Serotonin syndrome: A case report

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Serotonin syndrome or serotonin toxicity is defined as an iatrogenic drug-induced toxidrome associated with increased intrasynaptic serotonin concentration in the central nervous system. Most cases are provoked by therapeutic doses of a combination of two or more serotonergic agents. The incidence of serotonin syndrome is on the rise, because of increased use of serotonergic medications in current clinical practice. However, the actual incidence of perioperative serotonin syndrome and its morbidity are likely unknown. The diagnosis is difficult in the perioperative period, as clinical features may mimic other conditions commonly seen in the perioperative period or may be masked by the use of anaesthetic medications. Therefore, anaesthetists must be proactive in preventing, identifying and managing serotonin syndrome in the perioperative period.

Keywords: Serotonin syndrome, Serotonin toxicity, Serotonergic drugs, Toxidrome,

Case report

A 30-year-old gentleman scheduled for wound exploration was brought to the operating theatre following a firearm injury to his right leg. His past medical history revealed that he had been diagnosed with depressive disorder and had been on fluoxetine 20 mg daily for 06 months duration. His preoperative examination findings revealed a pulse rate of 74/min, blood pressure of 110/70 mmHg, respiratory rate of 14/min and temperature of 37^0C. His basic investigation findings didn't reveal any abnormalities. Before arriving in the operating theatre, according to the drug chart he was administered 1 g of paracetamol, 100 mg of diclofenac sodium suppository, 7.5 mg of subcutaneous morphine and 4 mg of IV ondansetron 6 hours ago. In addition, he was given 10 mg of IV metoclopramide and 50 mg of IV ranitidine 2 hours ago.

In the operating theatre, he was anaesthetized with a subarachnoid block with 2.75 ml of .5% hyperbaric bupivacaine and 12.5 micrograms of fentanyl. Within 10 minutes T 10 sensory level was achieved without haemodynamic instability and the patient remained asymptomatic throughout the surgery. It took 01 hour to conclude the surgery and then the patient was taken into post anaesthetic care unit (PACU). At the PACU, the patient was given 25 mg of IV pethidine, as the patient was shivering. Three to five minutes later, he complained of nausea and sweating. Then he was treated with 4 mg of IV ondansetron. At this time, his examination findings revealed agitation, sweating, flushing, clonus in upper limbs, pulse rate of 150/min, blood pressure of 190/110 mmHg and respiratory rate of 20/min. His body temperature and blood gas analysis were normal. Serotonin syndrome

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was suspected because these signs and symptoms appeared just after administering meperidine to a patient on fluoxetine and the clinical diagnosis was confirmed with Hunter's criteria. Subsequently, the patient was sedated with 6mg of IV midazolam (2mg incremental doses) and 25mg of IV labetalol (5mg incremental doses) to control the heart rate and blood pressure. Clinical features improved shortly thereafter, and cardiovascular parameters returned to baseline values.

Discussion

Serotonin syndrome or serotonin toxicity is defined as an iatrogenic drug-induced toxidrome associated with increased intrasynaptic serotonin concentration in the central nervous system[1]. Most cases are provoked by therapeutic doses of a combination of two or more serotonergic agents. Clinical features of serotonin toxicity are often described as a triad which includes neuromuscular hyperactivity (hyperreflexia, clonus and rigidity), autonomic nervous system hyperactivity (tachycardia, Hyperthermia, diaphoresis and mydriasis) and alteration in mental status (excitement, agitation, restlessness and confusion)[1,2]. Clinical features of serotonin syndrome appear within hours of administration or ingestion of medication which increase serotonin concentration in the nervous system. Symptoms vary from mild to severe. Mild toxicity may pass unnoticed, while severe toxicity may lead to life-threatening conditions such as acute kidney injury, rhabdomyolysis and disseminated intravascular coagulation[1,2,3].

