

Review Article

Revisiting Serotonin Syndrome

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Abstract

Serotonin syndrome is a potentially life-threatening adverse drug reaction caused due to excessive serotonergic activity characterized by mental, autonomic and neuromuscular changes. It is largely an avoidable adverse drug reaction. 5-HT_{1A} and 5-HT₂ receptors are considered important in the pathogenesis of the syndrome. Drugs commonly implicated are SSRIs, monoamine oxidase inhibitors and drugs causing serotonin release. Serotonin syndrome is usually of acute onset, within 6 to 24 hours of starting the offending medication, after a medication change or overdose with some cases manifesting within minutes in latter instances. Diagnosis entirely depends on the patient history and clinical examination. A history of increase in the dose of serotonergic medication or recent change of medications should alert the physician. Among the clinical signs, clonus is an important pointer towards the diagnosis. Hunter serotonin toxicity criteria is a commonly used diagnostic criteria. Withdrawal of all serotonergic drugs, supportive care to normalize the vital signs, administration of benzodiazepines and 5-HT₂ antagonists such as cyproheptadine are important based on the severity of serotonin toxicity.

Keywords: Serotonin syndrome, SSRI, MAOI, Hunter serotonin toxicity criteria, Serotonin toxicity

Introduction

Serotonin syndrome is a potentially life-threatening adverse drug reaction caused due to excessive serotonergic activity at the central and peripheral serotonergic receptors. This could occur during routine therapeutic use of drugs affecting the serotonergic system, inadvertent interactions between drugs or intentional poisoning.^[1,2] The syndrome is characterized by mental, autonomic and neuromuscular changes^[3]. Except for deliberate poisoning, serotonin syndrome is largely an avoidable adverse drug reaction. Moreover, awareness of the condition and prompt recognition of the syndrome can decrease the associated morbidity and mortality. While most of the cases are likely to be due to interaction between two or more serotonergic drugs, the syndrome may also be precipitated due to overdose/high therapeutic dose of a single agent such as selective serotonin reuptake inhibitors (SSRIs).^[2,4] Serotonin syndrome is commonly referred to as 'serotonin toxicity' since the clinical manifestations

represent a dose-dependent continuum with the classical manifestations of the syndrome occurring only in severe cases.

Pathogenesis

Serotonin is a neurotransmitter synthesized from the essential amino acid tryptophan. It has wide ranging central and peripheral actions including, but not limited to, influence on mood, sleep, pain perception, platelet aggregation, contraction of intestinal smooth muscles and emesis.^[5] The vast majority of serotonin (90%) is synthesized in the periphery, but brain serotonin levels are the main factor in development of serotonin toxicity.^[6] Its actions are brought about by interaction with seven receptor families.^[5] Among these, 5-HT_{1A} and 5-HT₂ receptors are considered important in the pathogenesis of the syndrome.^[7,8] Thus drugs which predominantly affect other serotonergic receptors or receptor antagonists such as atypical antipsychotics, antiemetics (5-HT₃ antagonists) are less likely to precipitate the reaction.

Drugs commonly implicated are SSRIs, monoamine oxidase inhibitors (MAOIs) and drugs causing serotonin release.^[4] Hence, the mechanisms in general, include 1) increased serotonin

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release from neurons (amphetamines); 2) decreased serotonin reuptake (SSRIs, atypical antidepressants, pethidine, fentanyl, dextromethorphan); 3) decreased metabolism (MAOIs, linezolid, cytochrome inhibitors).^[9] Certain other drugs have also been implicated although the mechanisms are not clear. A list of drugs implicated in the causation of serotonin syndrome either alone or in combination is listed in Table-1. Combining these drugs, when unavoidable, should be done with due precaution. SSRIs should not be started until at least 14 days following discontinuation of treatment with an MAOI and vice versa, except in case of fluoxetine. The presence of metabolite with long half-life necessitates at least 5 weeks interval between stopping fluoxetine and beginning a MAOI.^[10]

Table 1. Drugs implicated in the causation of serotonin syndrome

Drug class	Examples
Antidepressants	SSRIs, MAOIs, serotonin norepinephrine reuptake inhibitors, serotonin antagonists (trazodone, nefazodone)*, tricyclic antidepressants
Antianxiety drug	Bupirone
Mood stabilizer	Lithium
Atimigraine drugs	Triptans, Ergot derivatives
Analgesics	Pethidine, tramadol, fentanyl, methadone
Cough suppres - sant	Dextromethorphan
Psychostimulants	Amphetamines, cocaine, LSD
Dietary sup - plements	L-tryptophan, St. John's wort (Hypericum perforatum)
Antimicrobials	Linezolid
Others	Methylene blue, reserpine, cocaine

* Weak MAO inhibitors

Incidence

While serotonin syndrome was first described in 1956, it is only over the last two decades, with the introduction of the numerous serotonergic drugs, the syndrome is being increasingly recognized.^[9] Despite this, a large number of cases go

un- recognized due to lack of awareness about the condition, misdiagnosis of mild to moderate cases and the clinical manifestations not being apparent enough to prompt the clinician to consider its presence.^[12] Hence, despite the increasing reporting trend, the actual numbers are not known. Information from the US poison control centers in 2005 show that 18% of the 48279 ingestion cases presented with moderate to major effects and 0.2% deaths.^[1] Various other limited data are available with regard to the incidence of serotonin syndrome with a couple of studies estimating it around 14-16% in SSRI overdose cases,^[13,14] and another study reporting the incidence to be 0.4 case per 100 patient-months for those on nefazodone.^[15] In 2006, based on 29 case reports of serotonin syndrome, the United States Food and Drug Administration issued an alert recommending that patients receiving a triptan and SSRI/SNRI medications be informed of the possible risk of serotonin syndrome.^[6]

