ISMP Adverse Drug Reactions

Pregabalin-Induced Stuttering

Nitroglycerine-Induced Bradycardia Progressing to Asystole

Minocycline-Induced DRESS Leading to Liver Transplantation and Type 1 Diabetes

Increased Risk of Vertebral Fractures in Women Receiving Thiazide or Loop Diuretics

Gambling Disorder and Impulse Control Disorder with Aripiprazole

*Michael A. Mancano, PharmD**

The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA's) MedWatch program (800-FDA-1088). If you have reported an interesting, preventable ADR to MedWatch, please consider sharing the account with our readers. Write to Dr. Mancano at ISMP, 200 Lakeside Drive, Suite 200, Horsham, PA 19044 (phone: 215-707-4936; e-mail: mmancano@temple.edu). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MedWatch program and Temple University School of Pharmacy. ISMP is an FDA MedWatch partner.

PREGABALIN-INDUCED STUTTERING

A 31-year-old female was seen in a physical medicine and rehabilitation clinic for complaints of a painful, swollen left foot for the previous 2 months after an ankle sprain. The patient also had burning, tingling, and numbness in her foot along with redness of the skin. When the patient was examined, it was found that she had localized

swelling of the foot, sensitivity to touch, abnormally increased sweating and skin temperature, redness of skin color of her foot, and restricted, painful ankle movement. A myriad of possible causes were ruled out, which included deep vein thrombosis, peripheral vascular disease, diabetes mellitus, recurrent or habitual spontaneous abortion, smoking, or oral contraceptive use.

*Chair and Clinical Professor, Department of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, Pennsylvania; Clinical Advisor, Institute for Safe Medication Practices, Horsham, Pennsylvania

The patient was diagnosed with complex regional pain syndrome (CRPS) based on her signs and symptoms that fulfilled the Budapest diagnostic criteria for CRPS. The patient was started on pregabalin (*Lyrica*) 75 mg for the management of her neuropathic pain. After taking the second dose of pregabalin on the first day of therapy, her speech became slurred and she immediately stopped taking pregabalin. The patient was seen at an emergency department with difficulty speaking. The patient had no other medical illness other than CRPS and she exhibited no symptoms other than stuttering. The patient underwent a complete neurologic evaluation to rule out an acute neurologic disorder. A cranial CT scan and MRI did not reveal any abnormalities. The patient was followed daily for one week, and after one week her stuttering resolved completely.

Giray et al point out that pregabalin is an analogue of GABA and binds to the $\alpha 2\text{-}\delta$ subunit of voltage-gated calcium channels in the central nervous system (CNS); it reduces calcium flow therefore decreasing GABAergic neurotransmission. A speech disorder, as described in the patient, has not been described as a possible adverse effect of pregabalin. Stuttering has been attributed to dopaminergic hyperactivity in the CNS. It has been proposed that GABA is a major inhibitory neurotransmitter of the CNS that modulates dopaminergic activity. Imbalance between excitatory and inhibitory neurotransmission can lead to dysfunction in white matter fiber tracts that are associated with areas of the brain linked to speech production. Therefore, the GABA analogue pregabalin may deteriorate the neurotransmitter balance in these areas of the brain.

The authors reveal that gabapentin, which is a structural analogue of pregabalin, has been associated with stuttering. Other classes of medications that have an association with enhancing and reducing stuttering are antipsychotics and tricyclic antidepressants. The fact that medications may enhance stuttering may also be associated with a reduction in stuttering points to the multiple, interacting neurotransmitter systems involved in the mechanism of stuttering. The authors warn that stuttering should be recognized as a possible adverse effect of pregabalin therapy.

Giray E, Toprak CS, Sacakhdar R, et al. Pregabalin-associated stuttering in a patient with complex regional pain syndrome. A case report. *J Clin Psychopharmacol*. 2016;36(6):740-742.

