The Treatment of Migraine Headache in the Presence of Selective Serotonin Reuptake Inhibitor Use: Pharmacokinetic Considerations

CE 2.0 ANCC Contact Hours and Rx Hours

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A discussion and case study are presented regarding the management and pharmacokinetic considerations of a patient being dually treated for migraine headaches and anxiety/depression. The purpose is to review the common diagnosis of depression/anxiety and migraine headache and the first-line pharmacological treatments that accompany these diseases. This study includes an in-depth discussion of the CYP450 metabolism of the most common treatment drugs for these conditions and the serious interactions that can arise from certain drug combinations including serotonin syndrome. Implications for practice, including recommended prescribing practices and ways to avoid interactions, are also to be discussed. Individually, depression/anxiety and migraine headache are both challenging diagnoses that can take years of pharmacological trial and error to find an effective and appropriate treatment. CYP450 enzyme metabolism must be reviewed carefully when prescribing multiple drugs to treat both disorders. Serotonin syndrome is a deadly threat and can have serious implications for the patient if one or more serotonin-augmenting drugs are being prescribed to these patients.

Depression and Selective Serotonin Reuptake Inhibitors

Depression is one of the most common mental disorders in the world, with more than 350 million people experiencing this disease globally. It is also the leading cause of disability worldwide (World Health Organization, 2014a). Depression is predominantly diagnosed and treated in primary healthcare and referred to specialists only when first-line treatment is not successful.

The most effective intervention for achieving remission and preventing relapse in depression is medication. Outcome is improved when psychotherapy is incorporated; however, 40% of primary care patients with depression drop out of treatment (Reus, 2012). The most prescribed class of antidepressant medication in primary care are the selective serotonin reuptake inhibitors or SSRIs (Cipriani et al., 2009). Other commonly prescribed antidepressant classes include the tricyclic antidepressants and the serotonin–norepinephrine reuptake inhibitors (SNRIs). SSRIs in primary care (fluoxetine, sertraline, paroxetine, citalopram, and escitalopram) are a good ''starter'' medication because of their lower frequency of anticholinergic, sedating, and cardiovascular side effects as well as their safety in overdose and improved tolerability (Reus, 2012).

SSRIs are metabolized by cytochrome P450 enzymes and are considered inhibitors of these enzymes (Brown & Whelen, 2011). Specifically, CYP2D6 is involved in the metabolism of most SSRIs, and care should be used in combining SSRIs with drugs that are metabolized by CYPs 1A2, 2D6, 2C9, and 3A4 (O'Donnell & Shelton, 2011).

Migraine Headache and Triptans

Migraine headaches are one of the most common types of chronic headache disorders, affecting at least one adult in every seven adults worldwide (World Health Organization, 2014b). They are up to three times more common in women than men and can significantly impact family and quality of life. Uncomplicated migraine headache can be easily managed by primary care, often with lifestyle modification coupled with effective medication remedies.

First-line treatment for migraine headache always involves nonpharmacologic approaches including headache diaries, trigger avoidance, and lifestyle regulation. Although these therapies often manage migraines, acute attacks are often unavoidable and require a pharmacologic approach to abort the attack. The most common prescription medication used for migraine headache abortion are the 5-HT1B/1D receptor agonists, better known as the ''triptans'' (Goadsby & Raskin, 2012). This class of medications includes naratriptan, rizatriptan, eletriptan, sumatriptan, zolmitriptan, almotriptan, and

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The author declares no conflicts of interest.

DOI: 10.1097/JNN.0000000000000144

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frovatriptan. These drugs are metabolized in the liver primarily by CYP2D6 (rCYP2D6) and rCYP3A4 and, to a lesser extent, by rCYP2C9 and rCYP2C19 (Evans et al., 2003). Most of the triptans are categorized as substrates of these enzymes, with the exception of eletriptan, which is categorized as both a substrate and an inducer.

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening drug reaction caused by excessive serotonergic activity in the nervous system. It occurs most often when two or more drugs that affect the body's level of serotonin are taken in close proximity. The mechanisms of serotonin syndrome can involve increased serotonin synthesis or release, reduced serotonin uptake or metabolism, or direct serotonin receptor activation (Ables & Nagubilli, 2010). Clinical symptoms and features of serotonin syndrome include mental status changes, agitation, diarrhea, tachycardia, hypertension, nausea, and vomiting. Severe toxicity can further involve hallucinations, increased body temperature, ataxia, hyper-reflexivity, and rapid changes in blood pressure. Most cases of serotonin syndrome are mild and may be treated by withdrawal of the offending agent and supportive care. Benzodiazepines can also be used to treat agitation (Medline Plus, 2014).

