Domperidone withdrawal in a breastfeeding woman

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Introduction

Domperidone is a peripheral dopamine D_2-receptor antagonist with both gastrokinetic and antiemetic activity via its inhibitory effects on dopamine receptors in gastrointestinal smooth muscle and the chemoreceptor trigger zone.[1] Health Canada–approved indications include the management of symptoms associated with upper gastrointestinal motility disorders, as well as the prevention of gastrointestinal symptoms associated with the use of dopamine agonists in Parkinson disease.[2] Despite a lack of official indication, domperidone has also been used to improve lactation in nursing mothers by stimulating prolactin release from the pituitary gland.[1,3-6] Its efficacy as a galactogogue has been shown in a few small randomized controlled trials of moderate to high quality, and no maternal or neonatal adverse events have been observed in any of the trials.[3-6]

Current practice suggests doses of 60 mg per day (20 mg 3 times daily) up to 160 mg per day (40 mg 4 times daily) to improve breast milk volume.[2,7] It is generally recommended to taper domperidone upon discontinuation to prevent engorgement or a sudden drop in milk supply, but there are few reports regarding the negative effects of abruptly discontinuing domperidone, as well as tapering schedule recommendations.[8]

We report a case of domperidone withdrawal in a nursing woman, along with a tapering schedule that appears to decrease the likelihood of withdrawal symptoms. We believe this case will shed light on the importance of tapering domperidone as well as provide a description of the symptoms of domperidone withdrawal in this population.

Description of case

A 37-year-old female patient gave birth via cesarean section at 38 weeks term. This patient had an unremarkable medical history and was taking no medications. Five days after delivery, the patient still had no milk production and was consequently started on domperidone 20 mg 3 times daily, with the option of increasing the dose to 4 times daily if necessary. The patient found domperidone to be effective at stimulating milk production at this dose. When milk production was satisfactory, the patient was instructed to attempt a slow taper off domperidone to ensure that her milk supply did not drop drastically. After several failed attempts to taper off, due to sudden drops in milk supply with slight decreases in dose, the patient continued on domperidone at a dose of 20 mg 4 times daily. After 8 months, the patient decided to stop breastfeeding and began to taper the domperidone to prevent breast engorgement. She immediately tapered down to 20 mg 3 times daily for the next 2 days, noticed a substantial decrease in milk supply and proceeded to stop breastfeeding and domperidone altogether. The entire length of the taper was approximately 3 days.

Two weeks after discontinuing domperidone, the patient presented with symptoms of insomnia and anxiety. Initially, the patient had difficulty maintaining sleep, which then progressed into difficulty falling asleep. To alleviate this, her physician prescribed alternating trials of clonazepam 0.5 mg and zopiclone 7.5 mg at bedtime as needed for several weeks. While the medications did help her fall asleep, they failed to keep her asleep, did little to improve her other symptoms and also caused next-day hangover

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effects. The patient also became tachycardic, with her heart rate increasing above 90 beats per minute when her normal range was between 50 and 60 beats per minute.

After 8 weeks of experiencing these symptoms, the patient contacted her pharmacist and physician to determine if the symptoms could be related to the abrupt cessation of domperidone. Her physician tested for and ruled out anemia and thyroid disorder and recommended that she resume the full dose of domperidone and try to slowly taper off the medication in consultation with her pharmacist. A tapering regimen of 10 mg per week was adopted based on anecdotal evidence from Dr. Jack Newman of the Newman Breastfeeding, Inc. Clinic and Institute.[9] Within the first week of the 8-week taper, the patient reported an improvement in symptoms, and by the second week, the patient no longer required sleep aids and her heart rate normalized. The patient experienced no further symptoms of insomnia, anxiety or tachycardia throughout the remainder of the 8-week taper.

