Linezolid and Rasagiline – A culprit for serotonin syndrome

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INTRODUCTION

Serotonin syndrome refers to a disorder which results from excess serotonergic stimulation at central and peripheral serotonin receptors, usually caused by drugs or drug interactions. It was first defined in 1955, but the precipitating drugs, signs, and symptoms became more common only after 1990s. Despite its high prevalence; serotonin syndrome is often under-diagnosed. This case report highlights a rare incidence of serotonin syndrome due to drug interactions of linezolid with rasagiline; monoamine oxidase (MAO) inhibitor.

CASE REPORT

A 65-year-old female patient was admitted to the hospital with fever, chills and pain in left leg. She was a known case of parkinsonism and diabetes mellitus. She was prescribed levodopa / carbidopa, rasagiline, ropinirole, trihexyphenidyl, amantadine, metformin, and glipizide since 2 years. She also had multiple hospital and Intensive Care Unit (ICU) admissions for worsening parkinsonism. She was admitted to the ward for cellulitis and treated with intravenous clindamycin 600 mg thrice daily and intravenous piperacillin with tazobactam 4.5 gm thrice daily. Vancomycin was not considered taking into account her borderline renal parameters. On admission to the ICU, her hemodynamics improved with minimal inotropic supports. Her anti-parkinsonism drugs were continued; oral hypoglycemic agents were stopped and switched to insulin on ICU admission. Later, in the ICU she was confused, drowsy, disoriented and had altered sensorium. The patient also had myoclonus, tremors, jerky movements, and there was no neck stiffness. Computed tomography of the brain and cerebrospinal fluid analysis were not significant. Her laboratory investigation revealed improving white blood cell counts from 14,200 cells/mm$^3$ to 11,000 cells/mm$^3$ (normal range - 4500–12,500 cells/mm$^3$), better glycemic control and no other abnormalities. Her blood and pus cultures were sterile.

On the 3rd day of hospital admission, she had persistently high-temperature spikes (above 102°F), tachycardia and tachypnea. She became hypotensive and encephalopathic in the ward hence; she was shifted to ICU. Considering sepsis with multi-organ dysfunction syndrome antibiotics was escalated to intravenous linezolid 600 mg twice daily and intravenous piperacillin with tazobactam 4.5 gm thrice daily. Vancomycin was not considered taking into account her borderline renal parameters. On admission to the ICU, her hemodynamics improved with minimal inotropic supports. Her anti-parkinsonism drugs were continued; oral hypoglycemic agents were stopped and switched to insulin on ICU admission. Later, in the ICU she was confused, drowsy, disoriented and had altered sensorium. The patient also had myoclonus, tremors, jerky movements, and there was no neck stiffness. Computed tomography of the brain and cerebrospinal fluid analysis were not significant. Her laboratory investigation revealed improving white blood cell counts from 14,200 cells/mm$^3$ to 11,000 cells/mm$^3$ (normal range - 4500–12,500 cells/mm$^3$), better glycemic control and no other abnormalities. Her blood and pus cultures were sterile.

KEY WORDS: Linezolid, monoamine oxidase inhibitor, serotonin syndrome

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The second day of ICU admission, her status remained the same with a high temperature of 103°F, altered mental status, myoclonus, jerky movements and tremors. No other drugs were added, the same treatment was continued, and the medications she received were scrutinized. She was on rasagiline and started on linezolid 2 days since ICU admission. Serotonin syndrome was suspected after ruling out other possibilities such as infection, drug abuse, cerebrovascular, and metabolic etiologies. The suspected causal drug linezolid had a probable adverse drug reaction. Causal association of serotonin syndrome as assessed by Naranjo causality scale and World Health Organisation-Uppsala Monitoring Centre causality assessment system with a Naranjo score of six. The drug interaction probability scale assessment also revealed probable causality of serotonin syndrome due to rasagiline and linezolid. Hence, both the drugs were stopped on the 2nd day. After 8 hours temperature settled, next day the patient’s heart rate was normal, her sensorium improved and tremors completely subsided. Day 4, she was shifted out of the ICU. After 10 days, she started walking with support and was discharged from the hospital. The patient was discharged with anti-parkinsonism drugs and later added rasagiline. She has a regular follow-up with the neurologist. She was stable and remained asymptomatic for serotonin syndrome.

Discussion

Linezolid is an oxazolidinone class of antibiotic and a weak, reversible MAO inhibitor. In 2003, records from postmarketing voluntary adverse event reporting system database identified 29 cases of serotonin syndrome associated with linezolid.[21]

In this case, a combination of serotonergic drugs; linezolid and rasagiline were most likely to be responsible for serotonin syndrome. Diagnosis of serotonin syndrome is purely on the basis of patient presentation as there are no laboratory investigations or blood serotonin levels for confirmation. It requires a strong clinical suspicion, proper medication history of serotonergic drugs and identification of specific signs and symptoms. Clinical examination, laboratory investigations, imaging, and cultures ruled out the other possibilities that favour towards an infectious focus of fever in our case. We excluded substance abuse or withdrawal, metabolic, and psychiatric etiologies. Hence, non-infectious etiology for fever was suspected. The offending drugs in our case, linezolid and rasagiline were the only temporal cause for fever associated with serotonin syndrome.

The distinction between neuroleptic malignant syndrome and malignant hyperthermia is also important. The serotonergic toxidrome is identified using Hunter Serotonin Toxicity Criteria, Boyer’s and Sternbach’s criteria.[23] The clinical presentation is marked by a triad of cognitive changes (confusion, visual hallucinations, elevated mood, agitation, insomnia, nervousness, delirium or coma), autonomic instability (fever, hyperhidrosis, hypertension, palpitations, or tachycardia), and neuromuscular excitability (myoclonus, tremors, chills, rigidity, hyperreflexia or akathisia). Our case presented with fever, confusion, drowsiness, tremors, myoclonus, and jerky movements which were typical features to fulfill the diagnosis of serotonin syndrome.

The onset of serotonin syndrome ranges from few hours to 3 weeks of increase in dose or initiation of drugs that may increase serotonin levels. In our case report, the patient was on rasagiline and presented with serotonin syndrome within 36 hours of initiation of linezolid. Time to resolution of serotonin syndrome after discontinuation of the culprit drugs ranges from <6 hours to 5 days. In our case, signs and symptoms resolved 8 hours after stopping both serotonergic drugs without any other treatment.[6] Cyproheptadine, a serotonin antagonist, can be given in severe serotonin syndrome. An initial dose of 4–8 mg given orally, and maximum dose is 32 mg/day.[11]

Micromedex suggests concomitant use of linezolid and serotonergic agents are contraindicated. If linezolid is to be administered, it is recommended that the serotonergic drug must be discontinued, or there must be a washout period of at least 2 weeks and observe the patient for serotonin syndrome.[3] Patients with unresolving fever, prescribers should think of the drugs and drug interactions causing the serotonergic syndrome. Prescribers should know the medication history of the patient and washout period of serotonergic drugs. Serotonin syndrome is self-limiting if identified early, culprit drugs are discontinued, and supportive care is initiated.

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Conflicts of Interest

There are no conflicts of interest.

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