

CASE REPORT**Hydromorphone Precipitating Serotonin Syndrome**Sijie Jason Wang¹¹Concord Hospital, Department of Hospital Medicine, 250 Pleasant St, Concord, NH 03301

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Opioid medications are an underappreciated cause of serotonin syndrome. Fentanyl, meperidine, and methadone are more commonly associated with this potentially life-threatening side effect. Here, we present the case of a 60-year-old man taking duloxetine, oxycodone as needed, and long-acting hydromorphone for chronic pain, who developed serotonin syndrome two days after his hydromorphone dose was increased. Due to severe agitation he required intubation and his course was notable for marked adrenergic instability. Eventually, he improved after treatment with benzodiazepines and cyproheptadine. This case highlights a rare synergistic effect from the combination of hydromorphone, duloxetine, and oxycodone resulting in serotonin syndrome.

OBJECTIVE:

To alert clinicians about the risk of hydromorphone precipitating serotonin syndrome when given in conjunction with other serotonergic agents.

BACKGROUND:

Chronic pain is a challenging disorder to treat and is frequently associated with depression and anxiety. Opioids are often combined with serotonergic agents, where the serotonergic drugs may be used to treat concomitant psychiatric illness, or directly to treat pain itself. However, there remains a great deal of uncertainty regarding optimal drug combinations and potentiation of side effects.¹

Serotonin syndrome is a severe adverse reaction, which is typically associated with serotonergic drugs, such as selective serotonin reuptake inhibitors

(SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics, as well as illicit substances, such as ecstasy (MDMA) or amphetamines. However, there are a huge number of other drugs that act upon the serotonergic system in unpredictable ways, which may not always be apparent to the prescriber. The syndrome is characterized by a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities, but not all three need to be present to make the diagnosis.²

Most clinicians would probably not consider opioids to play a major role in serotonin syndrome, although certainly some specific agents, such as meperidine, have become well-known for this effect, as seen with the unfortunate case of Libby Zion. Nevertheless, the FDA has started to warn that all opioids may have this effect.³ This case report describes a patient who was taking a regimen for chronic pain with SNRI and opioids, and unfortunately developed

severe serotonin syndrome after his hydromorphone dose was increased.

CASE PRESENTATION:

A 60-year-old male presented to the Emergency Department (ED) due to anxiety. He had a history of coronary artery disease, paroxysmal atrial fibrillation, chronic obstructive pulmonary disease, spinal stenosis status post L3-L5 decompressive surgery, and residual back pain treated with chronic oral narcotics. His medication list is shown in Table 1. He had been noted by his primary care physician to be highly compliant with medications and was on a chronic narcotic contract.

Two days prior to presentation, the patient's oral hydromorphone dosage had been increased from 16 mg to 24 mg/day. After this medication change, the patient became acutely restless and agitated. He could not sleep at all the previous night. His wife went to work in the morning, and when she came that home in the evening she found him incredibly frantic, pacing, anxious, and unable to sit still.

In the ED his vitals were noted to be highly labile. His systolic blood pressures ranged from 93 to 183 mmHg and diastolic pressures ranged from 52 to 110 mmHg. He was afebrile. His heart rate ranged from 100 to 140 beats per minute. His respiratory rate was 20 breaths per minute. He appeared diaphoretic, could not lay still in the bed, and was noted to be pacing restlessly. Cardiopulmonary examination was unremarkable except for tachycardia. On neurologic exam, he was noted to have hyperreflexia throughout, inducible sustained myoclonus in the lower extremities bilaterally, and bilateral upgoing toes. No overt muscle rigidity was noted.

He was given several doses of intravenous lorazepam (6 mg total), but became increasingly combative. He was finally intubated due to his altered mental status and concern for airway compromise.

His initial laboratory values, including complete blood count, electrolytes, thyroid stimulating hormone, hepatic function tests, and urine drug screen were unremarkable. His lumbar puncture and computed tomography scan of the head were also unremarkable.

Table 1. Patient's medication list. All routes are oral unless specified.

