Possible Toxic Serotonin Syndrome in an Adolescent With Obsessive-Compulsive Disorder Precipitated by Esomeprazole

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Herein, the case is reported of an adolescent girl with obsessive-compulsive disorder (OCD) who responded favorably to an off-label supramaximal dose of escitalopram (30 mg/d) with great tolerability. However, addition of the proton pump inhibitor (PPI) esomeprazole likely precipitated serotonin syndrome. This case is followed by discussion of purported mechanisms and relevant literature. Prescribers should be mindful of this drug interaction. When clinically indicated, PPIs with minimal drug-drug interactions (eg, pantoprazole) are strongly recommended in lieu.

Case Report

A 13-year-old Lebanese girl was assessed in the outpatient clinic for ablutomania, whereby a *DSM-5* diagnosis of OCD with fair insight was made. She had a heavy genetic load but no tics. She was prescribed escitalopram (for possible pharmacogenetics) at 5 mg/d after meals and uptitrated (increments of 5 mg/week) to 20 mg/d over a month duration. The Yale-Brown Obsessive-Compulsive Scale[1] (YBOCS) severity was readministered with a score of 30 (severe), indicating that the patient was still under marked distress. We opted to continue escitalopram 30 mg/d for another 2 weeks, which resulted in tangible improvement based on patient/parent reports and a decline in YBOCS score to 16 (mild). She continued to do well with no tolerability issues apart from nausea and heartburn. Annoyed by epigastric pain, she was seen by a general practitioner who started her on esomeprazole 20 mg before meals. This dose was increased to 40 mg after 5 days. The patient was taking no other medications.

Her parents soon noticed that she was increasingly agitated, a bit confused, shivering, profusely sweating, flushed, and vomiting. She was taken to the emergency department where she was found on examination to be disoriented, rigid, and feverish, with bilateral Babinski, hyperreflexia with a clonus, sinus tachycardia with occasional premature ventricular contractions, tachypnea, mydriasis, and diaphoresis and borborygmi. Given her disturbed sensorium, she was admitted to the intensive care unit. Extensive workup was undertaken including toxicology screen, electroencephalography, and neuroimaging. A tentative diagnosis of serotonin syndrome was considered. All medications were stopped, and supportive measures were immediately instituted.

Discussion

Deploying this off-label supramaximal dose of escitalopram, although typical for OCD (compared to MDD), might have contributed to the development of toxic serotonin syndrome in this case. As the patient was generally faring well for 3 weeks with no apparent tolerability issue, this remains a remote possibility. Escitalopram is both a selective inhibitor and an allosteric modulator of serotonin transporter, which can be notorious in this regard. Genotyping and a poor cytochrome P450 (CYP) 2C19 status of this patient would have been informative if done and would otherwise have validated this contention. Addition of esomeprazole, which is known to inhibit CYP2C19, for which escitalopram is a substrate, likely further increased the level of this supramaximal dose and culminated ultimately in serotonin syndrome.

Serotonin syndrome is a toxic syndrome due to serotonin excess.[2] It classically involved the combination of a monoamine oxidase inhibitor and another serotonergic agent, but this is now rarely seen. Risk is increased with use of more than 1 serotonergic agent or with an overdose on serotonergic agents. Common offenders are legion and include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, St John's wort, linezolid, opioids, and stimulants. Serotonin syndrome typically presents as altered mental status, neuromuscular excitation, and dysautonomia.[3] It tends to have a quick onset and resolution (less than 24 hours). Although exact pathophysiology remains elusive, based on rat models, serotonin syndrome reflects 5-$HT_{1A/2A}$ overstimulation.[4] Diagnostic tools include

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Table 1. Hunter Serotonin Toxicity Criteria for Serotonin Syndrome[5]

Exposure to a serotonergic agent + 1 of these:
- Spontaneous clonus
- Inducible/ocular clonus + agitation/diaphoresis/hypertonia and fever
- Tremor + hyperreflexia

Sternbach, Hunter, and Radomiski criteria.[5,6] The Hunter Serotonin Toxicity Criteria,[5] capitalizing mainly on physical changes, are the most commonly used as shown in Table 1. Serotonin syndrome is generally self-limited, and treatment is based chiefly on removing the culprit agent and other supportive measures (eg, cooling blankets, antipyretics, intravenous fluids, benzodiazepines, dexmedetomidine, cyproheptadine[7]).

Esomeprazole is a PPI approved by the US Food and Drug Administration for gastroesophageal reflux disease, peptic ulcer disease, hypersecretory states, and *H pylori* eradication. Its relevance to psychiatric practice lies with pharmacokinetic and dynamic interactions with psychotropic drugs. Omeprazole interactions are similar and are better avoided as well. PPIs of choice are then pantoprazole and lansoprazole. Significant interactions include inhibition of CYP2C19 substrates, increasing levels of escitalopram (90%), diazepam (90%), clonazepam (90%), and sertraline (40%). Moreover, esomeprazole induces CYP1A2 substrates, eg, olanzapine and clozapine, with resultant pharmacokinetic failure and loss of therapeutic efficacy or lack thereof despite adequate dosing.[8] Esomeprazole can inhibit P-gp as well, potentiating central actions (eg, loperamide). An important pharmacodynamic interaction is PPI-related hypomagnesemia, which might potentiate torsadogenecity of psychotropic agents notorious to prolong QTc interval (eg, ziprasidone or sertindole).[9]

Conclusion

Prescribers should be vigilant and cognizant of this drug-drug interaction between escitalopram and esomeprazole/omeprazole, as this combination is quite ubiquitous, especially in psychogeriatrics wherein PPIs are often used to safeguard against possible SSRI-related gastrointestinal bleeding in this vulnerable population. In these clinical scenarios, PPIs with minimal drug-drug interactions (vide supra) are strongly recommended.

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