ISMP Adverse Drug Reactions

Recurrent Small Intestinal Ileus Due to Valsartan

Compulsive Behaviors Related to Rasagiline Use

Lacosamide-Induced Acute Pancreatitis

Brief Psychotic Disorder After Abrupt Withdrawal of
Hydroxyzine

Hydroxyurea-Associated Acral Erythema

Penicillamine-Induced Degenerative Dermatositis

*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.

RECURRENT SMALL INTESTINAL ILEUS DUE TO VALSARTAN

A 57-year-old male physician was admitted to the hospital after 3 days of diffuse severe abdominal pain. The patient had a history of several similar episodes over the previous 12 months with each episode lasting 5 to 7 days; each time he reported feeling well after resolution. During this admission, the patient also reported abdominal distention, nausea, and constipation. The patient did not have a history of abdominal surgery, abdominal trauma, or episodes of bowel obstruction. The patient's current medical

conditions included hypertension and hypercholesterolemia. His medication history included valsartan (*Diovan*) 160 mg daily, which he had been receiving for the past 2 years, and pravastatin 20 mg daily, which he had been receiving for the past 5 years.

On physical examination, the patient exhibited diffuse abdominal tenderness and decreased bowel sounds. All of the patient's blood tests were within normal limits, including a complete blood count, liver function tests, renal function tests, electrolytes, and amylase and lactic acid levels. However, imaging studies demonstrated a small bowel obstruc-

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

tion with dilation of the proximal jejunum, duodenum, and stomach. A laparotomy was performed, however no mechanical obstruction was found. The patient was treated conservatively and his symptoms resolved completely after 5 days. He was then discharged.

During the following year, the patient was admitted to the hospital 3 more times with the same complaints. During the admissions, the patient was treated conservatively with NPO and intravenous fluids. In each of the 3 instances, the patient's symptoms resolved after 5 to 7 days of conservative treatment. The patient received an upper endoscopy, colonoscopy with ileoscopy, and push enteroscopy; all studies had normal findings. Concurrent imaging studies did not reveal any abnormalities that could explain the patient's recurrent obstructions. Biopsies taken from the stomach, duodenum, jejunum, ileum, and colon were all normal.

Approximately 1 year after the onset of the patient's abdominal symptoms, he discontinued taking valsartan for an unknown reason. After the valsartan was discontinued, his symptoms completely resolved. At 1 year of follow-up, the patient feels well, without any abdominal pain, obstructive symptoms, or other gastrointestinal complaints.

The authors believe that there is a direct association between valsartan and the patient's abdominal symptoms. They hypothesize that a potential mechanism could be the presence of angiotensin receptors in the intestinal mucosa. Animal models have demonstrated the effect of angiotensin on bowel motility, and angiotensin receptors occur in the jejunum and ileum. Human data from the human esophagus and jejunum suggest that angiotensin 1 (AT1) receptors mediate muscular contractions and AT2 receptors regulate epithelial function. In an animal model, the effect on contractility of angiotensin II in the colon has been shown whereas losartan can antagonize these effects. These findings demonstrated the positive promotile effects of angiotensin II on the large and small intestine and the potential for angiotensin II receptor antagonists to block this effect.

The authors recommend that patients with chronic or recurrent abdominal pain and other signs of bowel obstruction who receive valsartan with or without other medications that effect the renin angiotensin system should be assessed for the role of these medications in causing abdominal symptoms.

Saadi T, Brun R, Chowder Y, et al. Recurrent small intestinal ileus secondary to valsartan treatment. *J Clin Gastroenterol*. 2014;48(5):462.

COMPULSIVE BEHAVIORS RELATED TO RASAGILINE USE

A 70-year-old male experienced counting compulsions and ritualistic behaviors and was admitted to a psychiatric ward. A medication history revealed that 1.5 years previously the patient had been started on ropinirole 12 mg daily and rasagiline (*Azilect*) 1 mg daily for the treatment of Parkinson's disease (PD). Despite a partial remission of PD symptoms and increased functionality, the patient had stopped using rasagiline approximately 1 year previously due to erectile dysfunction. However, 2 months previously, 1 mg daily of rasagiline had been added to his ongoing dose of ropinirole 12 mg daily because his symptoms of PD had worsened. A few days after reinitiating rasagiline, the patient began to repeatedly count the number set of 3, 13, and 23 before performing specific actions throughout the day. The patient reported anxiety symptoms only on the 23rd day of consecutive months. The patient had no personal or family history of psychiatric disorder, and a brain MRI revealed no significant abnormalities. A Mini-Mental State Examination was administered and the patient scored a 30 (scores ≥ 27 reveal normal cognition).

On admission, the patient scored an 18 on the Yale-Brown Obsessive Compulsive Scale (YBOCS). The YBOCS scoring is as follows: 0–7 = *sub-clinical*; 8–15 = *mild*; 16–23 = *moderate*; 24–31 = *severe*; and 32–40 = *extreme*. Neurologists treating the patient decided to continue the patient's rasagiline, because he had experienced significant improvement in his PD symptoms. Sertraline 25 mg daily was initiated and titrated up to 75 mg daily to treat the patient's compulsive symptoms, and his YBOCS score decreased to 13.

