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Transient Serotonin Syndrome Caused by Concurrent Use of Tramadol and Selective Serotonin Reuptake Inhibitor

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Female, 44
Final Diagnosis: Serotonin syndrome
Symptoms: Altered mental status • random spontaneous jerky movements in the extremities • generalized weakness • vomiting
Medication: —
Clinical Procedure: Holding SSRI and tramadol
Specialty: Critical Care Medicine

Objective: Rare disease
Background: Serotonin syndrome is a potentially life-threatening adverse drug reaction that most commonly results from adverse interactions between drugs. Because serotonin syndrome can be fatal and is often difficult to diagnose, it is vital for health professionals to know about this reaction. We report a typical case of transient serotonin syndrome secondary to tramadol-Citalopram combination. This case report highlights the value of awareness of the early and subtle signs of serotonin syndrome.
Case Report: A 44-year-old female with past medical history of chronic pancreatitis, back pain, and major depression was brought to the emergency room (ER) with altered mental status, jerky movements in extremities, generalized weakness, and vomiting.
Conclusions: Most physicians are aware of serotonin syndrome secondary to antidepressants but do not think about other classes of medications such as analgesics. Clinicians should also be aware of the possibility of serotonin syndrome when encountering a patient taking serotonergic drugs who presents with characteristic symptoms of serotonin syndrome.

MeSH Keywords: Depression • Serotonin Syndrome • Tramadol

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/892264>

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Background

Serotonin syndrome is potentially a life threatening adverse drug reaction that most commonly results from adverse interactions between drugs [1]. The incidence of this syndrome is increasing with common use of SSRIs and other drugs that have serotonergic effects or that inhibit the cytochrome P450 enzymes that metabolize these agents. Serotonin syndrome is characterized by a triad of altered mental status, autonomic symptoms, and neurological symptoms. It is considered to be caused by excessive stimulation of the 5-HT_{1A} receptors in the gray matter and spinal cord of the central nervous system [2].

There are few published case reports describing serotonin syndrome with combined use of tramadol in combination with selective serotonin reuptake inhibitors or selective serotonin/norepinephrine reuptake inhibitors [3–8]. Because serotonin syndrome can be fatal and is often difficult to diagnose, it is vital for health professionals to know about this reaction. We report a typical case of transient serotonin syndrome secondary to tramadol-Citalopram combination. This case report highlights the value of awareness of the early and subtle signs of serotonin syndrome.

Case Report

A 44-year-old female with past medical history of chronic pancreatitis, back pain, and major depression was brought to the emergency room (ER) with altered mental status, random spontaneous jerky movements in the extremities, generalized weakness, and vomiting. In the ER the patient was having intermittent irregular jerky movements in the extremities. Initial labs (CBC, LFT, drug screen) were normal, BMP showed sodium 131 mEq/L, potassium 6.2 mEq/L, chloride 88 mEq/L, bicarbonate 12 mEq/L, BUN 162.8 mg/dL, creatinine 10.50 mg/dL, estimated creatinine clearance 6.90 mL/min, acetaminophen level 26 mcg/mL, WBC 13.5 thou/mcL, HGB 11.0 gm/dL, MCV 101 fL, and acetaminophen level of 26 mcg/mL. Urine drug screen was positive for opiates but negative for benzodiazepine. Her CT head and chest X-ray were normal. The patient had been taking acetaminophen-hydrocodone (5–300 mg) 1 tablet every 6 hours, citalopram 40 mg daily, clonazepam 1 mg 2 times a day, gabapentin 300 mg 3 times a day, lisinopril 5 mg daily, and tramadol 100 mg every 6 hours as needed at home. She was transferred to the ICU for further management. She was not able to give a history because of altered mental status. Her blood pressure was 86/76 mm Hg, heart rate was 101 beats/min, respiratory rate was 27 breaths/min, and body temperature was 37°C. On physical examination, positive findings were abdominal tenderness on deep palpation, neurological examination was positive for confusion, tremors, generalized weakness, hyper-reflexia, and inducible and spontaneous

myoclonus without any focal neurological deficits. A central line was placed and 30 mL/kg normal saline fluid bolus was given. All the home medications were held. Further laboratory testing showed amylase 314 U/L and lipase 1764 U/L. After the initial fluid resuscitation, the patient became hypertensive and tachycardiac. Her renal functions rapidly improved over the next 2 days but hypertension, tachycardia, and neurological symptoms persisted over 4 days. Once the patient was stable, she told us that her primary care physician had started her on tramadol 100 mg every 6 hours as needed a week ago for better pain control and she was using the pain medications excessively. She had been taking the same dose of citalopram for the last 2 years without any adverse effects.

