Serotonin Syndrome With Quetiapine, Rizatriptan, Gabapentin, and Propranolol

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Serotonin syndrome (SS) is a potentially fatal medical emergency caused by increased serotonergic activity in the central and peripheral nervous systems. Diagnosis is based on clinical presentation, characteristically a triad: mental status alterations, autonomic dysfunction, and neuromuscular excitation. While severe symptoms and common culprit-offending agents can trigger clinicians' consideration of SS, research still supports that SS is often mistaken or misdiagnosed, leading to the true incidence being unknown.[1] In such cases, subsequent administration of serotonergic drugs can result in rapid deterioration and death. This case describes a middle-aged man with quetiapine-induced SS.

Case Report

A 58-year-old man presented to the emergency department (ED) due to muscle stiffness, uncontrollable limb movements, and the sensation as if his body was on fire. He reported discontinuing Suboxone 3 days prior, so initial suspicion was opioid withdrawal. Vitals were blood pressure of 160/70 mm Hg, heart rate of 104 bpm, and oxygen saturation of 91%. Medications prior to admission included quetiapine, rizatriptan, propranolol, and gabapentin. He had an abnormal laboratory urine drug screen (UDS), which was positive for buprenorphine, cannabinoids, and tricyclic antidepressant. Creatine phosphokinase (CPK) was elevated at 1,225 U/L.

Initial differential diagnosis included opioid withdrawal, acute encephalopathy, and rhabdomyolysis. Following psychiatry consult, suspicion was early SS, and serotonergic agents were held. On further review and assessment, he met the Hunter criteria for a diagnosis of SS. Clonus started to improve, and his CPK level trended down. He was monitored overnight and discharged home the following day with symptom resolution. He was recommended to stop taking methylprednisolone and rizatriptan and to slowly taper off quetiapine and gabapentin with no other prescription changes.

He presented the following month to the ED with increased psychomotor agitation. He was assessed and discharged home with a primary diagnosis of unspecified anxiety disorder.

The next day, he returned to the ED with worsening psychomotor agitation, agitation, hypervigilance spontaneous clonus, hyperreflexia, tactile hallucinations, and involuntary clonus of all extremities. Vital signs showed a low-grade fever of 100°F, respiratory rate of 22 breaths/minute, and an oxygen saturation of 92%. Medication review indicated that the patient was recently restarted on rizatriptan and was still taking quetiapine and propranolol. The UDS was positive for buprenorphine and benzodiazepines. Using the Hunter criteria, SS was the primary diagnosis.

Propranolol, rizatriptan, and quetiapine were identified as possible offenders and stopped. There was a subsequent reduction in autonomic and neuromuscular symptoms over the next 48 hours. Remaining symptoms were now better explained by opioid withdrawal, as sufficient time had passed for washout of offending agents and was within the predicted timeframe for withdrawal from the patient's last reported use of opioids. Following treatment for opioid withdrawal, he was discharged home without quetiapine.

Discussion

In management of SS, the first principle is to discontinue all serotonergic agents. If mild, only supportive care may be required. If moderate to severe, it is important to control agitation and repetitive muscle movements with benzodiazepines. Serotonin antagonists are used if benzodiazepines and supportive care fail to correct vital signs or agitation.

Antipsychotics are contraindicated to address agitation due to their serotonergic activity. Antipyretics are also futile, as the hyperthermia is a result of increased muscular activity rather than alteration in hypothalamic set point. If the temperature exceeds 106°F, immediate sedation, neuromuscular paralysis, and intubation are required.[2]

Historically, there has been diagnostic controversy. In the 1990s, the Sternbach criteria were released, outlining 10 nonspecific clinical features and requiring the presence of at least 3 of those findings in the setting of a serotonergic agent.[3] However, it did not require there to be any neuromuscular symptoms, so there were other nonserotonergic-related diseases that technically met criteria for SS. Radomski's proposed criteria, published in 2000 and gaining broader recognition in 2001, were more specific, adding rigidity and categorizing criteria as major or minor.[4] The latest research recommends utilizing the Hunter criteria, which are considered the most accurate and clinically practical diagnostic tool for serotonin syndrome.[2,5] These criteria require recent exposure to a serotonergic agent and the presence of one of several characteristic findings: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis;

tremor with hyperreflexia; or hypertonia with fever and either ocular or inducible clonus. Unfortunately, mild cases of SS can be easily missed, which can lead to the continuation of the offending agents and progression into more severe presentations.[6] This case highlights the necessity of considering SS on a differential diagnosis, as a misdiagnosis can be fatal. It also highlights the importance of knowing which medications have serotoninergic activity.[7] This patient was on 4 different classes of medications that all had serotonergic effects, with none of them being a selective serotonin reuptake inhibitor, which might alert providers to consider SS. In this case, SS led to 3 ED visits and 2 hospital admissions. The initial differential diagnosis did not include SS, and SS was only considered once the initial differential diagnoses were ruled out. Given the rates of polypharmacy, as well as the rise in prescribing serotonergic agents, further research would be beneficial to better recognize and distinguish early or mild SS.

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