The authors point out that dysfunctions of the mesocorticolimbic pathways may cause repetitive, compulsive behaviors in humans. The basis for drug-induced pathologic behaviors might be related to alterations in dopamine neurotransmission along these pathways. Dopamine replacement therapy leading to changes in dopamine levels and frontal lobe dysfunctions may precipitate the occurrence of these abnormal behaviors. Rasagiline increases the concentration of catecholamines and dopamine at the synaptic space by blocking MAO-B enzyme. Because of the possibility that it stimulates postsynaptic dopamine receptors at dysfunctional corticostriato-thalamo-cortical circuits, rasagiline may account for the compulsive behaviors developed by the patient.

Sevincok L, Kunt DA, Ozgur BG. Compulsive behaviors related to rasagiline: A case report. *J Clin Psychopharmacol*. 2014;34(4):529-530.

LACOSAMIDE-INDUCED ACUTE PANCREATITIS

A 46-year-old male was admitted to the hospital with complaints of epigastric pain and vomiting. The patient had not had any alcohol intake and had been receiving lacosamide (*Vimpat*) 100 mg daily for 1 year to treat his fibromyalgia. One month prior to his current admission, the patient had been admitted for necrotizing acute pancreatitis (AP) affecting 30% of the gland, with full recovery. After discharge from his prior admission, the patient continued to receive lacosamide 100 mg daily.

Laboratory test results obtained during the current admission revealed: amylase 409 U/L (reference range, 0-100 U/L), aspartate aminotransferase (AST) 16 U/L (reference range, 0-31 U/L), alanine aminotransferase (ALT) 8 U/L (reference range, 0-31 U/L), alkaline phosphatase 77 U/L (reference range, 35-104 U/L), gamma glutamyl transpeptidase 32 U/L (reference range, 7-32 U/L), total bilirubin 0.36 mg/dL (reference range, 0.1-1.1 mg/dL), C-reactive protein 19.2 mg/dL (reference range, 0-8 mg/dL), and hemoglobin 11.8 g/dL (reference range male, 13.8-17.2 g/dL). An abdominal ultrasound revealed no gall stones in the gall bladder and a heterogenous pancreas with a layer of peripancreatic fluid. Lacosamide was discontinued at that time.

An MRI cholangiography conducted 4 weeks after the discontinuation of lacosamide revealed fluid collection adjacent to the pancreas and a pseudocyst that displaced the stomach. The patient remained asymptomatic after a year of follow-up without lacosamide.

The authors concluded that lacosamide was the likely cause of the patient's pancreatitis. Although drug-induced pancreatitis is rare, clinicians should closely evaluate the patient's medication history with a focus on recently added medications when evaluating a patient with pancreatitis of unknown cause.

del Val Antoñana A, Blé Caso M, Higón Ballester MD, et al. Lacosamide-induced acute pancreatitis with positive rechallenge test. *J Clin Gastroenterol*. 2014;48(7):651.

BRIEF PSYCHOTIC DISORDER AFTER ABRUPT WITHDRAWAL OF HYDROXYZINE

A 32-year-old woman was admitted to the hospital because of unusual behavior that had started

the previous day. The woman was of Egyptian decent and a resident of Sweden. She was about to board an airplane with her sister and 2 children when security denied her access because of her apparent agitation and anxiety. The patient was seen by an emergency room physician and he recommended that she not fly in her current condition, so she returned to her hotel without any treatment. According to her sister's description, the patient's anxiety and agitation persisted and the next day she described strange people in her hotel room. This behavior progressed to the point where she did not recognize her own family members. At this time, her sister called for emergency services.

When the patient arrived at the hospital, she was given a mental examination. She was alert but not fully oriented (ie, misjudged a police officer as an Arabic relative), and she was barely cooperative (tried to escape from the hospital). Her speech was accelerated and her language switched between Arabic and English and was inappropriate for the conversation. The patient continued to be highly agitated and anxious.

On physical exam, the patient had a normal blood pressure and no evidence of dehydration. Chem-7 was within normal limits, except for an elevated blood glucose of 146 mg/dL (reference range, 70-99 mg/dL). The patient had not consumed alcohol or received any drugs of abuse. A CT scan of her brain showed no abnormal pathologic findings. Additional background information provided by the patient's sister revealed no history of psychiatric disorders but described stressful family situations during the previous weeks. In light of these events, the patient had developed anxiety and depression for which she sought medical attention. Three weeks prior to admission, the patient had been started on hydroxyzine hydrochloride (*Atarax*) 25 mg 3 times daily. Two days before her current symptoms, the patient had stopped her hydroxyzine abruptly because of substantial relief in her anxiety and tension.

The authors point out that hydroxyzine primarily blocks histamine (H_1) receptors but additionally acts on serotonin ($5HT_2$), muscarinic, dopamine (D_1/D_2), and α -adrenergic receptors. Hydroxyzine may be associated with hallucinations, most likely due to overdose or in combination with other sedatives, alcohol, or lithium. However, neither hydroxyzine overdose nor additional medication or substance abuse was the case in this patient. The patient denied any concomi-

tant medication prior to admission, and hydroxyzine was the only medication she was receiving.

