CLINICAL VIGNETTE

Doctor, I Can't Stop Shaking!

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Case Report

A 71- year old male with metastatic prostate cancer, chronic kidney disease, coronary artery disease, and aortic stenosis was hospitalized after a fall. His hospital course was complicated by pneumonia, sepsis, and atrial fibrillation with rapid ventricular rate. Outpatient medications included duloxetine, trazadone and as needed lorazepam. Additionally, his chronic pain from metastatic prostate cancer was treated with chronic opioids including scheduled and prn oxycodone. During the hospitalization, his longstanding anxiety and insomnia were exacerbated by his underlying illness and functional decline. Psychiatry was consulted and recommended the addition of buspirone.

He was subsequently discharged to a skilled nursing facility for rehabilitation. Despite the changes in medications, his anxiety worsened. He developed tremors, agitation and became more altered. He also developed nausea, abdominal pain and diarrhea. On exam, he had hemodynamic instability, diaphoresis and lower extremity myoclonus.

The constellation of symptoms, raised concern for serotonin syndrome. The combination of medications including duloxetine, trazodone, oxycodone and recent addition of buspirone, produced excess serotonin levels with altered mental status, autonomic instability and neuromuscular changes. Several suspected medications, were reduced and his symptoms eventually improved without aggressive intervention or significant sequelae from increased serotonergic burden.

Discussion

Serotonin syndrome is a condition associated with excessive serotonergic activity and postsynaptic hyperstimulation of serotonin receptors in the central and peripheral nervous system.[1] Serotonin causes the following effects: excitation/ inhibition of CNS neurons; stimulation of peripheral nociceptive nerve endings; vascular effects; and constriction from direct and via sympathetic innervation.[2] Serotonin excess can result from the following mechanisms: increased synthesis, increased release, increased receptor agonist activity, increased receptor sensitivity, decreased metabolism, and impaired reuptake from synaptic cleft to the presynaptic neuron.[3] Any medications or combination of medications that can increase the concentration of serotonin will increase risk of serotonin syndrome. Risk of serotonergic toxicity increases when multiple, culprit pro-serotonergic agents are used concomitantly. This can be potentially life threatening.

Polypharmacy and drug-drug interactions potentiate risk and can be a major concern in older adults. The pharmacodynamic and pharmacokinetic interactions of certain medications, including agonists, antagonists, and reuptake inhibitors, in serotonin syndrome can be complex. Some examples of drugs in these categories, are listed, although they are not all-inclusive. Some medications that decrease metabolism include: monoamine oxidase inhibitors and linezolid. Drugs that increase release include: amphetamines, cocaine, and opioids such as oxycodone. Agents that increase receptor agonist activity include: triptans, mirtazapine, and buspirone. A medication that augments sensitivity is lithium. Finally, psychotropics that reduce reuptake include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) like duloxetine, anti-emetics such as ondansetron, and other antidepressants like trazodone.[3]

Serotonin syndrome can result from any combination of drugs that increase the net effect of serotonergic neurotransmission. For example, trazodone inhibits serotonin reuptake, but also blocks 5-HT2A/C receptors and thus increases serotonergic concentration.[4] Antagonistic activity of certain 5-HT receptors can increase the sensitivity and lower the threshold of other receptors. In addition, certain antipsychotics have antagonistic effects with serotonin, but also can promote serotonergic activity of other drugs and increase the risk for serotonin syndrome.[5,6]

Numerous other medications, such as opioids, anti-emetics, antispasmodics, and anti-convulsants may significantly affect the pharmacokinetics and pharmacodynamics of other serotonergic agents, causing increased serotonin levels.[3] Some more obvious medications such as SSRIs have notable serotonergic activity and increase serotonin levels in the synaptic cleft. However, other less obvious medications when combined, can augment the serotonergic effect. Examples of less obvious drugs include opioid analgesics, certain anti-emetics, antibiotics and over-the-counter medications and herbal supplements.[6] Oxycodone is a centrally acting synthetic morphine analog acting on μ and κ receptors to provide analgesia. It can cause increased serotonergic activity by causing increased serotonin release or by mimicking serotonin activity via direct action on postsynaptic membranes.[7,8] In this

case, the patient had several medications that increased the serotonergic concentration including: oxycodone, duloxetine, trazodone and buspirone. Buspirone, was the new agent that increased receptor agonist activity and likely offset the serotonergic burden and precipitated serotonin syndrome.

