

Serotonin Syndrome Following Single Ingestion of High Dose Methamphetamine

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Abstract

Serotonin syndrome is a potentially life-threatening adverse drug reaction that may occur following therapeutic drug use, inadvertent interactions between drugs, overdose of particular drugs, or the recreational use of certain drugs. It is most commonly reported with combinations of serotonergic medications. Serotonin syndrome is not an idiosyncratic drug reaction.

Methamphetamine is a psycho stimulant drug which produces increased wakefulness and focus in association with decreased fatigue and appetite. A methamphetamine overdose is rarely fatal but can lead to a number of different symptoms, including psychosis, chest pain, and hypertension. It is among agents with moderate potency to produce Serotonin syndrome. Here we present the first reported case of serotonin syndrome after a single ingestion of high dose methamphetamine (body staffer of 2gr amphetamine) in 28 year-old previously healthy man without any drug history, 2 hours prior to admission. Clinical manifestation included hyperthermia, hypertension, tachycardia, sweating, dilated pupil, agitation, overactive reflexes (greater in the lower limbs than in the upper limbs) and clonus. Complete blood count was normal except for severely elevated white blood cell count of $22.3 \times 10^3/\mu\text{L}$ ($22.3 \times 10^9/\text{L}$) with 74% neutrophils and 24% lymphocytes. His serum blood urea nitrogen, creatinine, liver function tests, and electrolytes were normal. Mildly elevation in Serum creatinine kinase was seen. Coagulation studies and Urine analysis were normal. Serum glucose was 210 mg/dL. An arterial blood gas shows respiratory alkalosis. We intubated him by Rapid Sequence Intubation (RSI) method and then took an emergent abdominal CT scan for any need for surgical intervention; we admitted him in ICU ward and did supportive care including the control of agitation, hyperthermia and autonomic instability. After 2 days we could extubate him and after 5 days he discharged from hospital.

Keywords: Serotonin syndrome; Methamphetamine; Ingestion; RSI

Introduction

Serotonin syndrome is a potentially life-threatening adverse drug reaction that may occur following therapeutic drug use, inadvertent interactions between drugs, overdose of particular drugs, or the recreational use of certain drugs. Serotonin syndrome is not an idiosyncratic drug reaction; it is a predictable consequence of excess serotonergic activity at central nervous system (CNS) and peripheral serotonin receptors [1]. For this reason, some experts strongly prefer the terms serotonin toxicity or serotonin toxidrome because these more accurately reflect the fact that it is a form of poisoning. It may also be called serotonin sickness, serotonin storm, serotonin poisoning, hyperserotonemia, or serotonergic syndrome [2, 3]. The excess serotonin activity produces a spectrum of specific symptoms including cognitive, autonomic, and somatic effects. The symptoms may range from barely perceptible to fatal. [1] Numerous drugs and drug combinations have been reported to produce serotonin syndrome. Diagnosis of serotonin syndrome includes observing the symptoms produced and a thorough investigation of the patient's history. The syndrome has a characteristic picture but can be mistaken for other illnesses in some patients, particularly those with neuroleptic malignant syndrome. No laboratory tests can currently confirm the diagnosis [3].

Symptoms onset is usually rapid, often occurring within minutes. Serotonin syndrome encompasses a wide range of clinical findings. Mild symptoms may only consist of increased heart rate, shivering, sweating, dilated pupils, myoclonus (intermittent tremor or twitching), as well as over responsive reflexes [1]. Moderate intoxication includes additional abnormalities such as hyperactive bowel sounds, high blood pressure and hyperthermia; a temperature as high as 40 °C (104 °F) is common in moderate intoxication. The overactive reflexes and

clonus in moderate cases may be greater in the lower limbs than in the upper limbs. Mental status changes include hyper vigilance and agitation [1]. Severe symptoms include severe increases in heart rate and blood pressure that may lead to shock. Temperature may rise to above 41.1 °C (106.0 °F) in life-threatening cases. Other abnormalities include metabolic acidosis, rhabdomyolysis, seizure, renal failure, and disseminated intravascular coagulation; these effects usually arise as a consequence of hyperthermia [1,3].

The symptoms are often described as a clinical triad of abnormalities: [1, 4].

