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Serotonin Syndrome Associated with Metaxalone and Venlafaxine

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Abstract

Introduction: Metaxalone is a commonly prescribed muscle relaxant. However, due to its proposed mechanism of action as a weak monoamine oxidase inhibitor, it can interact with drugs with serotonergic activity instigating a potentially deadly set of symptoms identified as serotonin syndrome.

Methods and Results: This is a case of a 65-year old male with history of cryptogenic cirrhosis who was prescribed metaxalone while on the antidepressant venlafaxine, a serotonin and norepinephrine reuptake inhibitor. Shortly after starting metaxalone, he presented with symptoms of restlessness, diaphoresis, and clonus in extremities, fulfilling Hunter's Criteria for serotonin syndrome. Metaxalone is thought to have a weak monoamine oxidase inhibitor activity, which combined with a serotonin and norepinephrine reuptake inhibitor, resulted in serotonin syndrome. The patient was intubated to protect his airways and his symptoms were managed with supportive care, resulting in stabilization of his condition.

Conclusion: This case report highlights how unexpected drug-drug interactions can result in life-threatening situations. Therefore, stressing the importance of a thorough medical history, including the types of drugs in use. In this scenario, the patient had serotonin syndrome secondary to metaxalone and venlafaxine combination. Prescribers and patients taking serotonergic drugs should be aware of potential drug interactions that may result in serotonin syndrome when started on metaxalone.

Introduction

- Serotonin Syndrome (SS) is a life threatening pharmacological reaction that is caused by increased serotonergic activity in the nervous systems via multiple mechanisms such as increased serotonin synthesis, decreased serotonin metabolism, or inhibition of serotonin reuptake.^{2,4}
- Mild symptoms include tachycardia, shivering, diaphoresis, and mydriasis.
- Moderate symptoms include tachycardia, hypertension, hyperthermia with core temperature as high as 40°C, mydriasis, hyperactive bowel sounds, hyperreflexia and clonus noted in lower extremities more than upper extremities, mild agitation or hypervigilance, and possible horizontal ocular clonus.
- Severe symptoms include hypertension, tachycardia with possible shock, agitation with delirium, muscular rigidity and hypertonicity, hyperthermia, metabolic acidosis, rhabdomyolysis, renal failure, and disseminated intravascular coagulation (DIC).^{2,4}
- Diagnosis of SS is typically made by clinical judgment, but the Hunter Serotonin Toxicity Criteria aid in the diagnosis:³
 - Use of serotonergic agents within the past 5 weeks
 - Having any one of the following symptoms:
 - spontaneous clonus
 - inducible clonus and either agitation or diaphoresis
 - ocular clonus and either agitation or diaphoresis,
 - tremor and hyperreflexia
 - hypertonia with body temperature over 38°C and either ocular clonus or inducible clonus
- Metaxalone is a muscle relaxant where its mechanism of action is unknown, however, it may act as a CNS depressant as it is an oxazolindione structurally similar to toloxatone, which is a reversible MAOI.¹
- There are recent cases reported showing SS related to metaxalone.^{1,5}
- Here we report the case of a 65-year old male with history of cryptogenic cirrhosis who presented to the emergency room for SS after taking metaxalone and venlafaxine.
- The purpose of this report is to increase awareness of the possible induction of SS in patients taking metaxalone concomitantly with drugs that enhance serotonergic activity, like venlafaxine.

Case Presentation

Patient: 65-year-old male with history of cryptogenic cirrhosis had back pain resulting from a fall a week prior to his admission. Three days after his fall the patient was prescribed with metaxalone 800 mg and was advised to take ½ to 1 tablet every 8 hours. He took no more than 2 tablets per day, which did help alleviate his back pain.

Medical History: cryptogenic cirrhosis, right cerebral infarct with residual right hemiataxia, history of endocarditis with septic emboli, anxiety, and Major depressive disorder.

Home Medications: Venlafaxine, Spironolactone, Propranolol, Alprazolam, Rifaximin, Lactulose, and Quetiapine.

Social History: history of alcohol abuse, but last alcohol intake was a month prior to his admission. No history of tobacco or recreational drug use.

The night before admission, the patient took 1 tablet of metaxalone and rapidly started to become flushed and then severely diaphoretic two hours later. Although he was stable and mentating well, his wife noticed that he displayed odd behaviors.

On the morning prior to his admission, the patient's brother gave him 1 tablet of metaxalone, and he immediately had flushing and diaphoresis, and was taken immediately to the ED.

