Elmer Press

Case Report J Med Cases. 2014;5(11):567-569

Serotonin Syndrome With Standard-Dose Vilazodone (Viibryd®) Monotherapy

Taylor W. Butler[a, d], Robert A. Lucas[b], Wahid Barghouthy[c]

Abstract

There is a deficiency in published literature describing serotonin syndrome with standard vilazodone (Viibryd®) treatment. This is the case of a 28-year-old female with anxiety treated with vilazodone. Prior to the initiation of vilazodone, vital signs were normal and the patient exhibited no signs of excessive serotonin. The patient was prescribed vilazodone with the appropriate 2-week titration per the FDA-approved prescribing information. During the first week, the patient reported excessive perspiration and gastrointestinal symptoms. On day 17 of vilazodone therapy, the patient reported a major neurologic reaction and discontinued vilazodone. The patient was diagnosed with possible serotonin syndrome. Symptoms of elevated serotonin, including hyperhidrosis and nausea, did not resolve until 2 weeks after discontinuation of therapy. In this case, the patient developed early warning signs of excessive serotonin in the periphery and eventually a potential life-threatening neurologic adverse event on vilazodone monotherapy. Practitioners should counsel on early warning signs of excessive serotonin and the potential for serotonin syndrome, even with a single serotonergic agent.

Keywords: Serotonin; Serotonin syndrome; Vilazodone; Monotherapy; Psychopharmacology; Neuropharmacology

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are one of the most commonly prescribed antidepressant medications due to effectiveness and limited adverse effects. Vilazodone (Viibryd®) is the first combined serotonin reuptake inhibitor and was recently approved for major depressive disorder [1]. The primary mechanism of action is believed to be inhibition of serotonin uptake causing a persistence of serotonin postsynaptic neurotransmission, leading to an improvement of depressive symptoms. The effects take place not only in the central nervous system but also in the periphery. This increase in serotonin at the synapse is known to be associated with an increased risk of serotonin syndrome [2]. Vilazodone is also a partial agonist at the 5-HT_{1A} receptor [3, 4]. The difference in the mechanism of action of vilazodone and SSRIs, specifically the partial agonist action, is believed to lower the incidence of sexual dysfunction and lead to a decrease in anxiety [1, 5]. Treatment with an SSRI, especially with concomitant use of other serotonergic drugs or with overdose, has been linked to serotonin syndrome. Serotonin syndrome with vilazodone has not been well described and this case will help identify this risk [6, 7].

Of note, vilazodone requires a titration schedule due to potential gastrointestinal symptoms, such as nausea and diarrhea [8]. Patients with certain genetic variants are at greater risk for these gastrointestinal side effects. Patients positive for marker 2 (M2) were at tenfold higher risk to develop nausea and vomiting during the first 3 weeks of therapy [9].

Serotonin syndrome is currently under-diagnosed and therefore it is underreported. It was reported in 1999 that up to 85% of physicians are unaware of the diagnosis of serotonin syndrome [10]. It involves excessive serotonin in the central and peripheral nervous systems, which leads to an exaggerated serotonin neurotransmission. Hence, it is usually associated with a clinical triad of symptoms, including unstable vital signs, neurologic abnormalities, and atypical neuromuscular symptoms. These symptoms are nonspecific and often vary in severity, including potential life-threatening reactions. The lack of specificity of these symptoms for the diagnosis of serotonin syndrome with the Hunter criteria makes it difficult for practitioners to appropriately recognize and intervene when symptoms first develop. Other possible signs and symptoms include diarrhea, diaphoresis, disseminated intravascular coagulation, and multi-organ failure [2]. Prevalence appears to be increasing with the increased number of SSRI prescriptions but the true incidence is unknown because serotonin syndrome often goes unrecognized [10]. Serotonin syndrome is reported

