Serotonin Syndrome due to Concomitant use of Linezolid and Methadone

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Abstract

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We present a case of serotonin syndrome due to administration of linezolid in a patient with methadone addiction. This challenging entity is potentially life threatening but proper education and awareness about serotonin syndrome will improve the accuracy of diagnosis and prevent significant morbidity and mortality.

Keywords

Serotonin Syndrome, Drug Interaction, Linezolid, Methadone, MAO Inhibitors

Introduction

Linezolid is an oxazolidinone antibiotic against Methicillin resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococcus (VRE) and Drug resistant Streptococcus pneumoniae (DRSP) infections. The structure of linezolid is similar to a selective reversible monoamine oxidase inhibitor (MAO-A) toloxatone that used for depression treatment [1].

Regarding this structure–activity relationship similarities between Linezolid and toloxatone, this antibiotic has non-selective MAO-A inhibition properties [2]. Some drugs including SNRIs, TCAs, SSRIs, stimulants and opioid analgesics such as tramadol, meperidine, methadone and dextromethorphan increase serotonin levels and interact with linezolid [3, 4].The use of linezolid with this drugs increase concentrations of serotonin in the central nervous system and result in serotonin syndrome [1].

Serotonin syndrome (SS) is a rare and potentially fatal condition that was first reported by Mitchell [5] and caused by excessive stimulation of serotonin receptor in nervous system. Features of this syndrome include mental status alteration such as delirium, anxiety and confusion, autonomic stimulation for example hyperthermia, tachycardia, tremor, and neuromuscular abnormalities like myoclonus and rigidity [3]. The main cause of serotonin syndrome is drugs that increase the level of serotonin in CNS [6]. Serotonin syndrome can develop less than 24 hours of ingestion certain medication [6, 7].

In searches, we found only one case report has described serotonin syndrome with linezolid and methadone [8]. We describe a case of SS in 60-year-old drug-addict man who admitted to emergency department.

Case report

A 60-year-old drug-addict man was admitted to poisoning department of loghman hospital with dizziness, nausea, and vomiting. The patient's medical history was bipolar disorder and mental disability. In past drug history, he used lithium (300 mg once daily), Clonazepam (2 mg at bedtime), valproate sodium (500 mg twice a day), perphenazine (8 mg at bedtime)and methadone (unknown dose). On examination, his blood pressure was 95/61 mmHg, heart rate 110 bpm, respiratory rate 7 breaths per minute and meiotic pupils with negative neurological examination.

On admission, the patient was unconscious and did not respond to painful stimulation. Laboratory findings included white blood cell count 14.2×10^9 /l, platelet 183×10^9 /l, creatinine 6.8 mg/dl, potassium 7.3 mg/dl, CPK 4218 U/l and lactic acidosis. Drug concentration in serum included lithium 2.6 mEq/L (therapeutic level: 0.6-1.2 mEq/L) and valproate sodium 217.6 µg/ml (therapeutic level: 50-120 µg/ml) and toxicology urine test was positive for methadone and benzodiazepine and negative for tramadol and cannabinoids. Except for methadone, other patients drugs were placed on hold. A jugular catheter was inserted and the patient underwent hemodialysis for 3.5 hours in the emergency department then patient was intubated and transferred to the intensive care unit.

On the third day of hospitalization, the patient was febrile (38.8°C) and the chest X-ray revealed a bilateral opacities while computed tomography displayed consolidation and ground glass opacities (posterior segment of the upper lobes) in both pulmonary field, so empiric antibiotics for aspiration pneumonia (ceftriaxone 1000 mg twice a day intravenously and clindamycin 600 mg three times a day intravenously) was initiated immediately. Blood and urine culture after 3 days was negative but sputum culture was positive for Staphylococcus aureus (10^5 CFU/cell). In antibiogram, the microorganism is resistant to clindamycin and trimethoprim-sulfamethoxazole. Based on sputum culture and resistance pattern, antibiotics changed to linezolid 600 mg twice a day intravenously. However, two days after the initiation of linezolid the patient began to run a fever (39°C) with agitation, tremor, spontaneous clonus movement in hands and tachycardia (pulse rate 115/min). Complete workup was performed that chest X-ray did not change from before and urine analysis did not show any abnormality. In addition, there was also no evidence of seizures on the Electroencephalogram (EEG) and the findings of a brain CT scan were normal. Due to these manifestations, the first diagnosis for the patient was serotonin syndrome Based on hunter criteria (sensitive and specific criteria for diagnosis serotonin toxicity) [9]. Hunter's diagnostic criteria include at least one of the following features: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature above 100.4°F (38°C), and ocular or inducible clonus. There is no particular laboratory test for diagnosis of serotonin syndrome but in some literature, an elevation of the total creatine kinase and transaminase levels and leukocytosis have been reported [10, 11]. In treatment of SS, linezolid administration was promptly discontinued and vancomycin therapy was initiated (1000 mg twice a day intravenously). Supportive therapies including hydration (3 liter of electrolytic solution every 24 hours, metoclopramide 10 mg three times a day intravenously), cyproheptadine 4 mg three times a day via nasogastric tube and benzodiazepine for agitation were performed. Tremor, rigidity and clonus movement disappeared within 48 hours. The patient clinical situation improve but the level of consciousness was not different from before. The patient's hemodynamic status stabilized, and the course of antibiotic treatment was completed.

Finally, the patient was extubated after one week and transferred to the ward under stable condition.

Comment

The diagnosis of serotonin syndrome was difficult in the patient who presented with tremor, agitation and clonus movement. Discontinuation of reference agents and treatment of symptoms is effective. This syndrome must be prevented by educating patients to avoid self-medication and by limiting drug combinations.

Author's contribution

Farnoosh masbough and Soheil Roshanzamiri participated in manuscript preparation; Peyman Erfan Talab participated in concepts design, Mitra Rahimi and Zahra Sahraei participated in manuscript editing and review; All authors read and approved the final manuscript.

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