- Cognitive effects: headache, agitation, hypomania, mental confusion, hallucinations, coma
- Autonomic effects: shivering, sweating, hyperthermia, hypertension, tachycardia, nausea, diarrhea.
- Somatic effects: myoclonus (muscle twitching), hyperreflexia (manifested by clonus), tremor.

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A large number of medications either alone or in combination can produce serotonin syndrome, such as: Monoamine oxidase inhibitors (MAOIs), TCAs, SSRIs, SNRIs, tramadol, valproate, buspirone, lithium, linezolid, dextromethorphan, pethidine, fentanyl, sibutramine [1], nefazodone, trazodone [5], amphetamine, chlorpheniramine, methylphenidate, methamphetamine, LSD, L-Dopa, risperidone [6,7,8,9], olanzapine [10]. Many cases of serotonin toxicity occur in patients who have ingested drug combinations that synergistically increase synaptic serotonin [4]. It may also occur in patients following ingestion of a single serotonergic agent [11]. The combination of MAOIs and other serotonin agonists or precursors pose a particularly severe risk of a life-threatening serotonin syndrome. Many MAOIs inhibit monoamine oxidase irreversibly, so that the enzyme cannot function until it has been replaced by the body, which can take at least four weeks [12]. Bupropion has also been suggested to cause serotonin syndrome although as there is no evidence that it has any significant serotonergic activity, it is thought unlikely to produce the syndrome [13]. In 2006 the United States Food and Drug Administration issued an alert suggesting that the combined use of SSRIs or SNRIs and triptan medications or sibutramine could potentially lead to severe cases of serotonin syndrome.

Serotonin syndrome has been reported in patients of all ages, including the elderly, children, and even newborn infants due to in utero exposure [14].

Serotonin toxicity has a characteristic picture which is generally hard to confuse with other medical conditions, but in some situations it may go unrecognized because it may be mistaken for a viral illness, anxiety, neurological disorder, anticholinergic poisoning, sympathomimetic toxicity, or worsening psychiatric condition [1,3].

Case Report

Here we present a case of serotonin syndrome after a single ingestion of high dose methamphetamine, a 28-year-old previously physically healthy man was admitted to the emergency department (body weight, 65 kg). He ingested a high dose methamphetamine (body staffer of 2gr methamphetamine) 2 hours prior to admission. He did not have any drug or medical history. On arrival, the patient was hemodynamically unstable. Oral temperature was 39.5°C (101.5°F), pulse rate 160 beats per minute with a normal sinus rhythm, blood pressure 165/95 mm Hg, and his respiratory rate was 28 breaths/min with no abnormal breath sounds. The abdomen was soft and flat with hyperactive bowel sounds.

The initial oxygen saturation was 95% (in room air). He was alert, awake, but agitated. He complained of palpation and sweating.

In clinical examination he was warm and sweated, mildly confused, and have dilated pupils, tachycardia, overactive reflexes that greater in the lower limbs than in the upper limbs and clonus.

A 12-lead electrocardiogram (ECG) revealed sinus tachycardia at a rate of 160 bpm.

A complete blood count was normal except for severely elevated white blood cell count of $22.3 \times 10^3/\mu\text{L}$ ($22.3 \times 10^3/\text{L}$) hemoglobin 15.3 g/dL, hematocrit 44.5% with 74% neutrophils, 24% lymphocytes, 1% monocytes and 1% eosinophiles. His serum blood urea nitrogen, creatinine, liver function tests, and electrolytes were normal (sodium=143mEq/L, potassium=5mEq/L, Calcium (total)=9.8 mg/dL, magnesium=1.8 mg/dL). Coagulation studies, including a prothrombin time, activated partial thromboplastin time, were normal. Serum glucose was 210mg/dL. Urine analysis was normal. Arterial blood gas

shows respiratory alkalosis. Toxicology screening results was positive only for methamphetamines. We intubated him by Rapid Sequence Intubation (RSI) method and then took an emergent abdominal CT scan for any need for surgical intervention. We admitted him in ICU ward and did supportive care including the control of agitation, autonomic instability and hyperthermia. After 2 days we could extubate him and after 5 days he discharged from hospital.

