Serotonin Syndrome Associated With Clozapine Withdrawal

Elizabeth Stevenson, MD, MS; Frank Schembri, MD; Deborah M. Green, MD; Joseph D. Burns, MD

IMPORTANCE We describe a case of serotonin syndrome secondary to clozapine withdrawal and concomitant use of citalopram hydrobromide, a phenomenon that has been rarely reported.

OBSERVATIONS This is a case report of a 47-year-old woman admitted to an academic medical center intensive care unit with coma, hypersalivation, hyperreflexia, and stimulus-induced clonus. The patient received a diagnosis of serotonin syndrome attributed to abrupt clozapine withdrawal with concomitant use of citalopram. She improved only minimally with supportive treatment (intravenous fluids, benzodiazepines, and withdrawal of selective serotonin-reuptake inhibitor) and received cyproheptadine hydrochloride on her third day of symptoms. Four hours after she received the loading dose of cyproheptadine, she was alert and oriented and at her baseline mental status, although some clonus remained.

CONCLUSIONS AND RELEVANCE Serotonin syndrome can result from the abrupt withdrawal of a 5-hydroxytryptamine receptor 2A antagonist from a treatment regimen that also includes a medication that increases serotonin availability.

Published online June 10, 2013.

Clozapine is an atypical antipsychotic commonly used in the treatment of schizophrenia. Its efficacy is attributed to its antagonist actions at serotonin receptors (5-hydroxytryptamine receptor 2). The drug also antagonizes dopamine (D1 and D2) receptors and has significant antimuscarinic effects. The abrupt withdrawal of clozapine has been associated with cholinergic rebound and rapid onset of psychosis, and less frequently with emergent dystonias and dyskinesias. There are rare case reports of abrupt clozapine withdrawal inducing serotonin syndrome with and without concomitant use of a serotoninergic agent. Herein, we describe a case of serotonin syndrome that developed with the abrupt withdrawal of clozapine with concomitant use of citalopram hydrobromide, a selective serotonin reuptake inhibitor.

Report of a Case

A 47-year-old schizophrenic woman presented with 7 days of nausea and vomiting and was hospitalized with presumed viral gastroenteritis. Owing to an inaccuracy on her accompanying medication list, her longstanding treatment with clozapine (100 mg nightly) was inadvertently discontinued while her gastrointestinal symptoms gradually improved with bowel rest, intravenous fluid, and intermittent antiemetics (ondansetron hydrochloride, promethazine hydrochloride, and metoclopramide hydrochloride) that were last administered on day 3 of her hospitalization. 48 hours before her clinical deterioration. On day 5 of her hospital stay, she was found to be unresponsive with inducible clonus of her lower extremities. She was afebrile, hemodynamically stable, and breathing spontaneously, but she was intubated for airway control and brought to the intensive care unit.

In the intensive care unit, her temperature was 37.1°C (98.8°F), her pulse rate was 80 to 120 beats per minute, her blood pressure was 113/59 mm Hg, and her oxygen saturation was 100% on a fraction of inspired oxygen of 65%. On further examination, she was found to be intermittently agitated without eye opening or purposeful movements, but she did withdraw all 4 extremities to pain. Her face was symmetric, and she had normal gag and cough. Hypersalivation was noted. She did blink both eyes to visual threat, and her pupils were reactive from 4 to 3 mm. She had moderate upper extremity and severe lower extremity spasticity with inducible clonus of her ankles bilaterally. Muscle stretch reflexes were 3+ with spread in her upper extremities and 4+ with spread in her lower extremities. The results of arterial blood gas analysis were normal, and the results of serum and urine toxicology studies were negative. All additional serologic test results, including those for complete blood count, chemistry, creatine kinase, liver and thyroid function, vitamin B12, folate, and lactate levels, were also normal. Urinalysis was unremarkable. The results of electrocardiography, computed tomography of the head, and magnetic resonance imaging/magnetic resonance angiography of the head and neck were normal. Continuous video electroencephalograms recorded for 24 hours showed diffuse slowing but no epileptiform activity. Citalopram and antiemetics...
were discontinued, and the patient was treated supportively with intravenous fluid and intermittent benzodiazepines for agitation. Her mental status improved minimally, and she was extubated after 48 hours. At 72 hours, she was minimally responsive and rarely following commands; however, her spasticity and clonus remained.

At this point, an extensive medication reconciliation revealed the omission of clozapine. This information, together with her failure to improve and negative workup, lead to the suspicion of serotonin syndrome. Therefore, she was treated with a loading dose of 6 mg of cyproheptadine hydrochloride through her nasogastric tube, followed by 2 mg every 4 hours for 24 hours. Four hours after the loading dose, she was fully alert and oriented and at her baseline mental status, although her hyperreflexia and clonus remained. She was discharged from the hospital several days later while still being treated with cyproheptadine, which was titrated down as her clozapine was titrated back up to her preadmission dose. Her hyperreflexia and clonus resolved within weeks of hospital discharge.

Discussion

Abrupt withdrawal of clozapine has been associated with symptoms of “cholinergic rebound,” including nausea, vomiting, hypersalivation, diarrhea, diaphoresis, insomnia, and agitation, as well as rapid onset of psychosis.1-4 There are comparatively fewer reports of serotonin syndrome associated with the withdrawal of the serotonin receptor antagonist clozapine.5,6 Although our patient exhibited some symptoms of cholinergic rebound (agitation and hypersalivation), we believe that her abrupt decline in arousal and the development of clonus and hyperreflexia were the result of serotoninergic alteration secondary to clozapine withdrawal. Clozapine is a 5-hydroxytryptamine receptor 2A antagonist, and both acute and long-term clozapine use have been shown to downregulate the 5-hydroxytryptamine receptor 2A in the rat cerebral cortex.9 The abrupt discontinuation of the drug may therefore have led to a decrease in antagonism and upregulation of the receptor as shown by Huang and colleagues in their animal model.

In combination with the selective serotonin reuptake inhibitor citalopram, perhaps with additional influence from the antiemetics metoclopramide and ondansetron,2,11 this phenomenon may have been responsible for the serotoninergic overload experienced by our patient. Treatment with cyproheptadine, an antihistamine with anticholinergic properties,2 which also antagonizes the 5-hydroxytryptamine receptor 2A,8 resulted in the normalization of our patient’s mental status within 4 hours and the resolution of her other symptoms over the next several weeks as clozapine was slowly reintroduced. Clinicians should be aware that abrupt withdrawal of clozapine (and perhaps any other serotonin receptor antagonist) in the presence of an agent that increases availability of serotonin may lead to serotonin syndrome.5 If the discontinuation of treatment with clozapine is desired, it should be gradually tapered off over several weeks, rather than abruptly discontinued, except in cases of emergency, such as agranulocytosis, and then only with close monitoring of the patient.

REFERENCES