NITROGLYCERINE-INDUCED BRADYCARDIA PROGRESSING TO ASYSTOLE

A 53-year-old male was admitted to an emergency department with intermittent chest pressure. The patient had no prior history of cardiac disease, and his initial ECG revealed normal sinus rhythm. The patient received 0.4 mg of nitroglycerin; after his second dose, he became unresponsive. The cardiac monitor revealed asystole for a full 24 seconds. The patient had no palpable peripheral pulses, and chest compressions were started. The patient regained consciousness shortly after, however his heart rate remained in the 30s. The patient was then given atropine, and his heart rate increased into the 60s. A second ECG revealed a junctional rhythm with no ischemic changes; a third ECG minutes later revealed normal sinus rhythm without any ischemic changes. The patient was admitted to the hospital, and the next day he had a stress test. The result of the stress test was normal, and the patient was discharged.

Thomas et al published this case report to highlight this easily forgotten adverse effect of hypotensive bradycardia progressing to asystole with the use of nitroglycerin. This reaction was initially attributed to ongoing myocardial ischemia. However, this patient had no documented cardiac disease and had ECG data that did not indicate myocardial ischemia. The authors reviewed the literature and report that the small number of reported cases of nitroglycerin-induced asystole all resolved spontaneously to a bradycardiac rhythm. In reviewing the case reports, the authors note that there are no unifying factors that could be identified to predict which patients will experience this adverse effect. To further strengthen the interpatient variability of this adverse reaction, 5 patients who experienced nitroglycerin-induced bradycardia all took the medication at home with no negative sequelae but experienced the adverse effect in the hospital.

Thomas et al explain, "Researchers have focused on physiologic parameters to understand this alarming adverse effect; with reversal of bradycardia with atropine, vagal nerve involvement has been established. One popular theory is the Bezold-Jarisch reflex. Melenovsky et al tested this theory and showed that some patients have statistically significant delayed reactions to hypotension leading to cardiovascular collapse. Such patients are predisposed to experiencing nitroglycerin-induced asystole." The authors point out that while the adverse reaction is rare, it cannot be predicted without rigorous physiologic testing. They warn that it is prudent to be aware of this side effect caused by such a commonly used medication.

Thomas J, Saenz E, Haggerty P. Nitroglycerin-induced asystole: A common therapy with a rare adverse effect. *Am J Med.* 2016;129(10):e245-e246.

Melenovsky V, Wichterle D, Malik J, et al. Nitroglycerin induced syncope occurs in subjects with delayed phase shift of baroreflex action. *Pacing Clin Electrophysiol.* 2002;25: 828-832.

MINOCYCLINE-INDUCED DRESS LEADING TO LIVER TRANSPLANTATION AND TYPE 1 DIABETES

A 13-year-old female experienced a drug reaction with eosinophilia and systemic symptoms (DRESS) after 3 weeks of minocycline therapy for acne. At diagnosis, she had an eosinophil level of 1,992 cells/mcL (normal range, <500 cells/mcL), leukocyte level of 24,000 cells/mcL (normal range, 4,500-11,000 cells/mcL), temperature of 105.8°F (41°C), aspartate aminotransferase of 566 U/L (normal range, 10-30 U/L), alanine aminotransferase 655 U/L (normal range, 10-40 U/L), bilirubin level of 1.4 mg/dL (normal range, 0.3-1.2 mg/dL), creatinine level of 1.5 mg/dL (normal range female, 0.6-1.1 mg/dL), serum urea nitrogen 14 mg/dL (normal range, 8-23 mg/dL), and positive test result for activated human herpes virus virus-6 (HHV6). The patient was treated with high-dose corticosteroids; however within 48 hours, the patient developed liver failure and received a donor liver transplant the following day. The patient's posttransplant immunosuppressive regimen included tacrolimus, mycophenolate mofetil, and prednisone.