Discussion

Although the first reports of serotonin syndrome date back to the 1950s, the majority of the literature has been published in recent times. It is theorized that blocking the reuptake of serotonin in the synapse, thereby flooding postsynaptic receptors, and this overstimulation, especially at 5-hydroxytryptamine 2A (5-HT_{2A}) receptors and possibly 5-HT_{1A} receptors, produces the main symptoms of this syndrome [15]. Also, serotonin receptors are found centrally and peripherally, thereby affecting multiple organ systems, including the gastrointestinal tract, cardiovascular, and central nervous systems [16]. Other neurotransmitters may be affected, worsening symptom severity and clinical outcome, with norepinephrine being the most frequently implicated [15].

The emergence of symptoms occurs rapidly after a medication change, with close to 60% of patients seeking help within 6 hours of onset [15]. However, a delayed response can be seen in up to 7% of patients, generally older patients, resulting from age-related changes in serotonin receptors and neurotransmission. After discontinuation of the offending agent and initiation of treatment, symptoms typically resolve within 24 hours. It is important to note that the amount of the offending agent taken and its pharmacokinetics may not permit such a quick recovery [17]. Approximately 40% of patients will have persistent symptoms, and the incidence of mortality is estimated to range from 2% to 12% [17].

A diagnosis of serotonin syndrome can be made clinically after recognition of the signs and symptoms and careful review of a patient's medications. The triad of altered mental status, autonomic dysfunction, and neuromuscular abnormalities characterizes serotonin syndrome, and is a result of excess central and peripheral nervous system serotonergic activity [18,19]. Radomski et al. revised the diagnostic criteria for serotonin syndrome, which requires the addition of or increased dose of a serotonergic medication along with at least 4 major symptoms or 3 Major plus 2 minor symptoms (Table 1) [19,20]. Also, the symptoms cannot be due to a preexisting psychiatric disorder; an infectious, toxic-metabolic, or endocrine cause; or recent treatment with a neuroleptic agent. Clinical suspicion of serotonin syndrome and recognition of presenting signs and symptoms are fundamental to diagnosis and treatment.

There are no standardized pharmacological therapies for serotonin syndrome; however, benzodiazepines, cyproheptadine, and chlorpromazine have been reported to be helpful in severe cases, patients may require antihypertensive for high blood pressure, sedation, intubation and mechanical ventilation, and cooling blankets for hyperthermia [18,20,21].

Discontinuation of the offending agent and supportive care are the first steps in treating serotonin syndrome. Pharmacological treatment centers on cyproheptadine as the treatment of choice, although there is a lack of studies supporting its efficacy. Some patients may not respond to treatment with cyproheptadine or may require adjunctive medications. Additional treatment should focus on controlling specific symptoms—administering blood pressure medications for hypertension and benzodiazepines for agitation [22].

1. Addition of a serotonergic agent to an already established treatment (or increase in dosage) and manifestation of at least 4 major symptoms or 3 major symptoms plus 2 minor ones
- Mental (cognitive and behavioral) symptoms**
Major symptoms: confusion, elevated mood, coma or semicomatose
Minor symptoms: agitation and nervousness, insomnia
- Autonomic symptoms**
Major symptoms: fever, hyperhidrosis
Minor symptoms: tachycardia, tachypnea and dyspnea, diarrhea, low or high blood pressure
- Neurological symptoms**
Major symptoms: myoclonus, tremors, chills, rigidity, hyperreflexia
Minor symptoms: impaired co-ordination, mydriasis, akathisia
2. These symptoms must not correspond to a psychiatric disorder, or its aggravation, that occurred before the patient took the serotonergic agent.
 3. Infectious, metabolic, endocrine or toxic causes must be excluded.
 4. A neuroleptic treatment must not have been introduced, nor its dose increased, before the symptoms appeared.

Table 1: Radomski's Revised Diagnostic Criteria for Serotonin Syndrome.

Our patient presented with several symptoms of serotonin syndrome according to Radomski Revised Diagnostic Criteria for Serotonin Syndrome, which quickly progressed in severity over the course of a few hours. We admitted him in ICU ward and did supportive care including the control of agitation, autonomic instability and hyperthermia, with intubation and administering of benzodiazepines and active cooling. After 2 days we could extubate him and after 5 days he discharged from hospital. This case illustrates that serotonin syndrome can occur idiosyncratically after ingestion of methamphetamine and could be treated with supportive care only without administration of cyproheptadin.

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