Discussion

The Toxic Exposure Surveillance System identified 46 244 and 48 279 cases of exposures to selective serotonin reuptake inhibitors (SSRIs) in 2002 and 2005, respectively [9,10]. The true incidence of serotonin syndrome, however, may be under-reported for a number of reasons. Manifestations may be falsely attributed to another cause, mild cases may be dismissed, or clinicians may not suspect the condition. A study reported that over 85% of physicians are unaware of serotonin syndrome as a clinical diagnosis [11]. Serotonin syndrome usually results from combined use of 2 or more serotonergic drugs, leading to exaggerated serotonin effects in the central nervous system. Serotonin syndrome can also result from overdosage of 1 serotonergic drug [12].

There are only a few case reports in the literature regarding serotonin syndrome secondary to concurrent use of SSRIs and tramadol. There are 2 possible explanations of serotonin syndrome secondary to the combination of SSRIs and tramadol. First, the literature suggests that higher plasma concentrations of tramadol and/or SSRIs escalate the risk of serotonin syndrome. Many patients tolerate this combination very well and develop serotonin syndrome only when the dose of 1 or both drugs is increased. Tramadol is metabolized in the liver through hydroxylation and glucuronide conjugation, which may slow the metabolism of an SSRI through competitive inhibition. Genetic defects resulting in CYP450 isozymes deficiency may also increase the risk of serotonin syndrome by increasing plasma concentrations of SSRIs because SSRIs are extensively hepatically metabolized by this isozyme [13]. Secondly, tramadol is a synthetic codeine analogue that binds to the mu receptors and inhibits the monoamine reuptake of 5HT. Both explanations are likely correct [14]. Serotonin syndrome patients present with neuromuscular signs, autonomic instability, and cognitive-behavioral changes in the setting of serotonergic medication use. Mostly symptoms occur when serotonergic medications are added to therapeutic SSRI regimens or after

taking an overdose of a serotonergic agent. A complete and accurate medication history is critical in making the diagnosis. The clinical manifestations of serotonin syndrome are highly variable. The diagnosis should be based on the Hunter Serotonin Toxicity Criteria or Sternbach's criteria, although Hunter's criterion is more sensitive (84% vs. 75%) but almost equally specific (97% vs. 96%) as compared to Sternbach's criteria [12].

Our case illustrates an example of the tramadol-Citalopram combination that resulted in typical features suggestive of serotonin syndrome (altered mental status, autonomic symptoms, and neurological symptoms). Concurrent use of acetaminophen/hydrocodone certainly could have been contributory to the presentation, but there was no clinical evidence for opioid toxicity such as miosis and respiratory depression; opioid toxicity was not believed to be responsible for the clinical presentation. Similarly, there were no features of acetaminophen toxicity such as diaphoresis or gastrointestinal symptoms. Benzodiazepine withdrawal was also considered owing

to unstable vital signs and muscular twitching, but was believed to be less likely given the negative toxicology report and non-adherence.

Conclusions

Most physicians are aware of serotonin syndrome secondary to antidepressants but do not think about other classes of medications such as analgesics. Concurrent administration of tramadol with SSRIs or SNRIs appears to increase the risk of serotonin syndrome. In patients who may require higher doses of tramadol, it would be reasonable to avoid the combinations. When prescribing multiple medications, clinicians should be aware of this entity and should avoid combining medications having pharmacodynamic and pharmacokinetic interactions. Additionally, clinicians should also be aware of the possibility of serotonin syndrome when faced with patients taking serotonergic drugs and presenting with characteristic findings of serotonin syndrome.

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