Preventing serotonin syndrome in patients that require the use of multiple serotonergic drugs to treat various conditions can be challenging. In addition to trying to avoid prescribing combined use of serotonin-augmenting drugs, a provider must also steer clear of concurrent use of medications that interact with serotonergic drugs through the inhibition of the cytochrome P450 pathway. For example, extra caution should be observed if a patient is taking an SSRI in addition to a 5-HT1B/1D receptor agonist (triptan) because of the substrate properties of the triptan, combined with the inhibition properties of the SSRI with cytochrome P450 2D6 (CYP2D6; Ables & Nagubilli, 2010).

Interestingly, current treatment guidelines do not prohibit co-prescription of serotonin-syndrome-inducing drugs. There are no established guidelines for the prevention of serotonin syndrome. The recommendation is to minimize co-prescription of these drugs and to closely monitor and discuss the risk with patients who are on one or more of the serotonergic drugs (Ables & Nagubilli, 2010). Current neurology experts maintain that the actual risk of serotonin syndrome is small, and they do not advocate stopping the combined use of these drugs for people with migraine and the comorbidity of depression and anxiety in the absence of serotonin syndrome symptoms (Lindsay, 2006). Clinicians should weigh the possible risk of serotonin syndrome with the anticipated benefit of using the drug combination; discuss the possibility and symptoms of serotonin syndrome with patients; follow patients closely, particularly during treatment initiation, with dose increases or with the addition of another serotonergic medication; and instruct patients to seek medical attention immediately if they experience serotonin syndrome symptoms (Barclay, 2010).

Case Study

Nicole is a 34-year-old woman currently working as a criminal defense attorney at a small firm. She has been treated since the age of 23 years for anxiety and depression and is currently well managed by her primary care provider on fluoxetine of 40 mg by mouth (PO) daily and lorazepam of 2 mg PO twice per day as needed for anxiety. Approximately 5 years ago, Nicole was also diagnosed with chronic migraines by a local neurologist and has been taking almotriptan of 12.5 mg PO as needed at onset of headache (may repeat dose in 2 hours, not to exceed 25 mg/24 hours). She follows up with a neurological nurse practitioner approximately every 9–12 months, and at each visit, the provider reviews the risk and symptoms of serotonin syndrome with Nicole given her concomitant SSRI and ''triptan'' use. At each visit, Nicole verbalizes understanding of the syndrome and maintains she has never had any issues during the times she has had to take both her fluoxetine and almotriptan together. Nicole is otherwise healthy, and the only other medication she takes is the occasional over-the-counter ibuprofen or acetaminophen for various muscle aching after exercising.

After a particularly stressful work week, Nicole presents to the local emergency room (ER) complaining of severe nausea/vomiting associated with a particularly bad migraine she has been experiencing for the past 48 hours. Upon initial evaluation by the ER physician, her vital signs are stable (36.7C, 105/72, 75, 15), and aside from moderate anxiety secondary to her current symptoms, her examination is relatively unremarkable. She reports that she has taken four doses of almotriptan in the past 48 hours with moderate relief. She has also taken her daily dose of fluoxetine, along with a dose of her lorazepam each night for the past two nights to help with her anxiety and sleep. She reports that, since the onset of her migraine, she has experienced unrelenting nausea and has vomited several times. She states that her initial headache has subsided with the almotriptan; however, she feels the vomiting continues to exacerbate the condition.

The ER physician orders ondansetron of 32 mg intravenous (IV) x1 now and lorazepam of 2 mg IV x1 now to address the nausea and anxiety. Thirty minutes after administration of these drugs, the ER nurse documents that Nicole reports her nausea has significantly subsided. The nurse also notates that Nicole appears mildly diaphoretic and sedated; however, she attributes this to the IV lorazepam. Approximately 10 minutes later, the ER

nurse enters the room to check on Nicole and finds her shivering in her bed, appearing mildly agitated. Upon speaking to Nicole, the nurse also notices that her hand movements seem uncoordinated and sluggish and she is also confused as to where she is and why she is at the hospital. Alarmed, the nurse takes Nicole's vital signs and finds her febrile at 38.3C, 140/98, 115, 18. The nurse immediately notifies the ER physician who orders STAT blood work along with a STAT neurology consult. The neurologist reviews Nicole's medications, including what she has received while in the ER, and after performing a physical examination, promptly diagnoses her with serotonin syndrome. Nicole is admitted to the ICU as a precaution and immediately discontinued from taking any further fluoxetine, almotriptan, or ondansetron. She is given diazepam of 10 mg PO Q6hrs as needed for agitation and tremor.

After a 48-hour stay in the hospital, Nicole's symptoms have completely resolved, and her vital signs are stable. She is discharged with the instructions to follow up with her neurological nurse practitioner within 48 hours. She is also discontinued from her fluoxetine and cautioned to avoid her almotriptan until she has discussed it with her neurology provider.