Lan et al, in their case report, review the standard presentation and progression of DRESS, which includes rash, hematologic abnormalities, lymphadenopathy, and internal organ involvement. The initial signs of fever, rash, and increased transaminase levels usually resolve once the acute episode subsides. However, autoimmune sequelae can develop long after the initial DRESS event with patients possibly developing thyroid dysfunction, lupus, and type 1 diabetes mellitus. The type 1 diabetes that can develop is usually characterized as an extreme non-autoimmune rapid beta-cell destruction. However, some patients rarely develop an autoimmune type 1 diabetes.

Five months after transplantation, the patient became hyperglycemic with a blood glucose of 529 mg/dL (normal range, 70-110 mg/dL). Routine laboratory testing conducted one month earlier did not reveal hyperglycemia. The patient was receiving 1 mg/kg of prednisone on discharge from the hospital after transplantation, but the patient had been slowly tapered to 0.5 mg/kg for 2 months prior to her hyperglycemia. The patient did not report symptoms of diabetes such

as polyuria or polydipsia, but a hemoglobin A1c drawn at this time was 9.4% (normal range, ≤7%).

Tests of autoimmunity gave some interesting results. The patient had a glutamic acid decarboxylase antibodies detected of 2 U/mL (negative level < 0.5 U/mL). The patient however did not test positive for islet cell antibodies. She tested positive for antithyroid peroxidase with a level of 18 IU/mL (negative level < 9 IU/mL) and antithyroglobulin antibodies 6.7 IU/mL (negative level < 1 IU/mL). These tests indicate thyroid involvement, but the patient's thyroid stimulating hormone and free thyroxine levels were within normal limits. The patient's diabetes was managed with insulin therapy. Ten months later, the patient developed rapid-onset alopecia of unclear etiology, however an autoimmune pathogenesis was suspected.

Lan et al discuss the potential pathogenesis of post-DRESS autoimmunity. Although the exact mechanism post-DRESS autoimmunity is unclear, it is believed that T-regulatory cells play a significant role. T-regulatory cells increase significantly during the acute stages of DRESS. With this increase in T-regulatory cells and therefore increased immune suppression, viruses such as HHV6 can reactivate in an uncontrolled fashion. Epstein-Barr and cytomegalovirus are also associated with DRESS. The exact mechanism of how viruses contribute to post-DRESS autoimmunity needs further investigation. Additionally, minocycline is obviously a contributing factor. There have been reports of minocycline-induced autoimmunity without DRESS. Minocycline can cause various symptoms including polyarthralgia, autoimmune hepatitis, lupus, and vasculitis.

Lan et al warn that is important for health care professionals to be aware of potential complications of DRESS and to perform appropriate screenings and provide timely treatment. In this case, the patient's post-DRESS complication of diabetes was discovered incidentally. It is important for clinically relevant laboratory studies to be performed for a timely diagnosis to prevent serious complications during and in the post-DRESS period.

Lan J, Lahoti A, Lew DB. A severe case of minocycline-induced DRESS resulting in liver transplantation and autoimmune sequelae. *Ann Allergy Asthma Immunol.* 2016; 116:367-368.

INCREASED RISK OF VERTEBRAL FRACTURES IN WOMEN RECEIVING THIAZIDE OR LOOP DIURETICS

Paik et al conducted a prospective cohort study of thiazide diuretic use, loop diuretic use, and the risk of incident clinical vertebral fracture in 55,780

women, 55 to 82 years of age, without a prior history of any fracture, and participating in the Nurses' Health Study. Potential confounding variables related to vertebral fracture risk were controlled statistically. These confounding variables included age, body mass index, race, smoking status, physical activity, self-reported history of falls, hypertension, diabetes, osteoporosis, postmenopausal hormone use, antihypertension medication use, antidepressant medication use, bisphosphonate use, and oral steroid use. Vertebral fractures had to be clinician-diagnosed and confirmed by radiology report or medical report.

Thiazide diuretic use was found to be independently associated with an increased risk of vertebral fracture in women. After adjusting for confounding variables, thiazide use was associated with an increased risk of clinical vertebral fracture with a relative risk (RR) 1.47 (95% CI, 1.18-1.85). Loop diuretic use was also found to be independently associated with an increased risk of vertebral fracture in women. After adjusting for confounding variables, loop diuretic use was associated with an increased risk of clinical vertebral fracture with an RR 1.59 (95% CI, 1.12-2.25).