The "classic" triad of serotonin syndrome consists of: 1) mental status changes, 2) autonomic hyperactivity, and 3) neuromuscular changes.[1,9] Altered mental state can include agitation, anxiety, confusion or stupor. Autonomic dysfunction and hyperactivity may present as labile blood pressure and heart rate, hyperthermia, dysrhythmias, flushing, sweating and mydriasis. Neuromuscular dysfunction can manifest as rigidity, hyper-reflexia, tremors and myoclonus. However, as with many triads, all three elements may not present in majority of patients and requires a lower index of suspicion with the subtle presentation of symptoms.

Older adults can develop more subtle and vague presentation of symptoms that can make the diagnosis more challenging. It requires judicious use of serotonergic medications and their additive effects. The presentation can be more indolent with gradual progression of symptoms and varied sequelae. The progression can start as akathisias and tremors, then inducible clonus that leads to sustained clonus, rigidity, hyperthermia, seizures, and coma. If left untreated, serotonin syndrome can be fatal. Clonus and rigidity are often more pronounced in the lower extremities, and once severe muscular rigidity develops, it may mask the clonus or hyper-reflexia. [9]

Serotonin syndrome is a clinical diagnosis that relies on the constellation of excess serotonin symptoms in association with the use of serotonergic agents. There are no clear diagnostic criteria, although more comprehensive evaluation may be necessary to narrow the differential diagnosis. In addition to routine laboratory and infectious workup, further studies may include blood gas, cardiac monitoring, labs for creatinine kinase and coagulation studies, urine for myoglobin and drugs of abuse, and head imaging depending on clinical status.[9]

Treatment requires immediate discontinuation of the offending agents and timely supportive care in the appropriate setting. Agitation and tremors may require sedation with benzodiazepines.[9] Antipsychotic agents should be avoided due to concerns for worsening motor symptoms. The patient should be moved to a critical care setting if ongoing, continued monitoring is needed or if organ support is required. Hyperthermia may benefit from the use of 5-HT2A antagonists such as cyproheptadine; however, severe elevations in temperature (>41.1C) should be managed with immediate sedation, neuromuscular blockade, and intubation.[3,9] It is important to understand that antipyretics such as acetaminophen are not effective for hyperthermia due to muscular activity causing raised temperature rather than alteration in hypothalamic thermoregulation mechanisms. After the resolution and stabilization of symptoms, it is prudent to re-evaluate further use of the causative serotonergic medications, with the goal to minimize risk of future episodes. It is essential to evaluate if aggressive interventions are appropriate in geriatric patients. Appropriate treatment should align with patient's goals of care to provide an individualized, patient-centered approach for older patient population.

Conclusion

Serotonin syndrome is a condition that results from excess serotonergic stimulation in the nervous system. The incidence of this syndrome appears to be increasing, and correlates with the widespread use of medications that increase serotonergic tone, including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Low index of suspicion for serotonin syndrome should lead to early identification of common and uncommon culprits in addition to immediate discontinuation of offending agents. Timely supportive care aimed at mitigating altered mental state, autonomic dysfunction and neuromuscular changes is key. Familiarity with drugs associated with serotonin syndrome and recognizing the manifestations of serotonin excess are paramount. Use of serotonergic agents, especially psychotropics in older patients with psychiatric disorders or cognitive impairment, warrants increased monitoring of behavioral improvement, side effects, drug-drug interactions, and definitive duration before continuation. Ongoing medication reconciliation should involve pragmatic de-escalation of serotonergic burden to prevent adverse events and potential sequelae in our growing, vulnerable older patient population.

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