Discussion

When analyzing this case study, it might be easy to conclude that Nicole's diagnosis of serotonin syndrome stemmed from the combination of 40 mg of fluoxetine daily mixed with 50 mg of almotriptan over the course of 48 hours. Although this combination could most definitely be a contributing factor to her diagnosis, closer review of the medications she received in the ER is warranted.

A review of the metabolism of the drugs Nicole was taking at home finds that indeed the fluoxetine is metabolized by cytochrome P450 enzymes, specifically CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, and is both a substrate and an inhibitor of these enzymes. In addition, as is common with serotonin syndrome, the almotriptan is also metabolized by the CYP450 enzymes, specifically 2D6 and 3A4, and is considered a substrate. The pairing of these drugs alone causing Nicole's serotonin syndrome is a possibility, however unlikely given her asymptomatic tolerance of this drug combination over the past 5 years. Instead, one must take a closer look at the drugs given in the emergency room. Lorazepam is an unlikely suspect, because it is not metabolized by the CYP450 system and is actually used as a treatment for serotonin syndrome to control agitation and tremors. That leaves the ER physician's order for ondansetron of 32 mg IV. Ondansetron is metabolized by CYP450, specifically 2D6 and 3A4, as a substrate and an inhibitor (SuperCYP, 2014). The powerful combination of these three separate drugs, all metabolized by CYP2D6 and CYP3A4 and all acting as a substrate or inhibitor, aids the conclusion that this was the lethal combination causing excessive serotonergic activity in Nicole's nervous system, which led to her diagnosis of serotonin syndrome.

Implications for Practice

Serotonin syndrome is a challenging condition to try to avoid and/or manage in practice, whether it be a family practice setting or neurology. As stated above, currently, there are no practice guidelines for the prevention of serotonin syndrome. Most patients, when given an SSRI in combination with a triptan, will tolerate the combination and never develop serotonin syndrome (Lindsay, 2006). However, it is of vital importance to pay close attention to other drugs these patients are ingesting, especially their relationship within the CYP450 metabolism enzymes. It is important to have other options for treatment when dealing with high-risk patients who are taking several serotonergic drugs, drugs that interact with the CYP450 metabolism of these drugs, or patients who have experienced serotonin syndrome in the past.

When treating anxiety/depression concurrently with migraines, which are managed with triptans, there are several treatment options that can be explored. Bupropion is an acceptable first-line medication for anxiety/depression with a mild side effect profile and does not have appreciable serotonin activity. Another option, which may have more appreciable side effects but no serotonin activity, is desipramine (Benowitz, 2014).

Conversely, there are also other pharmacologic options for treating migraines in patients who are well managed on SSRIs (or SNRIs) for their anxiety/depression. There are several drugs available that are used as a prophylaxis or prevention of migraines. Some of the widely used ones include topiramate and propranolol. Other abortive migraine medications include ergotamine.

It is also important to note that, in the instance of this case study, the ultimate precursor to serotonin syndrome was the ondansetron given for nausea. As mentioned, it is possible that this drug combined with either the SSRI or the triptan individually could cause the illness as well without the combination of the other drug because this class of antinausea drugs are all serotonin antagonists. Some alternative drugs that are available to treat nausea/vomiting and do not involve serotonin activity include scopolamine and chlorphenoxamine.

Finally, as an acceptable alternative, amitriptyline is a tricyclic antidepressant that has been shown in the literature to address depression and can be used as a prophylactic treatment for migraine headache. Typically a third-line medication for depression because of its increased side effects, risk of overdose, and multiple drug interactions, it may be a viable option for a patient who has experienced serotonin syndrome and can no longer take the SSRIs or SNRIs (Goadsby & Raskin, 2012).

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Nursing Implications: Signs/Symptoms of Serotonin Syndrome

Initial symptoms usually occur within several hours of increasing drug dosage or taking a new drug.

- Restlessness/agitation
- Confusion
- Dilated pupils
- Headache
- Diarrhea
- Diaphoresis/rigors
- Tachycardia
- Loss of muscle coordination

Severe progression of the illness includes the following:

- High fever
- Cardiac arrhythmia
- Seizure
- Loss of consciousness

Conclusion

Individually, depression/anxiety and migraine headache are both challenging diagnoses that can take years of pharmacological trial and error to find an effective and appropriate treatment. Together, with the threat of serotonin syndrome lurking in the background, the dual diagnosis can be frustrating and timely. Practitioners must take polypharmacy into consideration when treating these conditions, and special attention should be paid to the CYP450 metabolism of all drugs given to these patients. Although rare, serotonin syndrome is a deadly threat and can have serious implications for the patient. However, with thorough patient education, careful management and observation, and pharmacological patience, these disorders can be successfully treated and managed.

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