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Case Report Open Access

Serotonin Syndrome: Opportunity for Missed Diagnosis

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Abstract

Background: Serotonin syndrome is a clinical entity recognized with increasing frequency due to the prevalence with which pro-serotonergic drugs are prescribed and combined across the different medical fields. The common clinical presentation of serotonin syndrome involves autonomic instability, neuromuscular abnormalities, and mental status changes. Objectives: This case report seeks to describe a case where current recommendations regarding observation and disposition could have led to a missed diagnosis and disastrous results. Case Report: We present a 32-year-old female with depression, on daily selective serotonin reuptake inhibitor (SSRI) therapy, who presents after suicide attempt involving the pro-serotonergic agents fluoxetine (80mg) and tramadol (1600mg) and ultimately develops severe serotonin syndrome requiring ICU transfer after remaining essentially asymptomatic for 12 hours. Conclusion: Emergency and critical care providers should be familiar with serotonin syndrome and aware that an overdose of multiple serotonergic agents may require prolonged observation or conservative medical admission of asymptomatic patients prior to transfer to a psychiatric care unit where the development of symptoms may go unrecognized or improperly treated.

Introduction

Serotonin syndrome, as best defined by the Hunter Toxicity Criteria Decision Rules, is classically a result of co-administration of two serotonergic drugs or with an increase in the dose of one agent [1,2]. The common clinical presentation of serotonin syndrome involves autonomic instability, neuromuscular abnormalities, and mental status changes. This syndrome is a clinical entity recognized with increasing frequency due to the prevalence with which pro-serotonergic drugs are prescribed and combined across the different medical fields. The true incidence of serotonin syndrome and associated morbidity are unknown for a number of reasons. The most likely reason being the possibility that more than 85% of physicians are unaware of the syndrome's existence [2]. Serotonin syndrome will often develop within 6 hours and current recommendations are for 4-6 hours of observation of an asymptomatic patient before disposition [3].

Case

In our case, we present a woman who remained essentially asymptomatic until 12 hours following an acute overdose of multiple medications, two of which were pro-serotonergic agents.

A 32-year-old female, medical history includes only depression and chronic low back pain, presented to the emergency department after an intentional overdose of Etodolac (800 mg), Naproxen (30 gm), Tramadol (1.6 gm), Fluoxetine (80 mg), Metaxalone (2.4 gm) and Percocet 5/325 (25 mg/1625 mg). The patient, expressing regret over her suicide attempt, was alert and oriented. She specifically denied any consumption of monoamine oxidase inhibitors (MAOI's). Her initial vital signs upon presentation were significant for a HR of 100 and a BP of 181/112 with an oral temperature of 100.1 F (37.8 C). Initial physical examination was normal, with no evidence of tremor, hyperreflexia, hypertonia, ocular clonus, or other significant abnormalities. The laboratory work drawn (CBC, CMP, UA, and UDS) was normal. Her serum fluoxetine level was later resulted at 143 ng/mL (therapeutic range: 47-469), and the tramadol level was determined to be 800 ng/mL (therapeutic range: 230-770). After an initial dose of activated charcoal, the patient was admitted to the hospital for observation and appeared stable until approximately twelve hours after ingestion.

During the initial twelve hours, the patient's BP decreased to 130/70 mm Hg and her temperature declined to 98.8 F (37.1 C). Suddenly, however, the patient's HR increased to 135 and she developed rapid onset of altered mental status, rigidity and clonus with hyperreflexia. Within two hours the patient had a rectal temperature of 108.8 F (42.7 C) with a HR of 188 and BP of 86/52. Rapid external cooling measures with evaporative cooling and ice packs were initiated, along with benzodiazepine therapy with lorazepam. Dopamine and intravenous fluid resuscitation was also started, but patient progressed into rhabdomyolysis and acute respiratory distress syndrome (ARDS) necessitating prolonged ICU hospitalization. Fortunately, she eventually recovered fully three weeks later and left the hospital without any physical or neurological sequelae.

Discussion

Serotonin syndrome, as evidenced by this case, is a serious disorder that must be recognized by emergency department and critical care physicians in order to mitigate the potentially fatal consequences of such a syndrome. This was a case of polypharmacological ingestions, but the paucity of serotonergic properties of the other agents seemed to suggest that the acute excessive ingestion of tramadol and fluoxetine was directly responsible for the development of serotonin syndrome in this patient.

The pathogenesis of fluoxetine and tramadol in producing serotonin syndrome can be better elucidated by considering both mechanism of action and pharmacokinetic properties in reference to drug metabolism. Tramadol is a known 5-HT serotonin uptake antagonist and pre-synaptic release stimulator, which leads to an increase in the concentration of synaptic serotonin [4]. In addition

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to the direct serotonergic mechanism of action, fluoxetine is a potent antagonist to the cytochrome P450 enzyme (CYP2D6), which in turn is directly responsible for causing a deceleration in the body's metabolism of tramadol [5].

Due to the fact that serotonin concentrations do not correlate with clinical findings and there are no specific confirmatory tests for serotonin syndrome, once a provider has clinical suspicion for the diagnosis, there are four acute management steps that should be undertaken in short order. The first is discontinuation of all serotonergic agents, followed by supportive care in an attempt to normalize vital signs (avoiding prolonged hyperthermia and autonomic instability, with fluid resuscitation for hypotension and to avoid rhabdomyolysis). A third step would be administration of benzodiazepines to control agitation and reduce hypertension and tachycardia. Finally, if supportive measures fail, antidotal therapy with cyproheptadine (histamine-1 receptor antagonist with nonspecific 5-HT1A and 5-HT2A antagonistic properties) is recommended [6] Boyer, in his serotonin review article in 2009, recommends a standard initial dose of 12 mg followed by 2 mg every two hours until clinical response [3]. In our case, cyproheptadine therapy was not administered as recommended.

A salient point regarding serotonin syndrome, as evidenced by our case, relates to time of emergency department (ED) observation before disposition. Our patient was initially asymptomatic after 6 hours of observation with arguably minimally abnormal vital signs. According to current literature, such cases can be dispositioned either home or to a psychiatric care facility [2,3]. In this particular case, such a disposition could have lead to unrecognized symptomologic progression and disastrous results possibly including death.

Conclusion

In summary, this case report reinforces that the emergency medicine or critical care provider needs to be intimately familiar with serotonin syndrome and alert for atypical presentations. It is possible that longer periods of observation could be considered for acute poly-pharmacy overdoses which include multiple serotonergic agents, especially those with effects on the CP450 enzyme. The treating provider may also wish to consider a lower threshold for early institution of higher doses of serotonergic antagonists at optimal dosages.

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