Ondansetron-Induced Myoclonus With Escitalopram and HAART:
Role of Drug Interactions

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Patients with HIV are frequently treated with highly active antiretroviral therapy (HAART). Two combination drugs often used are Genvoya and Stribild. The combination in Genvoya is elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg.[1] The combination in Stribild is elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg.[1] Both drugs differ in their tenofovir drug composition and dosage.[1] A double-blind phase 3 clinical trial[1] was done to study the difference between these 2 medications. Patients who were taking tenofovir alafenamide had significantly less proteinuria, smaller mean creatinine increase, and a smaller decrease in bone mineral density in the hip and spine compared to patients who were taking tenofovir disoproxil fumarate. Both of these medications have a 16% risk of inducing nausea,[1] and ondansetron is commonly prescribed to treat it.

We report a case of ondansetron-induced myoclonus in a patient on escitalopram and HAART.

Case Report

A 26-year-old HIV-infected man was started on Stribild, which resulted in nausea, so he was started on ondansetron. He was also started on escitalopram 5 mg and alprazolam 0.5 mg 4 times a day for generalized anxiety disorder; escitalopram was titrated gradually to 15 mg within 4 months. He was using ondansetron up to 5 times a day. The patient started experiencing myoclonic jerks in his upper extremities 5 to 6 times a day with the 40 mg of ondansetron and 15 mg of escitalopram. The frequency of jerks was higher, at up to 12 times a day when he missed his alprazolam doses. His frequency of myoclonic jerks improved to 1 to 2 episodes per day when he reduced his ondansetron to 3 times a day. After a reduction of escitalopram to 10 mg, he was still experiencing myoclonus once or twice a week. No other symptoms of serotonin toxicity were present. To help address nausea, Stribild was changed to Genvoya. His nausea improved with the switch to Genvoya, and with minimal ondansetron use, his myoclonus disappeared. Three months later, his escitalopram was increased again to 15 mg with no exacerbation of myoclonus. His pharmacokinetic genetic testing revealed him to be an intermediate metabolizer of cytochrome P450 2D6 (CYP2D6).

Discussion

In this case, the patient presented with myoclonus, a symptom of serotonergic toxicity, in a background of ondansetron ingestion.[2] However, a shift to Genvoya made the patient less nauseous, and he tolerated the lower dose of tenofovir compositions better.

Nausea and vomiting are the most common side effects of HAART and the most common reason for nonadherence and discontinuation of HIV therapy.[3] Primarily for this reason, patients on HAART often need antiemetics during their therapy, and ondansetron is believed to be a well-tolerated drug.[3] Ondansetron is a selective serotonin 5-HT_3 receptor antagonist.[4] By blocking the action of serotonin on the 5-HT_3 receptor, the vagally mediated vomiting reflex is inhibited. Ondansetron is metabolized in the liver by CYP3A4, CYP1A2, and CYP2D6.[4] Escitalopram is a selective serotonin reuptake inhibitor (SSRI). By blocking the reuptake, escitalopram can increase the levels of serotonin in the body. It is metabolized by CYP3A4 and CYP2C19.[5] Escitalopram is a weak CYP2D6 inhibitor and can increase the plasma levels of CYP2D6 substrates like ondansetron.[5]

Cobicistat inhibits the CYP3A family and is intended to increase the levels of other antiretroviral agents.[6] Inadvertently, cobicistat can increase the level of ondansetron and escitalopram too. With our patient an intermediate CYP2D6 metabolizer, serum ondansetron levels were further increased by escitalopram's modest CYP2D6 inhibition. We hypothesize that the higher levels of escitalopram and ondansetron, and their serotonergic actions, increased the risk of serotonin toxicity in our patient.

Experts have questioned the use of 5-HT_3 receptor antagonists in causing serotonin toxicity when combined with other serotonergic drugs.[7] This case report suggests that such a possibility cannot be ruled out. Nearly 16% of

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patients with HIV suffer from generalized anxiety disorder, and SSRIs are the first-line pharmacologic treatment options.[8] With nausea as a common side effect of HAART medications and with ondansetron a commonly used antiemetic with HAART, we recommend an enhanced vigilance for serotonergic toxicity when serotonergic antidepressants and ondansetron are used for patients on HAART.

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