Prior research with the use of hydroxyzine found that abrupt discontinuation did not demonstrate rebound or withdrawal symptoms. This information is in accordance with recommendations that tapering of hydroxyzine is generally not necessary. However, as evidenced by the current patient, psychiatric adverse effects should be taken into consideration upon abrupt withdrawal.

After the patient was admitted, she was initiated on haloperidol 5 mg twice daily and lorazepam 1 mg 4 times daily. The patient quickly had relief of her symptoms, and the dosages of haloperidol and lorazepam were reduced and tapered completely until her discharge 10 days later. The patient was discharged fully oriented and without psychotic symptoms. She denied having anxiety, but her mood was rather depressed and continuous psychiatric treatment was recommended.

The authors summarize that hydroxyzine is an effective drug for the treatment of anxiety and tension, but patients should be informed that abrupt withdrawal of hydroxyzine can be associated with psychotic symptoms. Therefore, the authors recommend a gradual taper of hydroxyzine.

Bock O, Wenzel C, Herrmann J, et al. Brief psychotic disorder after abrupt withdrawal of hydroxyzine hydrochloride. *J Clin Psychopharmacol*. 2014;34(4):526-527.

HYDROXYUREA-ASSOCIATED ACRAL ERYTHEMA

A 64-year-old male complained of 3 years of progressive redness, burning, and peeling of the skin on the palms of his hands and soles of his feet. The patient had a history of cutaneous squamous cell carcinoma, malignant melanoma, gout, and polycythemia vera. He had been diagnosed with polycythemia vera 10 years earlier. He was initially treated with hydroxyurea (*Hydrea*) 1 g daily with dose escalation to 1.5 g daily over the last 3 years for management of his polycythemia and worsening splenomegaly.

On physical examination, the patient had desquamating erythema of the palms and soles, extending proximally to the flexures of the wrists and heels. The patient reported that his symptoms worsened as the dose of hydroxyurea was increased over the previous 3 years.

The authors diagnosed the patient with hydroxyurea-associated acral erythema. This condition manifests as erythema and desquamation of the palms and soles and has been referred to as palmar-plantar

erythrodysesthesia, toxic erythema of chemotherapy, or hand-foot syndrome. This condition has been associated with a variety of medications, particularly chemotherapeutic agents. Severe cases of acral erythema can result in the focal formation of blisters. Upon review of the literature, the authors point out that this condition is associated with long-term hydroxyurea use, usually at doses equal to or greater than 1 g daily. Symptoms can begin anywhere from weeks to years after initiation of an offending agent. The reaction is variably reversible with discontinuation of the offending agent, but symptoms of pain and discomfort can persist for months. This condition is well described with various medications, but the exact pathogenesis is unknown.

Butler D, Nambudiri VE, Nandi T. Hydroxyurea-associated acral erythema in a patient with polycythemia vera. *Am J Hematol*. 2014;89:931-932.

PENICILLAMINE-INDUCED DEGENERATIVE DERMATOSIS

A 60-year-old male presented to the physician with asymptomatic brownish-red papules organized in multiple curved to ring-like formations on his upper trunk and arms. The patient had significant cutis laxa (inelastic or loose skin) and cutis rhomboidalis nuchae. Cutis rhomboidalis nuchae is a condition in which the skin on the back of the neck becomes leathery and furrowed and appears to have rhomboid configurations. The patient noted he had been treated with penicillamine (*Cuprimine*) 1 to 1.5 g daily for more than 40 years to treat his Wilson's disease.

Upon histopathologic examination, the patient's skin had channels through the epidermis formed by follicular epithelium. There was significant cellular debris, neutrophils, and corneocytes. An accumulation of altered elastic fibers were present within the upper part of the dermis. These findings lead to the diagnosis of elastosis perforans serpiginosa (EPS) caused by long-term ingestion of penicillamine.

Wilson's disease is a rare autosomal condition caused by a genetic defect in the copper-transporting ATPase ATP7B. Copper accumulation in the liver and basal ganglia of the brain may lead to hepatocerebral degeneration. Penicillamine is an effective treatment for Wilson's disease, because it is a chelating agent that depletes copper. Long-term penicillamine therapy can induce EPS by reducing the activity of lysyl-oxidase, a copper-dependent enzyme that cross-links dermal elastic fibers, and by the

formation of complexes with precursors of elastic fibers. The authors point out that their patient had been receiving penicillamine for more than 40 years, which is well above the average 10-year interval after which EPS may be acquired. In patients with penicillamine-induced EPS, an alternative copper-chelating agent such as trientine dihydrochloride

may be utilized. The authors offered liquid nitrogen cryotherapy or ablative laser resurfacing to the patient to treat the condition, but the patient did not return for follow-up visits.

Hellriegel S, Bertsch HP, Emmert S, et al. Elastosis perforans serpiginosa: A case of penicillamine-induced degenerative dermatosis. *JAMA Derm.* 2014;150(7):785-787. ■