Manuscript accepted for publication September 25, 2014

[a]Department of Pharmacy Practice, Nova Southeastern University, 11501 N. Military Trail, Palm Beach Gardens, FL 33410, USA
[b]Department of Pharmacy, Blount Memorial Hospital, 907 E Lamar Alexander Pkwy, Maryville, TN 37804, USA
[c]College of Pharmacy, Nova Southeastern University, 11501 N. Military Trail, Palm Beach Gardens, FL 33410, USA
[d]Corresponding Author: Taylor W. Butler, Department of Pharmacy Practice, Nova Southeastern University, 11501 N. Military Trail, Palm Beach Gardens, FL 33410, USA. Email: Tbutler1@nova.edu

doi: http://dx.doi.org/10.14740/jmc1956w

in vilazodone overdose and with use of concomitant serotonergic agents. Although referenced in the prescribing information, there are no reports describing serotonin syndrome in vilazodone monotherapy at approved doses [6].

Case Report

A 28-year-old female experiencing nightly insomnia sought medical treatment through her primary care physician. Her past medical history was insignificant. The patient had no known drug allergies and her medications and supplements included combination birth control (norethindrone 0.8 mg + ethinyl estradiol 0.025 mg), promethazine 25 mg as needed for nausea, double-strength trimethoprim-sulfamethoxazole, and omeprazole 40 mg. Her body mass index was classified as normal. During the appointment, she was diagnosed with anxiety and prescribed sertraline 75 mg daily. The patient returned after several months with worsening symptoms. The prescriber abruptly discontinued sertraline and initiated vilazodone. Vilazodone was correctly titrated at 10 mg daily for 7 days followed by an increase to 20 mg daily for 7 days, and finally 40 mg daily. The patient was never counseled about the potential for serotonin syndrome and was not educated about the signs and symptoms.

After the first week of therapy, the patient experienced excessive perspiration. She complained of being hot with sweat primarily in her torso. Additionally, gastrointestinal symptoms, such as nausea and diarrhea, began on day 10. The patient self-administered promethazine 25 mg at bedtime on days 10 - 14. On day 17, the patient reported an exacerbation of her nausea immediately after taking the vilazodone tablet. The patient reported difficulty sleeping that evening and experienced severe nausea. She reported having uncontrollable jerking movements with her arms and legs, e.g. tremor and hyperreflexia. During this episode, she reported an elevated heart rate, respiratory rate, and hallucinations. According to the patient's family, the patient was aphasic. The episode was estimated to last 20 minutes. No similar events occurred prior to that evening. The patient awakened fatigued but otherwise had normal function. She discontinued the vilazodone treatment. Three days after discontinuing vilazodone, the patient's vital signs were normal except her pulse was elevated at 115 beats per minute. The physician referred her to a psychiatrist for management of possible serotonin syndrome. She did not receive any treatment or new prescriptions. The patient did not seek medical attention from a psychiatrist.

The patient went to the emergency room on the fourth day after discontinuing vilazodone treatment. Her vital signs were normal. Labs were within normal limits, including complete blood count, human chorionic gonadotropin, international normalized ratio, basic metabolic panel, and D-dimer. An electrocardiogram and chest X-ray were both normal. Her urine drug screen was negative. No treatment was given in the emergency department because the patient's symptoms had resolved. The emergency medicine physician diagnosed her with serotonin syndrome from vilazodone and she was discharged that evening. The physician instructed her to return if symptoms reoccurred. The patient continued to experience excessive perspiration for 2 weeks after discontinuation of therapy. The patient was not re-challenged with vilazodone and has not experienced similar neurologic symptoms in the 12 months following the occurrence.

Discussion

This patient was diagnosed with serotonin syndrome by primary care and emergency medicine physicians. Her case appears to meet the Hunter criteria through the self-reported symptoms of hypertonia, hyperreflexia, diaphoresis, nausea, agitation, tachycardia, and tachypnea. Her confirmed tremor and hyperreflexia while taking a serotonergic agent meets the Hunter criteria while her other symptomatology strengthens the clinical suspicion as well [10]. The Naranjo scale classifies this drug reaction as a probable causality. Serotonin syndrome is a clinical diagnosis without laboratory confirmation, which is part of the reason why it is difficult to make a stronger correlation on the Naranjo scale [11].

