Hosp Pharm 2015;50(8):662–666

www.hospital-pharmacy.com
doi: 10.1310/hpj5008-662

ISMP Adverse Drug Reactions

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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.

TRIMETHOPRIM-SULFAMETHOXAZOLE–INDUCED RHABDOMYOLYSIS

A 64-year-old male in good health was admitted to a hospital in Romania after complaining of bilateral lower extremity pain, severely impaired walking, and tea-colored urine. The patient stated he had been to the emergency department 2 days earlier for the same pain and dark urine, but his condition progressively worsened over the previous several days. The patient's medication history revealed he had been self-medicating with trimethoprim-sulfamethoxazole (TMP-SMX) 40 mg/800 mg. He had been taking 3 tablets daily for the previous 2 weeks for what he termed a urinary tract infection (UTI). The patient stated that he had a UTI in the past and the doctor had given him TMP-SMX, so he had obtained some and was treating the condition himself.

The patient reported that while he was taking TMP-SMX, he began to experience lower extremity pain. He described the pain as gradual and increasing in intensity. He initially sought medical attention at the emergency department 2 days earlier but was

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discharged and referred to a neurologist in 2 days, with suspected polymyositis. His creatine kinase (CK) at the time was 1,524 U/L (normal range, 30-170 U/L). After initial discharge, the patient's pain increased and he began to take ibuprofen 200 mg daily, celecoxib 200 mg daily, and piroxicam 20 mg daily. He had taken *Algocalmine* (sodium metamizole 500 mg) 2 tablets daily. This product is an analgesic and antipyretic not available in the United States. He also took *Antinevralgic* (acetylsalicylic acid [ASA] 250 mg, phenacetin 150 mg, caffeine 50 mg) 2 pills daily (also a foreign product). The patient consulted a rheumatologist and received the parenteral nonsteroidal anti-inflammatory drugs (NSAIDs) ketorolac 30 mg and meloxicam 15 mg.

When the patient returned to the emergency room, he could barely walk and was having intense pain in the lumbar region and in his legs. The patient also had dark urine and oliguria. Labs taken at this time revealed a CK of 64,691 U/L, elevated transaminases, lactate dehydrogenase, mild acidosis, hyponatremia, and hyperuricemia, however he had normal blood urea nitrogen (BUN) and serum creatinine levels. The patient's urinalysis revealed the presence of myoglobin. A muscle biopsy demonstrated muscle fibers without striations and a loss of homogeneity. Some areas showed presence of erythrocytes, without any other inflammatory cell infiltrates. Additional tests were performed and all excluded all possible causes of nontraumatic rhabdomyolysis, therefore drug-induced rhabdomyolysis was diagnosed.

TMP-SMX and NSAIDs were discontinued, and the patient was treated with aggressive fluid therapy. By day 16 of his hospital stay, the patient's CK was within normal limits and he no longer reported any myalgias. The authors emphasize that the patient had been treated with TMP-SMX previously at a standard dosage and did not report any ill effects. In addition the patient was immunocompetent; it should be noted that immunosuppression can predispose a patient to develop rhabdomyolysis. The authors theorize that a potential drug-drug interaction between the NSAIDs that the patient had taken may have contributed to his condition, however his initial pain and need for NSAIDs was most likely due to the pain he felt during early rhabdomyolysis.

The authors point out that clinicians should be aware of this rare adverse effect of TMP-SMX and patients should be educated about utilizing the correct dosage as well as common adverse effects and possible drug interactions. This case represents the second reported case of TMP-SMX–associated rhabdomyolysis, however it is the first reported case in an immunocompetent patient.

Petrov M, Yatsynovich Y, Lionte C. An unusual case of rhabdomyolysis in emergency setting: Challenges of diagnosis. *Am J Emerg Med.* 2015;33:123.e1-123.e3.

GABAPENTIN-INDUCED HYPOGLYCEMIA IN DIABETIC AND NONDIABETIC PATIENTS

The authors report a collection of 6 severe cases of hypoglycemia associated with the use of gabapentin in patients who were nondiabetic and diabetic. The report comes from the Netherlands Pharmacovigilance Centre Lareb, which collects and analyzes reports of adverse reactions of medicines and vaccines. Health care professionals, patients, and manufacturers can report adverse drug experiences to the center.

