Proceedings of UCLA Healthcare
-VOLUME 18 (2014)-

CLINICAL VIGNETTE

The Serotonin Syndrome

Neil Patel, M.D.

Case Presentation

A 46-year-old male was brought from his home to the Emergency Department by the paramedics. His chief complaint was the complaint of a "seizure". On arrival to the ED, the patient was unable to provide a history, however EMS stated that the patient's girlfriend had found him in bed, unresponsive and "shaking all over." No true tonic-clonic movements were noted. Blood sugar was 180 in the field and past medical history included PTSD and hypertension. The patient was reportedly taking paroxetine 50mg and hydrochlorothiazide 25mg daily. There was no history of prior seizures.

On arrival in the ED, his rectal temperature was 38.8°C, BP 196/110, pulse 122, respiratory rate 20 and O2 saturation 99% on room air. The patient was to be non-verbal and had an intact, though diminished gag reflex. A rapid neurological exam revealed reactive pupillary mydriasis, a fine tremor in both upper and lower extremities, increased bilateral lower extremity tone with inducible clonus and exaggerated patellar and heel deep-tendon reflexes. The patient localized to painful stimuli with both upper extremities. He was also noted to be rather diaphoretic with hyperactive bowel sounds and slightly increased oral salivation. The remainder of the exam was unremarkable.

Given the patient's mental status, he was intubated for airway protection using etomidate and succinylcholine and was immediately sent for a CT Head that was negative for acute disease process. During this time, telephone contact with the patient's girlfriend revealed that 6 hours prior to EMS activation, the patient had consumed approximately a half-bottle (200cc) of over-the-counter dextromethorphan cough syrup in an attempt to relieve a dry cough that he had been suffering from for the past 2 days.

A preliminary diagnosis of serotonin syndrome was made and the patient was given 12mg of cyproheptadine, a serotonin receptor antagonist via nasogastric tube. Chest x-ray revealed no acute infiltrate and the rest of the patient's ED work-up was negative for an infectious etiology, and the patient was admitted to the ICU for close observation.

In the ICU, the patient's mental status gradually improved and he was extubated. No significant laboratory derangements were noted. The patient was discharged home with a diagnosis of serotonin syndrome. He was taught which medications to avoid when taking an SSRI such as paroxetine.

Discussion

Serotonin syndrome is thought to result from the over-stimulation of serotonin (5-HT) receptors in the CNS, usually as the result of pharmacological agents. This is usually due to an overdose of a single serotonergic agent (such as an SSRI) or less commonly, from a drug-drug interaction between two or more serotonergic drugs that results in excess levels of 5-HT in the synaptic cleft[1]. Indeed, approximately 10% of single-agent SSRI overdose cases resulted in the serotonin syndrome[2]. Often, the offending agent is not commonly known to have serotonergic properties and thus therapeutic misadventure can easily result. A survey done in the UK in the late 1990s revealed that approximately 85% of clinicians were unaware of the existence of the serotonin syndrome[3]. Therefore, it is not surprising that commonly prescribed medications such as dextromethorphan, meperidine and tramadol can lead to the serotonin syndrome when combined with the SSRI class of antidepressants[4].

In addition, commonly available drugs of abuse such as cocaine, methylenedioxymethamphetamine (MDMA or "ecstasy") and lysergic acid diethylamide (LSD) can lead also precipitate this syndrome when combined with SSRIs. Caution should also be exercised when combining SSRI with other psychotropic medications such as tricyclic antidepressants (TCAs), MAOIs and lithium as well as with the anti-emetics odansetron and metoclopramide[5]. Therefore, it is of vital importance that clinicians familiarize themselves with the serotonin syndrome and check for drug-drug

interactions that can lead to this potentially fatal syndrome.

The serotonin syndrome is exclusively a clinical diagnosis without any confirmatory laboratory or radiographic findings. It is often thought of as a clinical triad involving autonomic hyperactivity, alteration in mental status and neuromuscular dysfunction. However, as with many classic triads, not all features are necessarily present in all patients[5].