Serotonin (5- hydroxytryptamine) is found in neurons, gastrointestinal tract and platelets. After releasing serotonin into the synaptic cleft in nervous system, it is taken back into presynaptic nerve terminal through selective serotonin transporter (SERT) whereby nerve transmission is terminated. Once serotonin is transported into presynaptic nerve terminal through SERT, it is either recycled into vesicles or inactivated by monoamine oxidase into 5- hydroxyindoleacetic acid (5-HIAA). Any medication which increases serotonin concentration may lead to serotonin toxicity and these drugs are called serotonergic drugs. In clinical practice, there are different categories of these drugs[1,2,3,4]. (Table 1)

Table 1: *Categories of serotonergic drugs*

	Category	**Examples**
1	Selective serotonin reuptake inhibitors	Fluoxetine, Citalopram, Sertraline
2	Serotonin-norepinephrine reuptake inhibitors	Venlafaxine, Paroxetine, Duloxetine
3	Tricyclic antidepressants	Amitriptyline, Nortriptyline, Imipramine
4	Serotonin releasers	Amphetamines, Lithium, Ecstasy, Cocaine
5	Monoamine oxidase inhibitors	Phenelzine, Selegiline, Linezolid, Methylene blue
6	Serotonin precursors	L-tryptophan
7	Serotonin receptor agonists	Olanzapine, Lithium, Buspirone, Sumatriptan
8	Opioid analgesic drugs	Meperidine, Fentanyl, Alfentanil, Tramadol

In this case, the patient was on selective serotonin reuptake inhibitors while being administered Meperidine and Ondansetron in the post operative period. Meperidine and 5 HT3 inhibitors impair serotonin reuptake from the synaptic cleft into the presynaptic neuron.

Diagnosis of serotonin syndrome is merely based on clinical features and sensitivity has been increased by the application of diagnostic criteria systems. Hunter's criteria are the most used criteria among available diagnostic criteria systems to diagnose serotonin syndrome[3]. However, the diagnosis of serotonin syndrome is challenging during the perioperative period[1,4]. Many of these signs and symptoms are hindered due to pharmacological and physiological changes during the perioperative period[1,5]. For instance, neuromuscular blocking drugs eliminate clinical features of neuromuscular hyperactivity, assessment of mydriasis is difficult because of the effects of anticholinergics and opioids on the iris, heart rate is altered due to effects of drugs and surgical stimulation, assessment of mental state is impossible with general anaesthesia. Moreover, symptoms and signs common to other disorders (which include malignant hyperthermia, neuroleptic malignant syndrome, hyperthyroidism, sepsis, meningoencephalitis and anticholinergic syndrome) may complicate the diagnosis of serotonin syndrome[1,5].

To diagnose serotonin syndrome, the patient should meet one of the following with a background history of serotonergic drug administration[2](Hunter's Criteria).

1. Spontaneous clonus
2. Inducible clonus with agitation or diaphoresis
3. Ocular clonus with agitation or diaphoresis
4. Tremor with hyperreflexia
5. Hypertonia with temperature above 38^0C with ocular clonus or inducible clonus

Treatment

Management of serotonin syndrome based on the following principles:

1. Discontinuation of all serotonergic drugs
2. Provision of supportive care
3. Administration of benzodiazepines
4. Treatment with a serotonin antagonist

The urgency and the application of these principles depend on the severity of serotonin toxicity.

In mild cases, discontinuation of inciting drug, sedation with benzodiazepines and supportive care are generally adequate[1,6]. Tachycardia and hypertension can be treated with short acting intra venous betablockers such as esmolol. Intravenous labetalol can also be used to control blood pressure in this situation.

In severe form, cases need more aggressive treatment of autonomic instability, treatment with serotonin antagonists and reduction of body temperature[6,7]. Presence of rapidly rising body temperature, muscle rigidity and hypertonia indicate a life-threatening condition and it is called serotonin storm or crisis. Muscle rigidity in trunk impairs ventilation which further worsens acidosis and oxygenation. Continuous muscle contractions result in hyperthermia (38.5^0C) in severe form of toxicity. If severe form is left untreated, patient ends up in multiorgan failure (rhabdomyolysis, acute kidney injury, disseminated intravascular coagulation, respiratory distress syndrome, cardiomyopathy, etc.)[1,2,3,6]. Failure to respond to aggressive treatment with benzodiazepines requires paralysis, intubation, ventilation and active cooling to prevent progression of crisis[6,7]. Serotonin antagonist such as oral cyproheptadine or

intravenous chlorpromazine can be used, although there is no adequate evidence to prove its efficacy in serotonin toxicity.

Conclusion

Serotonin syndrome is strictly a clinical diagnosis. Hence, the anesthesiologist should be more aware of serotonergic drugs, clinical features of serotonin syndrome and similar conditions that make the diagnosis difficult, especially in the perioperative period. Furthermore, if the diagnosis is missed, this may lead to life-threatening consequences. Therefore, early identification and effective treatment will improve outcomes.

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