CASE REPORT

Linezolid-induced serotonin syndrome

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SUMMARY

A young drug abuser was admitted to our intensive care unit for organophosphorus poisoning. He required mechanical ventilation and was started empirically on linezolid for suspected nosocomial infection. The patient developed high-grade fever with altered sensorium and clonus. Serotonin syndrome was suspected and the patient was started on cyproheptadine. He recovered within 3 days of withdrawing linezolid and administering cyproheptadine.

BACKGROUND

The serotonin syndrome is a potentially life-threatening adverse drug reaction. The diagnosis may be easily missed because of protean and subtle manifestation which may be thought to be unrelated or inconsequential or misattributed to other conditions like anxiety. Prompt withdrawal of the offending drug and administration of cyproheptadine along with supportive care is a corner stone for management.

CASE PRESENTATION

A 30-year-old man was found unconscious at a railway station in Mumbai with frothing from his mouth. He was brought to our hospital by his friend. Preliminary examination showed that there was no history of fever, fasciculation or obvious trauma. He was afebrile, pulse was 68/min and blood pressure was 90/60 mm Hg. Both pupils were 2–3 mm in diameter and responsive to light. His Glasgow Coma Scale was E1M1V1. His plantars were equivocal. The rest of the systemic examinations were normal. However, he was having a pungent garlic-like (organophosphorus) odour in his breath. In view of increased secretions and the altered sensorium, the patient was intubated immediately and put on mechanical ventilator. The gastric content obtained after lavage also had the pungent garlic-like smell of an organophosphorus compound and was sent for chemical analysis. He was started on atropine drip and injection, pralidoxime along with antibiotics and hydration.

Subsequent routine investigations showed the following details: haemoglobin 15 mg/dl, total leucocyte count 18 000/cc, platelet count 40 000/cc and random blood sugar 217 mg/dl. Creatinine 1.3 mg %, serum Na 140 mEq/l, K 4 mEq/l, Ca 8.3 mEq/l. Serum acetylcholine-esterase levels were 480 iu/l (N 5000–12 000), which confirmed the case to be one of the organophosphorus poisoning. Urine toxicology screen was negative. The patient continued to be on mechanical ventilation. Tracheostomy was performed, owing to difficulty in weaning the

patient off the ventilator, considering his increased secretions and altered sensorium.

Three days after the patient was admitted, his demeanour became very irritable and restless. Suspecting this to be indicative of drug withdrawal syndrome, the patient's relatives were questioned about the patient's history specifically with respect to possible drug abuse. According to them, the patient used to be away from home on most nights and remained sleepy during daytimes and skipped his office duties and stayed withdrawn. This increased the index of suspicion about drug abuse.

After a few more days, the patient developed high-grade fever about 40°C; not associated with increased secretion, burning micturition or abdominal pain. The patient was started empirically on injection piperacillin-tazobactam 4.5 gm 6 hourly and injection linezolid 600 mg twice daily as the patient was intolerant to vancomycin (patient developed rash and hypotension).

One week after the patient was admitted, he developed fever associated with profuse sweating, tremors, abnormal perioral movement, tachycardia and altered mental status with respiratory depression; consequently, he had to be put back on a ventilator. Such episodes recurred for the next 3 days. During such episodes, he used to be febrile at 40°C. In view of dystonia, the patient was started on injection phenergan (promethazine). However, no improvement was seen. Upon examination, the patient was febrile, pulse was 118/min, blood pressure was 180/100 mm Hg. Pupils dilated 6–7 mm bilaterally and were reacting to light. On central nervous system examination hypertonia was present in all four extremities. Cog wheel rigidity was present. Reflexes were all brisk and ankle clonus was present. Plantars were flexors.

In view of the above new symptoms, that is, muscle rigidity, fever not responding to antibiotics, autonomic dysfunction (tachycardia, hypertension, mydriasis), hyper-reflexia with clonus, diagnosis of serotonin syndrome was suspected on the third day of linezolid infusion; however, no history of any other offending drugs except illicit drug abuse was found.

Linezolid was discontinued and he was started on cyproheptadine 4 mg thrice daily, after starting of which, within 48 h the patient symptomatically improved (tremor, cog wheel rigidity, fever decreased), subsequently the patient became conscious on treatment and mobile after 2 weeks.

During subsequent counselling the patient confessed of drug abuse; however, he declined to name the drug and frequency. The patient has now recovered completely and is gainfully employed.

Final diagnosis: Linezolid-induced serotonin syndrome.