Paik et al noted that the higher risk of vertebral fracture in their study with thiazide diuretic use was unexpected, because prior research studies have shown thiazides to possibly be protective for hip and vertebral fractures. Other studies have found no statistically significant association between thiazides and vertebral fracture. Thiazides are known to decrease urinary calcium excretion and improve calcium balance, which preserves bone mineral density at the vertebral body. However, thiazides can induce hyponatremia, and several recent studies suggest that hyponatremia is associated with increased fracture risk. Hyponatremia directly affects bone, mainly via activation of osteoclasts. Raised osteoclast activity increases bone resorption without concomitant bone formation, impairing local repair of microdamage and decreasing bone quality, thereby increasing fracture risk, all of which is not identified by bone mineral density measurements. Skeletal bone is a rich reservoir of sodium and may play a key role in maintaining sodium homeostasis, possibly at the expense of bone's structural integrity.

Loop diuretics are known to increase urinary calcium excretion, which could lower bone mineral density, which is a known risk factor for vertebral fracture; conversely loop diuretics rarely cause hypo-

natremia. The mechanisms by which loop diuretic use increases vertebral fracture risk are likely different from the mechanisms for thiazide diuretics. Possible mechanisms include the calciuric effect of loop diuretics, subsequent increase in plasma parathyroid hormone level, and decreased bone mineral density.

The authors state, "Among women with hypertension who are at high risk for vertebral fracture, diuretics should be used cautiously. Further research is warranted on diuretics and vertebral fracture risk, especially because thiazides are so commonly prescribed for the treatment of hypertension."

Paik JM, Rosen HN, Gordon CM, et al. Diuretic use and risk of vertebral fracture in women. *Am J Med*. 2016;129:1299-1306.

GAMBLING DISORDER AND IMPULSE CONTROL DISORDER WITH ARIPIPIRAZOLE

Etminan et al conducted a pharmacoepidemiologic nested case-control study to demonstrate the link between aripiprazole and impulse control problems. The investigators utilized the data from a large health claims database in the United States. They identified patients diagnosed with gambling disorder or impulse control disorder and matched control patients based on age, follow-up time, and calendar time. The risk of gambling disorder or impulse control disorder was assessed versus 2 positive controls (pramipexole and ropinirole) that have been associated with an increased risk of gambling.

Etminan et al identified 355 cases of gambling disorder in the health claims database. The patients were an average age of 44 years old, with the population being 51% male. Compared with nonusers, patients receiving aripiprazole had an adjusted RR 5.23 (95% CI 1.78-15.38) for a gambling disorder. The mean time for exposure to aripiprazole was 20 days. The investigators identified 4,341 cases of impulse control disorder in the claims database. The patients were an average of 37 years old, with the population being 63.6% male. Compared with nonusers, patients receiving aripiprazole had an adjusted RR 7.71 (95% CI, 5.81-10.34) for an impulse control disorder. The mean time for exposure to aripiprazole was 54 days.

The authors state, "The results of our study are consistent with reports and the FDA warning of an increase in risk of gambling and impulse control behavior with aripiprazole, pramipexole, and ropinirole although generally these events are rare. Our data

also suggest that bipolar patients taking aripiprazole have a higher risk of developing a gambling disorder compared with patients with bipolar disorder not on aripiprazole.” They also identified several mechanisms by which dopamine agonists may increase the propensity of gambling and impulse control problems.

These medications activate D3 receptors within the limbic circuit of the brain, and D3 receptors are thought to be involved in gambling disorder.

Etminan M, Sodhi M, Samii A, et al. Risk of gambling disorder and impulse control disorder with aripiprazole, pramipexole and ropinirole. *J Clin Psychopharmacol*. 2017;37:102-104. ■