Discussion

We believe the symptoms experienced by our patient were related to the abrupt discontinuation of domperidone after 8 months of consecutive use. To our knowledge, this is the first published report of domperidone withdrawal consisting of tachycardia, insomnia and anxiety, but there is evidence that histamine H_2-receptor antagonist withdrawal can produce similar symptoms via a mechanism that may also explain the domperidone withdrawal that we observed.[10] There is also another published case of domperidone withdrawal, but it occurred in an elderly woman with dementia who had probable withdrawal psychosis after abrupt cessation of domperidone after being on it for 10 years.[11] In the studies that examined the efficacy of domperidone as a galactogogue, the duration of treatment with domperidone was 2 weeks or less and the dose was 30 mg per day, much less than that of our patient (80 mg/day for 8 months).[3,4-6] Both the extended duration of treatment as well as the higher dose of domperidone may have contributed to the withdrawal symptoms by inducing tolerance to the medication.

The strength of the observed association between domperidone cessation and symptom development relates to time course, lack of other possible explanations for the observed symptoms and biologic plausibility. The time course was consistent with the theory of a domperidone withdrawal syndrome. The symptoms of tachycardia, insomnia and anxiety began a few weeks after discontinuation of domperidone and continued until shortly after the drug was readministered. The Naranjo adverse drug reaction probability scale designates probabilities as doubtful, possible, probable or definite. According to this scale, the abrupt withdrawal of domperidone is a probable cause of the undesirable symptoms experienced by our patient.[12]

Other possible explanations for the observed symptoms include diagnoses of an acute anxiety disorder or insomnia. However, clonazepam and zopiclone were relatively ineffective at reducing the severity of the patient's symptoms and were no longer required 2 weeks after restarting domperidone. Additionally, there were no notable triggering stressors that the patient could pinpoint as the cause of her symptoms. Finally, hyperthyroidism and anemia were also ruled out as possible explanations for the patient's symptoms through blood tests.

In order for a domperidone withdrawal syndrome to be biologically plausible, a certain degree of domperidone tolerance must develop over the treatment period. Because domperidone does not appear to cross the blood-brain barrier in any significant amount, domperidone withdrawal symptoms cannot be accounted for by direct central nervous system effects of the drug. We propose that the withdrawal effects observed following cessation of domperidone are mediated by abrupt drops in plasma prolactin subsequent to sustained hyperprolactinemia induced by long-term domperidone treatment. This notion is supported by a study by Rampello et al.,[10] in which patients who discontinued long-term cimetidine and ranitidine, H_2-receptor antagonists that can induce hyperprolactinemia, experienced withdrawal symptoms that included those described by our patient. The emergence of withdrawal symptoms was associated with a drop in prolactin levels, and treatment with domperidone restored prolactin levels and improved withdrawal symptoms in the patients. This explanation appears to be consistent with the rationale for recommending a domperidone taper in nursing women.[9]

As stated previously, the intended purpose of this case report was to present a feasible

tapering schedule for patients on long-term domperidone who reported withdrawal symptoms. Consequently, patients with these symptoms who have recently received domperidone therapy should be questioned to determine whether they stopped the drug abruptly. If that is the case, an attempt to restart the medication at the full dose and slowly taper by approximately 10 mg per week may be a reasonable option. Note that because our recommendations are anecdotal at best, further study is required to validate this approach. Subsequently, it is not yet clear whether this approach can be extrapolated to other patient populations, such as those using domperidone to treat gastrointestinal motility disorders.

Conclusion

Studies have shown the efficacy and safety of the off-label use of domperidone as a galactogogue, but there is currently a lack of information regarding 1) the withdrawal symptoms associated with an abrupt discontinuation of long-term domperidone and 2) an optimal tapering regimen to minimize these withdrawal symptoms. Our case report demonstrates insomnia, anxiety and tachycardia as examples of potential withdrawal symptoms. In addition, our case report supports a 10 mg per week taper as an effective and safe regimen for nursing mothers on long-term domperidone therapy. Nevertheless, further studies on this subject are warranted to provide better evidence for the optimal care of nursing mothers and their newborn infants. ■

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