NEARLY FATAL SEROTONIN SYNDROME: RARE SIDE EFFECT OF LENOZELID?

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ABSTRACT
A 60 year old man was admitted to our intensive care unit for bronchopneumonia with severe sepsis and was started empirically on linezolid pending the result of culture report. The patient developed high-grade fever with generalised muscle rigidity like rigor mortis, altered sensorium and clonus. Serotonin syndrome was suspected and the patient recovered within 24 hour of withdrawing linezolid.

KEYWORDS: Linezolid, antibiotic, serotonin syndrome.

INTRODUCTION
Linezolid is an oxazolidinone antibiotic that is highly effective against drug resistant gram-positive cocci (eg, Methicillin Resistant Staphylococcus Aureus and Vancomycine Resistant Enterococci) commonly used in intensive care units.[1] Originally it was discovered as a psychototropic agent with antidepressant effects through mild reversible nonselective inhibition of monoamine oxidase (MAO).[1] In patients taking linezolid along with serotonin agonists, there may be a risk for serotonin syndrome which is characterized by mental status changes, autonomic hyperactivity, and neuromuscular abnormalities like generalised muscle rigidity that may range in severity from almost imperceptible to lethal.[2] Few case reports are available in a patient taking serotonin agonist developed serotonin syndrome after linezolid.[2-6] Here we report a case of 60 year old man who developed this syndrome after initiation of linezolid to treat acute bronchopneumonia with sepsis inspite of he was not on any serotonin agonist drugs.
CASE REPORT
A 60-year-old elderly male, from rural background, presented with acute onset high-grade fever, cough with greenish-yellow expectoration and breathlessness since 5 days. He had received antipyretics, mucolytics, expectorants, antibiotics (amoxicillin and clavulanate) from medical practitioner without any improvement so referred here in tertiary care hospital. He denied any history of pulmonary tuberculosis, bronchial asthma, hypertension and diabetes in past. He also denied history of any psychiatric medication. He was non smoker and non alcoholic. On admission, he was febrile with temperature of 101°F temperature, pulse rate of 126/min, and tachypnoic with respiratory rate of 30 per minute. His blood pressure was 126/80 mm Hg in right arm supine position. He was hyoxic and oxygen saturation was only 80% on room air. Systemic examination revealed bilateral scattered coarse crepitations and diminished breath sound in lower chest. He was put on oxygen with BIPAP ventilation. His saturation improved to100% and also feeling better. On laboratory investigation his complete blood count revealed leukocytosis (15,640/cmm) and neutrophilia (85%). Her blood glucose (115 mg/dL), blood urea (45 mg/dL), and serum creatinine (1.1 mg/dL) were within normal limits. His liver function test (serum bilirubin 2.8 mg/dl, AST 68 and ALT IU/L) was slightly deranged. Her chest roentgenogram showed bilateral patchy consolidation suggestive of bronchopneumonia. [fig 1] His HIV status was negative. Patient was put on intravenous linezolid (600 mg twice daily) pending the blood culture report. He was also put on paracetamol, nebulisation with bronchodilators, mucolytics (ambroxol), and chest physiotherapy. Within the first 4-6 hours of antibiotic treatment, the patient had a rapid clinical deterioration with restlessness, generalised muscle rigidity with exaggerated deep tendon reflexes, hypoxia (SPO2-80% with 6-8 L of oxygen) and high fever (103°F), along with mental status changes such as not following verbal commands. Immediately he was put on mechanical ventilation with volume controlled mode. In view of neurological symptoms, cranial computerized tomography and lumbar puncture for the exclusion of central nervous system (CNS) infection were performed but were unremarkable. His serum calcium was also normal as we thought of tetany as well. We suspected serotonin syndrome clinically. Linezolid were discontinued and Pneumonia was treated with intravenous piperacillin tazobactum and meropenam. He was also started with diazepam drip slowly in view of muscle rigidity. Patient started showing signs of improvement few hours later. Withdrawal of diazepam and ventilator weaning took
place 24 hours later. His pneumonia resolved gradually and patient was discharged after two weeks.

DISCUSSION

Linezolid is a totally synthetic compound that was initially synthesized as a reversible MAOI class antidepressant. Due to its weak, nonspecific MAO inhibition, concomitant therapy with an adrenergic or serotonergic agent may increase the risk of SS.\[^1\]\ Its oral bioavailability is nearly equal to intravenous administration, with plasma half-life of 4-6 h. Linezolid is metabolized via oxidation procedure in a way independent of cytochrome P450 (CYP-450); consequently there is no possible pharmacokinetic mechanism of interaction between linezolid and other medication metabolized through CYP450 pathways. Linezolid is generally well-tolerated, with some minor side-effects like gastrointestinal disturbances, headache, and rashes. Rarely, myelosuppression including anaemia, leukopenia, thrombocytopenia, and peripheral as well as optic neuropathy have been reported on prolonged use (>8 weeks).\[^1\]\

SS is characterized by restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, and mental status changes, such as confusion. It usually consists of a constellation of neurological and mental state symptoms and commonly diagnosed clinically. There are no tests to confirm the diagnosis of serotonin syndrome, but suggested criteria as given by Boyer...
According to Boyer’s Criteria, any 1 of the following required: Tremor and hyperreflexia, Spontaneous clonus, Muscle rigidity, temperature > 38°C, and ocular or inducible clonus and diaphoresis or agitation. Diagnostic criteria to assist in its diagnosis as suggested by Sternbach are a) Recent addition or increase in a known serotonergic agent; b) No recent addition or increase of neuroloepics; c) Absence of other possible aetiologies like infection or drug abuse; d) At least three of the following symptoms agitation, ataxia, diaphoresis, diarrhoea, hyperreflexia, mental-status changes, myoclonus, shivering, tremor or hyperthermia.

The pathophysiological mechanism of SS is considered to be a predictable and preventable pharmacodynamic consequence of the excess of serotonergic agonism in CNS and peripheral serotonergic receptors. This is not idiosyncratic, neither idiopathic nor pharmacokinetic drug reactions so symptoms usually improve with the withdrawal of suspected drugs plus supportive care, as there is no specific evidence-based treatment of the SS. [1] Our patient had episodes of sweating, agitation, hypertension, generalised muscle rigidity like rigor mortis after linezolid infusions, necessitating mechanical ventilation. In this case, there was no doubt that addition of antibiotic linezolid temporally led to the constellation of the neuromuscular features in the absence of other CNS pathology, so we kept the diagnosis of SS. We ruled out the possibility of drug interactions, as none of them (paracetamol, salmetrol as bronchodilator and ambroxol) possess either adrenergic or serotonergic properties supplemented by literature search. However more studies are required to confirm and accept this hypothesis.

REFERENCES