To assist clinicians in the diagnosis of this syndrome, the Hunter Serotonin Toxicity Criteria, have been developed which report a sensitivity and specificity of 84% and 97%, respectively in identifying this syndrome[6]. According to these criteria, a patient must have exposure to a serotonergic agent along with one of the following:

- Spontaneous clonus
- Inducible clonus + agitation or diaphoresis
- Ocular clonus + agitation or diaphoresis
- Hypertonia
- Temperature >38°C + inducible or ocular clonus

As is expected, the serotonin syndrome can range in severity from mild to severe and can be life-threatening. Symptoms tend to manifest within several hours of taking the offending agent[5]. At the mild end of the spectrum, patients may exhibit only a mild tremor and possibly hypertension, whereas in its severe form, patients can be severely hyperthermic and increased neuromuscular activity can lead to rhabdomyolysis and acute renal failure.

A review of 127 cases reported the most common clinical findings were myoclonus, hyperreflexia, tachycardia, confusion, hyperthermia and diaphoresis. They also found that serum levels of serotonergic drugs was either therapeutic or sub-therapeutic, making the syndrome possible even in the absence of overdose[7]. Therefore, a high index of suspicion must be maintained for this diagnosis in the correct clinical setting.

As can be imagined, the differential diagnosis for a patient presenting with the signs and symptoms of the serotonin syndrome is diverse and includes hypoglycemia, intracranial hemorrhage, sepsis, cocaine/amphetamine ingestion, alcohol/benzodiazepine withdrawal and seizure. However, the neuroleptic malignant syndrome (NMS) and malignant hyperthermia are most often confused with the serotonin syndrome. In NMS, one often finds that there is a ”lead-pipe” rigidity to the musculature rather than clonus and history suggests the intake of a neuroleptic (rather than a serotonergic) agent, making the two entities clinically distinguishable[8]. Malignant hyperthermia, on the other hand, usually occurs within minutes after administration of succinylcholine or an inhaled anesthetic and presents with hyporeflexia (rather than the hyperreflexia of serotonin syndrome)[9].

Once the diagnosis is suspected, treatment generally focuses on supportive care and the cessation of all serotonergic agents. Protection of the airway is the highest concern and patients with persistent altered mental status should be intubated. Patients with significant neuromuscular activity leading to hyperthermia and/or rhabdomyolysis, intubation and skeletal muscle paralysis with long-acting non-depolarizing agents such as vecuronium should be highly considered[10].

Once the airway is stable and serotonergic drugs have been discontinued, treatment focuses on the normalization of vital signs and chemical sedation of the agitated or anxious patient. IV crystalloid fluids should be provided to restore intravascular volume and replace increased insensible losses from elevated neuromuscular activity. Benzodiazepines should also be used to achieve chemical sedation as physical restrains will not reduce neuromuscular activity and puts patients at increased risk of rhabdomyolysis[11]. Indeed, benzodiazepines have been shown to improve survival in animal models[12, 13].

Though shown to be effective in only small trials, adjunctive treatment with 5-HT receptor antagonists such as cyproheptadine remains the recommended therapy for moderate to severe cases of the serotonin syndrome[13, 14]. Cyproheptadine acts as a $5HT_{1A}$ and $5\text{-}HT_2$ receptor antagonist, and should be given at an initial adult dose of 8 to 12 mg, followed by 2 mg every two hours until a clinical response is achieved[15]. Of note, this drug is only available in oral form and is administered via nasogastric tube in intubated patients. In severe cases, chlorpromazine (a neuroleptic agent with non-specific serotonin receptor antagonism properties) can be used in doses of 50 to 100 mg and can be given parenterally (either IM or IV). However, one must be sure to differentiate serotonin syndrome from the neuroleptic malignant syndrome as use of chlorpromazine can exacerbate the latter condition[13].

Patients will typically improve within 24 to 72 hours with the cessation of all serotonergic agents and the selective use of the above therapies, as was noted in our subject patient[5]. The key in limiting morbidity and mortality from the serotonin syndrome lies in its prevention. Therefore, it is critically important that

clinicians become aware of this rare, though clinically important, syndrome and take measures, such as the use of electronic pharmacopeias and medication reconciliation, to ensure that drugs they are prescribing do not interfere with serotonergic agents that a patient may already be taking.

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Submitted on November 21, 2013