There are several confounding factors that may have put the patient at an increased risk of serotonin syndrome. The patient took a short course of promethazine, which cannot be ruled out for potential exacerbation of the patient's symptoms. However, promethazine has weak action at serotonin receptors and has rarely shown an association with serotonin syndrome. Also, this patient developed symptoms of excessive serotonin prior to the initiation of promethazine. Further, the promethazine was also only administered at day 10 to day 14, while the patient met the criteria for serotonin syndrome on day 17. Based on the half-life of promethazine, the serum concentration would have been very low at the time of the patient's episode. Finally, the patient had never experienced a neurologic event with previous administrations of promethazine. Another possible confounding factor is that there was no washout period for sertraline. Sertraline has an elimination half-life of 26 h, which means it should have been eliminated after 5 - 7 days. The half-life is variable and it is possible that detectable sertraline serum levels existed when the hyperhidrosis started. However, it would seem unlikely that sertraline was available on day 17 to potentiate the patient's probable serotonin syndrome. It is also important to recognize that the patient never experienced similar symptoms on sertraline monotherapy.

It is unknown whether vilazodone's bimodal mechanism of action may have caused an increased risk of serotonin syndrome. These vilazodone mechanisms are believed to be similar to combination therapy with an SSRI and buspirone, which are both serotonergic agents. Of note, the only well-documented genetic mutation affecting vilazodone has only shown a correlation with increased gastrointestinal symptoms [9]. It is unknown whether this patient has this genetic mutation. Further study may be warranted to determine if this genetic variant may potentially increase risk of serotonin syndrome with standard-dose vilazodone.

The patient did not seek medical attention until well after her symptoms had resolved. Serotonin syndrome can be life-threatening and immediate attention is necessary. The serious-

ness of serotonin syndrome highlights the importance of counseling every patient on the signs and symptoms associated with this side effect, even with a single serotonergic agent.

Conclusion

Standard-dose vilazodone treatment has rarely been associated with serotonin syndrome and there are no reports describing any actual cases or rates of occurrence. We have described a possible case of vilazodone-induced serotonin syndrome. Physicians should be aware of the relationship between vilazodone and serotonin syndrome. It is unclear if vilazodone presents an increased risk of serotonin syndrome because of its combined mechanism of action and this may require increased monitoring. Patients should be warned of the early warning signs of serotonin syndrome when started on vilazodone and practitioners need to be vigilant in identifying these warning signs upon initiation and titration of vilazodone.

References

1. Hopkins CR. ACS chemical neuroscience molecule spotlight on viibryd (Vilazodone). ACS Chem Neurosci. 2011;2(10):554.
2. Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. Am Fam Physician. 2010;81(9):1139-1142.
3. Iranikhah M, Wensel TM, Thomson AR. Vilazodone for treatment of major depressive disorder. Pharmacotherapy 2012;32(10):958-65.
4. Guay DR. Vilazodone hydrochloride, a combined SSRI and 5-HT1A receptor agonist for major depressive disorder. Consult Pharm. 2012;27(12):857-867.
5. Clayton AH, Kennedy SH, Edwards JB, Gallipoli S, Reed CR. The effect of vilazodone on sexual function during the treatment of major depressive disorder. J Sex Med. 2013;10(10):2465-2476.
6. Forest Pharmaceuticals. Viibryd (vilazodone) package insert. St. Louis, MO; July 2014.
7. Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract. 2012;66(4):356-368.
8. Laughren TP, Gobburu J, Temple RJ, Unger EF, Bhattaram A, Dinh PV, Fossom L, et al. Vilazodone: clinical basis for the US Food and Drug Administration's approval of a new antidepressant. J Clin Psychiatry. 2011;72(9):1166-1173.
9. Athanasiou M, Reed C, Rickels K. Vilazodone, a novel, dual-acting antidepressant: current status, future promise and potential for individualized treatment of depression. Per Med. 2009;6(2):217.
10. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352(11):1112-1120.
11. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-245.