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DISCUSSION

Serotonin syndrome is a potentially life-threatening condition caused by excessive serotonergic activity in the nervous system.¹ In 2004, the Toxic Exposure Surveillance System identified 48 204 exposures to selective serotonin reuptake inhibitors (SSRIs) that resulted in moderate or major outcomes in 8187 patients and death in 103 patients; the vast majority of these deaths were associated with coingestants.² The serotonin syndrome is often described as a clinical triad of mental-status changes, autonomic hyperactivity and neuromuscular abnormalities, but not all of these findings are consistently present in all patients with the disorder.^{3–5}

In 1991, Sternbach⁴ developed diagnostic criteria to assist in diagnosis, which include

1. Recent addition or increase in a known serotonergic agent;
2. No recent addition or increase of neuroleptics;
3. Absence of other possible aetiologies like infection or drug abuse;
4. At least three of the following symptoms agitation, ataxia, diaphoresis, diarrhoea, hyperreflexia, mental-status changes, myoclonus, shivering, tremor or hyperthermia.

Our patient had repeated episodes of sweating, agitation, tremors, tachycardia, hypertension, muscle rigidity and clonus after linezolid infusions, necessitating mechanical ventilation. The fact that the patient could be weaned off the ventilator in between the episodes makes primary organophosphorus poisoning-induced respiratory involvement or intermediate syndrome unlikely.

The serotonin syndrome encompasses a range of clinical findings. A mild case may have only tachycardia with features of autonomic hyperactivity like sweating or dilated pupils. Moderate cases may have fever, hyper-reflexia and clonus along with findings of autonomic hyperactivity. A patient with a severe case of the serotonin syndrome may have severe hypertension and tachycardia that may abruptly deteriorate into frank shock. Such patients may have agitated delirium as well as muscular rigidity and hypertonicity.⁵

No laboratory tests confirm the diagnosis of the serotonin syndrome. The presence of tremor, clonus or akathisia without additional extrapyramidal signs should lead clinicians to consider the diagnosis. Laboratory abnormalities that occur in severe cases may include metabolic acidosis, rhabdomyolysis, elevated levels of serum aminotransferase and creatine, seizures, renal failure and disseminated intravascular coagulopathy. Many of these abnormalities arise, however, as a consequence of poorly treated hyperthermia.

Drugs which cause serotonin syndrome are monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, SSRIs, opiate analgesics, antibiotics like linezolid as in this case, weight-reduction agents-sibutramine, antiemetics like ondansetron, antimigraine agents-sumatriptan, drugs of abuse like methylenedioxymethamphetamine and herbal products; the withdrawal of medications has also been associated with the syndrome.^{3 4 6}

MAOIs are associated with severe cases of the syndrome, especially when used in combination with meperidine, dextromethorphan, SSRIs. The presence of tremor, clonus or akathisia without additional extrapyramidal signs should lead clinicians to consider the diagnosis.

Clinicians should inquire about the use of prescription and over-the-counter drugs, illicit substances and dietary supplements, since all of these agents have been implicated in the development of the serotonin syndrome.

The serotonin syndrome should be differentiated from anticholinergic poisoning, malignant hyperthermia and the neuroleptic malignant syndrome. Anticholinergic poisoning will have normal reflexes. The rigor mortis-like rigidity of skeletal muscles and hyporeflexia that are seen in malignant hyperthermia distinguish this condition from the serotonin syndrome.⁷

Signs and symptoms of the neuroleptic malignant syndrome typically evolve during several days, in contrast to the rapid onset and hyperkinesia of the serotonin syndrome. Knowledge of the precipitating drug also helps in distinguishing between syndromes: dopamine antagonists produce bradykinesia, whereas serotonin agonists produce hyperkinesia.⁸

A high index of suspicion is vital for the diagnosis of serotonin syndrome. The diagnosis may be easily missed because of protean and subtle manifestation which may be thought to be unrelated or inconsequential or misattributed to other conditions like anxiety.

Removal of the precipitating drugs is the most important step in the management of the serotonin syndrome.⁹

Administration of 5-HT(5-hydroxytryptamine)2A antagonists like cyproheptadine is recommended. Treatment of the serotonin syndrome in adults may require 12–32 mg of the drug during a 24 h period, a dose that binds 85–95% of serotonin receptors.¹⁰

Benzodiazepines should be used to control agitation. Neuromuscular paralysis and orotracheal intubation with sedation will be required in more severe cases.

Control of autonomic instability and the control of hyperthermia with supportive care remains a mainstay of the therapy.

Learning points

- Serotonin syndrome is complex and rare but avoidable potentially fatal adverse drug reaction in medical intensive care units (ICUs).
- Early manifestation in ICU may be misattributed to infection, anxiety or inconsequential and hence diagnosis is missed.
- Early suspicion and prompt withdrawal was key in positive outcome of our patient.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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