The 6 cases discussed occurred between July 2002 and July 2012. It should be noted that hypoglycemia ranged from a low of 23 mg/dL in one patient to 70 mg/dL in the patient with the highest value. The definition of hypoglycemia utilized by the authors is an abnormally low plasma glucose (≤70 mg/dL) accompanied by palpitations, hunger, tremor, sweating, and central nervous system (CNS) symptoms.

Three of the patient cases are discussed in detail, and these patients received total daily doses of gabapentin of 1,800 mg up to 4,200 mg. Their nadir blood glucose values were 29 mg/dL, 23 mg/dL, and 34 mg/dL after initiation of gabapentin. Each patient recovered after discontinuation of gabapentin and administration of intravenous glucose.

The authors then discuss the possible mechanisms by which gabapentin could cause hypoglycemia. They note 2 possibilities, with the first being, "GABA is present in the cytoplasm, insulin granules and microvesicles of the β-cells of the pancreas and can bind to $GABA_A$ and $GABA_B$ receptors. Activation of the $GABA_B$ receptor is thought to inhibit insulin secretion whereas activation of the $GABA_A$ receptor leads to membrane depolarization and subsequent calcium influx, allowing the release of insulin." A second proposed mechanism could be the direct binding of gabapentin to the $alpha_2$-$delta_2$ receptor of the voltage-gated calcium channels. As with $GABA_A$ receptor activation, binding to the $alpha_2$-$delta_2$ receptor subunit could result in calcium influx and subsequent insulin release. In closing, the authors

warn that patients using gabapentin who experience symptoms indicative of hypoglycemia should be evaluated closely.

Scholl JHG, van Eekeren R, van Puijenbroek EP. Six cases of (severe) hypoglycemia associated with gabapentin use in both diabetic and non-diabetic patients. *Br J Clin Pharmacol.* 2014;79(5):870-871.

PURPLE GLOVE SYNDROME AFTER ORAL PHENYTOIN ADMINISTRATION

A 35-year-old man was admitted to the hospital with an episode of status epilepticus. The patient received lorazepam 4 mg intravenously and 1,000 mg of phenytoin in 100 mL of normal saline over 50 minutes at a rate of 20 mg/min. This initial treatment controlled the patient's seizures. The patient also reported a history of low-grade fever with a rise in the evening, frequent holocranial headaches, and recurrent episodes of vomiting over the previous 6 months. After a complete work-up, the patient was diagnosed with chronic meningitis with a possible tubercular etiology that was later confirmed by a positive polymerase chain reaction test for the detection of tuberculosis (TB-PCR).

The patient was initiated on a 5-drug regimen for his meningeal tuberculosis along with intravenous dexamethasone and 300 mg daily of oral phenytoin. The patient tolerated all of his medications well with improvement in headaches and no further recurrence of seizures. The patient continued his medication as directed for 20 days; at that time, he developed pain and purple discoloration of both hands with no skin excoriation, ulcer, or elevated temperature in affected limbs. The patient's capillary refill under the nail bed was normal, and all the pulses in his limbs were equally palpable. The patient underwent an arterial and venous Doppler study with the results not suggesting an abnormality of blood flow. The patient's phenytoin level was within the normal range at 12 µg/mL (normal range, 10-20 µg/mL) upon admission. The patient was evaluated by a dermatologist; immediately his phenytoin was discontinued and valproate 1,000 mg daily in divided doses was initiated. All of the patient's other medications were continued at this time. The patient received anti-inflammatory medications, and his affected limbs were kept elevated. Over the next 10 days, the patient's condition completely improved, which further substantiated the suspicion of phenytoin-induced purple glove syndrome.

The authors point out that purple glove syndrome is a rare condition that almost always occurs after intravenous administration of phenytoin. The purple discoloration typically occurs distal to the site of intravenous phenytoin administration. What makes this case unique is that it occurred after 20 days of oral therapy in a patient with a therapeutic phenytoin level. The authors postulate that the possible mechanism for the patient's purple glove syndrome is the "accumulation of free phenytoin in small veins and capillaries that may induce vasoconstriction and microthrombi formation, further leading to skin discoloration and edema."

