limits. The other medications she was taking in addition to linezolid and sertraline were tramadol as needed, meperidine as needed, midazolam as needed, metoclopramide, diclofenac sodium, imipenem, amikasin, caspofungin, sandostatin, ranitidine, and pheniramine.

The patient had never taken an antipsychotic medication before or during this period, so neuroleptic malignant syndrome was not considered. The combination of widespread spontaneous myoclonus, diaphoresis, tremor, agitation, and hyperreflexia led the treatment team to consider serotonin syndrome as the most probable diagnosis. By reviewing all the medications the patient was taking and considering the emergence of the symptoms after the addition of linezolid to her regimen while she taking sertraline, serotonin syndrome due to concomitant use of linezolid and sertraline was diagnosed. Sertraline and linezolid were discontinued, alprazolam 0.75 mg d⁻¹ 3 times a day was added for symptom control, and intravenous hydration started as a supportive measure. Seventy-two hours after linezolid and sertraline were discontinued, spontaneous myoclonus and hyperreflexia, diaphoresis, and tremor disappeared, and

her orientation improved. She was taking other drugs that can cause serotonin syndrome due to interaction with sertraline and linezolid. Tramadol and meperidine were two of them, but according to hospital records and nurses' reports these drugs were prescribed as needed and used very rarely during this period and hospital stay.

In a few days the patient again developed agitation, insomnia, and disorientation to time; this new clinical picture was considered delirium due to multiple drug use and, therefore, antipsychotic therapy (quetiapine 25 mg d⁻¹) was started. Despite a good response to this therapy, the patient died from complications and sepsis due to the primary disease.

DISCUSSION

Due to developments in medical oncology in recent years, many patients survive longer than they previously did. A substantial portion of these patients use multiple medications for their diseases or for the complications related to them, and may suffer from known and unknown drug-drug interactions. Except for some of the aminoglycosides, vancomycin, digoxin, and cyclosporine acting in a narrow therapeutic window, drug level monitoring is not performed routinely. In patients treated with multiple drug regimens, side effects and drug-drug interactions should always be monitored. Furthermore, many newly developed medications are administered to this patient group. Due to the many limitations of clinical phase trials, clinicians should expect known and unknown complications, and side effects when treating with these drugs.

The present case was receiving chemotherapy for advanced ovarian cancer and antidepressant therapy (sertraline) for her depression that developed during the illness. Spontaneous myoclonus, hyperreflexia, agitation, confusion, hyperhidrosis, and tremor developed following the concomitant use of sertraline and linezolid, a weak MAO inhibitor. Sertraline is a strong serotonin reuptake inhibitor like paroxetine and fluoxetine. Linezolid is the preferred oxazolidinone antibiotic for the treatment of resistant hospital infections. Linezolid is a reversible weak MAO inhibitor; its concomitant use with adrenergic and serotonergic agents may result in serotonin syndrome. In clinical phase trials serotonin syndrome was not reported, but with the clinical use of linezolid cases were reported, showing that linezolid use, especially concomitant with SSRI antidepressants, may cause serotonin syndrome (Gillman, 1998; Lavery et al., 2001; Wiggen et al., 2002; Bernard et al., 2003; Hachem et al.,

2003; Jones et al., 2004; Tahir et al., 2004; Bergeron et al., 2005; Klasko, 2005; Morales et al., 2005; Packer and Berman, 2007).

Serotonin syndrome was first described in 1995. In 1991 Sternbach et al. indicated that in patients using a known serotonergic agent, after excluding infection, metabolic disorders, and substance use, serotonin syndrome can be diagnosed based on the existence of at least 3 of these symptoms: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, flushing, tremor, diarrhea, motor incoordination, and fever (Sternbach, 1991). But, these criteria were criticized because all of the symptoms could be seen in other disorders and toxicity. Dunkley et al. evaluated 2222 subjects retrospectively, defined the diagnostic criteria for serotonin syndrome, and developed a decision tree. According to these criteria, known as Hunter serotonin toxicity criteria, detection of spontaneous or induced myoclonus, ocular clonus, agitation, diaphoresis, tremor, and hyperreflexia in different combinations is required for the accurate diagnosis of serotonin syndrome (Dunkley et al., 2003).

In the presented case both Sternbach and Hunter serotonin syndrome criteria were fulfilled. Symptoms were first observed on the sixth day of linezolid therapy and completely disappeared 4 days after linezolid and sertraline were discontinued. The symptoms of serotonin toxicity are generally reported to occur between the 1st day and 1st week after starting the concomitant use of serotonergic agents (Isbister and Buckley, 2005). Symptoms are reported to subside 2-7 days after discontinuation of the causative agents in most cases (Kenneth et al., 2005).

Neuroleptic malignant syndrome was not considered in the differential diagnosis of the presented case due to the lack of antipsychotic use. A metabolic abnormality or infection capable of explaining all the symptoms was not detected. Delirium due to concomitant multiple medication use was also considered at first evaluation, but the presence of spontaneous myoclonus and other symptoms, and the disappearance of the symptoms after cessation of sertraline and linezolid supported the diagnosis of serotonin syndrome.

Many researchers recommend refraining from concomitant use of linezolid and serotonergic agents. For patients receiving antidepressant drug treatment, antibiotics other than linezolid are recommended, if possible. For cases in which linezolid use is necessary, cessation of antidepressants and short-term use of benzodiazepines to relieve the symptoms are recommended. A washout

period of 14 days between linezolid and antidepressants is generally recommended (Klasko, 2005), but generally there is no time for such a washout period. Some researchers suggest allowing the concomitant use of medications, but with meticulous follow-up of the symptoms signaling serotonin syndrome (Taylor et al., 2006). We recommend a specific plan for every patient based on a consideration of such factors as patient age, general condition, other medications used, and the urgency of treatment. In medical and surgical inpatient units where the turn-over is high and patient follow-up is limited, antidepressant use with linezolid must be discontinued. In patients treated with long half-life antidepressants linezolid use must be avoided, and if there is an abso-

lute indication for linezolid use antidepressant medication must be stopped and patients must be followed-up closely.

In this report serotonin syndrome following linezolid use in a patient on SSRI antidepressant therapy was reported. SSRI antidepressants are frequently and increasingly used due to their safety and efficacy in patients with advanced age, malignant diseases, multiple medical problems, and multiple medications use. In particular, consultation-liaison psychiatrists are recommended to follow the medications of their patients closely, and evaluate newly emerging symptoms in the light of this new knowledge, as a measure to prevent serotonin syndrome.

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