Aspirin 81 mg daily
Albuterol metered dose inhaler, 90 mcg/actuation, 2 puffs inhaled every 4-6 hours as needed for wheezing
Baclofen 10 mg three times daily
Duloxetine 60 mg twice daily
Docusate 100 mg as needed for constipation
Fluticasone-salmeterol 100/50 mcg 1 puff inhaled twice daily
Furosemide 20 mg daily
Hydromorphone sustained-release 24 mg daily
Lisinopril 20 mg daily
Metoprolol succinate 100 mg daily
Oxycodone 5 mg daily as needed for breakthrough pain
Rosuvastatin 40 mg daily
Sildenafil 50 mg as needed for erectile dysfunction
Spirolactone 12.5 mg daily
Warfarin (dose varies)

The patient's presentation was felt to be consistent with serotonin syndrome precipitated by the hydromorphone dose increase and fulfilled the Hunter criteria (see discussion). He was sedated with midazolam and dexmedetomidine, and cyproheptadine was started at a loading dose of 12 mg, followed by 4 mg every 6 hours. He was extubated on hospital day #3, but remained delirious for several days thereafter. Over the next few days he also developed mild rhabdomyolysis and had intermittent fevers as high as 38.3°C with negative infectious workup.

He was eventually discharged from the hospital and has since tapered off duloxetine and hydromorphone completely. He remains on a small dose of oxycodone and has been started on gabapentin and medical cannabis.

DISCUSSION

The neurotransmitter 5-hydroxytryptamine, otherwise known as serotonin, is synthesized from the amino acid tryptophan. Its regulation, metabolism, and reuptake mechanisms are complex and will not be discussed in detail here. However, it is important to recall that the enzyme monoamine oxidase breaks down serotonin; hence, MAO inhibitors such as phenelzine can precipitate serotonin syndrome. Drugs which cause massive release of serotonin (such as ecstasy), inhibition of reuptake (such as SSRIs), or direct receptor agonism (such as fentanyl and buspirone) can cause serotonin syndrome. It is also important to recognize that hepatic cytochrome P450 enzyme inhibitors can increase drug levels.² For example, in one case, a child taking a stable dose of sertraline suffered serotonin syndrome after being exposed to erythromycin.⁴

Serotonin syndrome is a potentially life-threatening side effect of serotonergic drugs.

It can be diagnosed via the Hunter Criteria, which stipulates that the patient must be on a serotonergic agent and meet one of the following conditions⁵:

- Spontaneous clonus
- Inducible clonus PLUS agitation or diaphoresis
- Ocular clonus PLUS agitation or diaphoresis
- Tremor PLUS hyperreflexia
- Hypertonia PLUS temperature above 38°C PLUS ocular clonus or inducible clonus

Symptoms present relatively quickly after a medication is started or a dose is increased – typically within 24-48 hours. These symptoms occur along a spectrum of severity, which makes both initial diagnosis and prevention of progression challenging. Patients may experience some mild diarrhea or tremor which many clinicians may not associate with serotonin syndrome. Many patients may not report some of these symptoms to their physicians at all. More severe cases can cause autonomic instability, diaphoresis, mydriasis, hyperreflexia, clonus, or severe agitation as seen in this case. Interestingly, after his recovery, this patient recalled that he felt “like a kettle ready to boil” in the days leading up to the hydromorphone dose increase which ultimately precipitated the full-blown syndrome. He did not mention this to his physician, and it is very possible that even if he had, his vague complaint may not have been attributed to serotonin syndrome. After all, he was on a stable dose of duloxetine, and hydromorphone is not typically associated with the syndrome.

There is an increasing evidence that all opioids can precipitate serotonin syndrome, although the mechanisms are likely heterogeneous.^{3,6} This patient's reaction represents a dose-related adverse drug reaction caused by hydromorphone

dose increase in setting of stable chronic doses of duloxetine and oxycodone. Chronic pain is frequently treated with a combination of antidepressants and opioids.⁷ When prescribing this combination, clinicians must be aware of this potentially severe interaction.

Notes

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