Jain RS, Nagpal K, Kumar S, et al. Purple glove syndrome occurring after oral administration of phenytoin in therapeutic doses: Mechanism still a dilemma. *Am J Emerg Med.* 2015;33:123.e5-123.e6.

ACUTE DYSTONIC REACTION AFTER METHYLPHENIDATE INITIATION

A 15-year-old female was diagnosed with attention deficit hyperactivity disorder (ADHD) and was ordered methylphenidate modified release 27 mg daily. She was not receiving any additional medications and had no comorbidities. The patient initiated methylphenidate treatment. After 9 days of treatment, she experienced an involuntary extensor muscular contraction of her right hand and wrist. The contraction had been witnessed by her parents for 4 hours. The patient reported tension and severe pain. She was given 2 mg of biperiden with only minimal improvement. She was then given 5 mg of diazepam intramuscularly, and the dystonia subsided completely.

Upon questioning, the patient revealed that she had received methylphenidate immediate release a few years earlier, and she had experienced a muscular contraction in her foot that dissipated after discontinuation of methylphenidate. At this time, the patient refused to take methylphenidate again, and therefore there was no opportunity to rechallenge the adverse reaction. On examination, the patient was found to be in good physical condition with no abnormal findings on a head MRI and electroencephalography. The patient had normal motor, social, and language development with no history of a movement disorder.

The authors noted that acute dystonia is a well-known adverse effect of dopamine antagonist medications. However, dystonia can be triggered by all drugs that alter dopamine signaling. Methylphenidate increases extracellular dopamine levels in the striatum, prefrontal cortex, olfactory tubercle, and nucleus accumbens via inhibiting dopamine reuptake. Methylphenidate also has appreciable effects on

norepinephrine reuptake. The authors point out that the mechanism for this adverse reaction is unclear but the acute dystonia in this patient "suggests that secondary dystonia may paradoxically be caused via dopamine stimulation in susceptible children." The authors warn that clinicians should consider acute dystonia a rare adverse event that might emerge during modified-release methylphenidate treatment.

Tekin U, Soyata AZ, Oflaz S. Acute focal dystonic reaction after acute methylphenidate treatment in an adolescent patient. *J Clin Psychopharmacol*. 2015;35(2):209-211.

SEROTONIN SYNDROME WITH VILAZODONE MONOTHERAPY

A 28-year-old female was prescribed sertraline 75 mg daily for anxiety. Her other medications included a combined estrogen progestin birth control pill, promethazine 25 mg as needed for nausea, omeprazole 40 mg, and TMP-SMX double strength. After several months of sertraline, the patient returned with worsening symptoms. The prescriber discontinued her sertraline and initiated vilazodone (*Viibryd*). Vilazodone was correctly titrated with 10 mg daily for 7 days followed by an increase to 20 mg daily for 7 days and finally a maintenance dose of 40 mg daily.

After 1 week of vilazodone therapy, the patient experienced excessive perspiration and complained of being hot. The patient would sweat primarily in her torso area. She experienced gastrointestinal symptoms with nausea and diarrhea that began on day 10 of vilazodone therapy. The patient had a supply of promethazine 25 mg that she began to administer for her nausea at bedtime on days 10 through 14 of vilazodone therapy. On day 17, the patient experienced an exacerbation of her nausea immediately after taking her vilazodone dose. The patient also reported difficulty sleeping that evening and experienced severe nausea. She experienced uncontrollable jerking movements in her arms and legs. While this was occurring, the patient reported an increased heart rate, respiratory rate, and hallucinations. In addition to these symptoms, a family member reported that the patient was aphasic. This episode was estimated to have lasted 20 minutes. The patient had not experienced any prior events similar to this episode, however it should be noted that the patient was receiving the recommended maintenance dosage of vilazodone 40 mg daily. At this time, the patient discontinued her treatment with vilazodone. Three days after discontinuing vilazodone, the patient's vital signs were normal except for an elevated pulse of 115 bpm. The patient's physician did not give her any additional prescriptions but recommended that she see a psychiatrist for the management of possible serotonin syndrome; the patient did not seek medical treatment from the psychiatrist as recommended.