Clinical presentation

Serotonin syndrome is usually of acute onset, within six to 24 hours of starting the offending medication, after a medication change or overdose with some cases manifesting within minutes in latter in- stances.^[1,7] The manifestations include a triad of: ^[4,12,17]

- Neuromuscular signs – clonus, hyperreflexia, rigidity, myoclonus, tremors, bilateral babinski sign
- Autonomic instability – hyperthermia, tachycardia, diaphoresis, mydriasis, hypertension, vomiting, diarrhea
- Mental changes – agitation, confusion, anxiety, restlessness, delirium

As is evident from the signs and symptoms, many of these occurring in isolation are difficult to distinguish from drug related adverse effects occurring during routine therapy. But diagnosis entirely depends on the patient history and clinical examination. Laboratory investigations are not useful to confirm the diagnosis.^[12,17] A history of increase in the dose of serotonergic medication or recent change of medications should alert the physician. Among the clinical signs, clonus is an important pointer towards the diagnosis. While milder cases may be difficult to diagnose, what is more important either ways is not to escalate the dose of the serotonergic drug or add a second drug with serotonergic effects or which inhibits metabolism of the first drug. This by itself will prevent further worsening of the clinical situation.^[4]

The two most commonly used diagnostic criteria's for serotonin syndrome are the Sternbach's criteria and Hunter serotonin toxicity criteria. The latter is more sensitive and specific than the former and hence is commonly used.^[2] Sternbach's criteria requires the presence of three out of ten clinical features (agitation, diaphoresis, diarrhea, hyperreflexia, incoordination, confusion, hypomania, myoclonus, shivering, tremor) in a patient with addition or recent increase in dose of a known serotonergic drug. Hunter's criteria requires one of the following features or groups of features in a patient known to have taken a serotonergic drug: 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.^[1] Apart from other clinical conditions, serotonin syndrome needs to be differentiated from other drug toxicities such as neuroleptic malignant syndrome, malignant hyperthermia, anticholinergic toxicity, poisoning by amphetamines, cocaine, lithium, salicylates etc.^[1,3]

Management

Moderate to severe cases of serotonin syndrome require intensive management. In all the cases, the following measures should be considered either alone or in combination depending on the severity, signs and symptoms. Withdrawal of all serotonergic drugs is the first essential step of treatment and the only measure necessary in mild to moderate cases. Supportive care aimed at normalizing the vital signs is necessary in rest of the cases. Drug therapy includes the administration of diazepam for sedation and use of serotonin antagonists such as cyproheptadine or chlorpromazine.^[12,18] Resolution may be expected at least partially within 24 hours of initiating treatment. However, with drugs such as MAO inhibitors the syndrome may persist for a longer time. Similarly, a delayed onset following discontinuation may be expected for drugs with long half-life such as SSRIs.^[17] The need for reintroduction of a serotonergic drug may be considered after complete resolution of symptoms.^[12,17]

Withdrawal of offending agent: This involves not only discontinuing the causative drug (s) but also a search for possible interacting medications which may have a adjuvant role in causation of the syndrome. Also, one needs to carefully avoid introduction of any medication that can increase serotonin concentrations as mechanistically unrelated drugs have been known to contribute to the problem.

Supportive care: Ensuring adequate hydration

(crystalloids) and careful monitoring of temperature, pulse, blood pressure, oxygen saturation and urine output are necessary.^[4] Sedation, neuromuscular paralysis and intubation may be required particularly in hyperthermic patients. Succinylcholine should be avoided due to risk of arrhythmias as a result of rhabdomyolysis induced hypokalemia.^[12] Aggressive cooling techniques may be required for hyperthermia. This may involve cool water sprays, ice packs, and even paralysis and ventilation.^[3] Antipyretics are not useful as the elevation in body temperature is due to excessive muscle activity.^[12]

Pharmacotherapy: Sedation with benzodiazepines (oral diazepam, intravenous lorazepam or midazolam infusion) is an essential step in agitated patients and those with muscular hyperactivity. This helps to prevent lactic acidosis and hyperthermia. It also takes care of autonomic instability such as increased BP and heart rate to some extent. Sedation with antipsychotics should be avoided as they have anticholinergic action which can worsen hyperthermia. For severe hypertension and tachycardia a rapidly titratable agent such as esmolol or sodium nitroprusside should be used.^[17] Hypotension due to MAOI can be treated with a directly acting sympathomimetic like phenylephrine.^[12] 5-HT_{2A} antagonists have a role in the management of severe forms of serotonin syndrome. Cyproheptadine is the drug classically used. It has H₁ antihistaminic and 5-HT_{2A} antagonistic action. It may be administered orally or via a nasogastric tube in a dose of 12mg initially followed by 2mg every two hours until symptoms improve followed by 8mg every sixth hourly. Sublingual olanzapine or intramuscular chlorpromazine have also been tried as they have 5-HT_{2A} antagonistic action.^[12] Use of propranolol, bromocriptine or dantrolene is not recommended.^[12,17] An important aspect not to be overlooked is the management of depressed patients after resolution of the syndrome. All patients newly started on antidepressant medications should be assessed for suicidal thoughts. These patients are at a higher risk and hence require more frequent monitoring following re-initiation of therapy.

Conclusion

Serotonin syndrome is an avoidable adverse drug reaction. Polypharmacy, especially when one of the medications is a serotonergic drug, should alert the physician to look for possible interacting medications. Moreover, with the increasing use of selective serotonin reuptake inhibitors in psychiatric disorders the chances of developing the toxicity is higher. Increasing awareness regarding the condition, avoidance of interacting drug combinations, prompt recognition and early management of the toxicity is essential to

reduce the risk of serotonin syndrome and its consequences.

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