- Upon arrival in the ED, the patient appeared excessively diaphoretic, flushed, dilated pupils, febrile with temperature of 100.7°C, spastic calf muscles with Grade 4/4 deep tendon reflex bilaterally suggesting hyperreflexia with clonus at the ankles. He was agitated with aggressive behavior and appeared to be in moderate respiratory distress with audible wheezing present. He was subsequently intubated for airway protection.
- After the patient was intubated his condition stabilized. Urine and serum drug screens were all negative with the exception of serum metaxalone level, which was 11 µg/ml (peak plasma concentration averaged 0.9 µg/ml at 3.3 hours following a single 400 mg oral dose and 1.7 µg/ml at 3.0 hours following an 800 mg dose).
- Upon literature search of adverse side effects of metaxalone, it was learned that this medication may result in SS if combined with serotonergic drugs. The patient was on an SSRI drug, venlafaxine, which may have interacted with metaxalone to cause SS.
- The patient presented with inducible clonus, agitation and diaphoresis; fulfilling the Hunter Toxicity Criteria for Serotonin Syndrome.
- Supportive measures were initiated to treat serotonin syndrome, with metaxalone and venlafaxine held as part of the treatment.
- Gradually patient's confusion improved and his mental status returned to baseline.
- In addition to SS, the patient also had hepatic encephalopathy with elevated ammonia levels and was treated with lactulose and rifaximin.
- Due to history of cryptogenic cirrhosis, the patient had abdominal ascites and subsequently underwent paracentesis.
- He had limited upper gastrointestinal bleeding secondary to moderate portal hypertensive gastropathy and small amount of gastric varices, for which it was recommended by gastroenterologist to continue on beta blocker (propranolol) and proton pump inhibitor.
- Patient was transferred to rehabilitation in stable condition with discontinuation of metaxalone and resuming venlafaxine along with the rest of his home medications.

Discussion

- SS occurs when there is increased amount of serotonin neurotransmitters at synapses. SSRI drugs such as venlafaxine function by inhibiting reuptake of serotonin back into the presynaptic neurons.
- Metaxalone has been correlated to SS, especially when given in addition to drugs with serotonergic activity.
- Metaxalone is an analog of oxazolindione, which also includes the antibiotic linezolid.⁵ Linezolid was initially developed as an antidepressant due to having a reversible monoamine oxidase inhibitory activity (MAOI).⁵
- MAOIs function by preventing the breakdown of serotonin. Therefore because of its suggested MAOI activity, Metaxalone may cause SS via overdose or in combination with serotonergic drugs.¹
- Bosak and Skolnik presented a suicide case of a 23-yr old female in 2014 who took 12 grams of metaxalone and 1.5 grams of tramadol. Tramadol is said to increase serotonergic activity by stimulating serotonin release from presynaptic neurons and also to inhibit reuptake of serotonin back into the presynaptic neurons. The patient developed SS within 12 hours of drug ingestion with symptoms of somnolence, diaphoresis, and rigid lower extremities with sustained spontaneous and inducible clonus. Her serum metaxalone level was 34 µg/mL (mean peak plasma concentration 0.87 µg/mL at 3.3±1.2 h following 400-mg dose). She was intubated and treated symptomatically to control her seizure and fever. The patient gradually stabilized, was extubated, and was discharged home.
- Martini et al. in 2015 presented a case of a 27-year old male with history of chronic neck pain and depression who took three extra tablets of metaxalone 800 mg for back pain relief. He was also taking escitalopram, an SSRI, for depression. The combination resulted in SS with symptoms of agitation, confusion, diaphoresis, ocular clonus and hyperreflexia in lower extremities with sustained clonus. His serum metaxalone level was 58 µg/mL. He was treated symptomatically by controlling his agitation with IV diazepam and fluids. Gradually the patient returned to baseline mental status and was discharged home.
- In both cases, the patients were treated with supportive care for SS, similar to our 65-year old patient.
- The two cases mentioned were reports that occurred within 2 years since our case happened. It is very much possible that there were more cases of SS associated to metaxalone in the past that were unreported or undiagnosed.
- It is essential that prescribing physician are familiar with these drug interactions. There are numerous patients who have chronic pain syndrome and depression and thus get prescribed with anti-depressants and muscle relaxants for symptom relief. However when there is an increased awareness about these adverse drug reactions, there would be increased cautiousness prior to prescribing these combination, especially when it comes to patient safety.

Conclusions

- This is a case report of a 65-year old male who presented with serotonin syndrome secondary to metaxalone and venlafaxine drug interactions. SS resulted from the weak MAOI activity of metaxalone, combined with the SSRI venlafaxine.
- The patient was treated via supportive care and gradually recovered to neurologic baseline and was discharged to rehabilitation in stable condition.
- The purpose of this case report is to raise awareness when treating patients with history of chronic pain syndrome and depression and in need of pain management, especially in the elderly population.
- By increasing awareness, prescribers should be more cautious of ordering metaxalone for pain relief in patients with history of depression and on SSRIs or SNRIs to avoid harmful drug reactions such as SS.
- It is also important to identify early signs of SS to initiate treatment rapidly.
- At the same time patients should also be wary when taking muscle relaxants and anti-depressants together as the combinations of the two drugs can be life threatening.

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