Four days after discontinuing vilazodone, the patient presented to the emergency department. Her vital signs were normal and her laboratory values were normal including complete blood count, human chorionic gonadotropin, international normalized ratio, basic metabolic panel, urine drug screen, and D-dimer. An EKG and a chest x-ray were performed, and they were also normal. The patient did not receive treatment while in the emergency department and she reported her symptoms had resolved. The emergency room physician diagnosed the patient with serotonin syndrome secondary to vilazodone therapy. The patient continued to experience excessive perspiration for 2 weeks after discontinuation of vilazodone. The patient did not restart vilazodone and she has not experienced similar neurologic symptoms in the 12 months since her initial symptoms.

The authors analyzed the patient's case information and state that it appears to meet the Hunter criteria for serotonin toxicity based on the patient's self-reporting of hypertonia, hyperreflexia, diaphoresis, nausea, agitation, tachycardia, and tachypnea. The Hunter Serotonin Toxicity Criteria (HSTC) are a set of validated decision tools featuring neurological and body temperature measurements to detect any clinically relevant serotonin toxicity (Dunkley et al). They also note that serotonin syndrome is a clinical diagnosis without laboratory confirmation, so objective criteria are essential. The authors state that "the mechanisms of action of vilazodone are believed to be similar to combination therapy with an SSRI and buspirone, which are both serotoninergic agents."

The patient did not seek medical attention until well after her symptoms resolved. The authors warn that serotonin syndrome can be life-threatening and immediate attention is necessary. They also emphasize the importance of counseling every patient on the signs and symptoms associated with serotonin syndrome.

Butler TW, Lucas RA, Barghouthy W. Serotonin syndrome with standard-dose vilazodone (*Viibryd*) monotherapy. *J Med Cases*. 2014;5(11):567-569.

Dunkley EJC, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. *Q J Med*. 2003;96:635-642.

CABOZANTINIB-ASSOCIATED DERMATOLOGIC ADVERSE REACTIONS

Cabozantinib is a tyrosine kinase inhibitor (TKI) with potential efficacy in the treatment of several cancers. TKIs have commonly been associated with cutaneous adverse effects. These adverse effects can significantly affect a patient's quality of life and drug adherence and represent a major therapeutic challenge to optimizing targeted drug therapy. A phase 2 clinical trial was undertaken at the National Cancer Institute in Bethesda, Maryland, to evaluate the efficacy of cabozantinib (*Cometriq*) in the treatment of advanced/metastatic bladder cancer. Patients received 60 mg daily of cabozantinib in 28-day cycles. To quantify the extent of cutaneous adverse reactions, patients were examined at each treatment visit and questioned about skin reactions. Patients received a full body examination and clinical photographs of cutaneous lesions were taken.

The researchers found that of the 41 patients who received cabozantinib in the study, 30 (73%) experienced one or more cutaneous toxic effects. Adverse reactions included hand-foot skin reaction (HFSR) 54%, generalized pigment dilution and/or hair depigmentation 44%, xerosis 20%, scrotal erythema/ulceration 15%, and nail splinter hemorrhages 12%. Eighteen patients (44%) had 2 or more cutaneous adverse events. Reactions developed during the first month of therapy in 57% of the patients and by the second month of treatment in 80%. In patients with toxic skin effects, dose reduction was required for symptom management in 30% of patients and treatment discontinuation was required in 13% of patients.

The authors concluded, "While TKIs represent a major milestone in cancer treatment, these potent agents are associated with numerous adverse effects, many of which are cutaneous and can affect patient's quality of life and impede their adherence to long-term treatment." They call for clinicians to be cognizant of the TKI-associated skin reactions because early detection and prompt treatment can increase adherence to this important therapy.

Zuo RC, Apolo AB, DiGiovanna JJ, et al. Cutaneous adverse effects associated with the tyrosine-kinase inhibitor cabozantinib. *JAMA Dermatol.* 2015;151(2):170-177. ■