ISMP Adverse Drug Reactions

Methemoglobinemia Caused by Topical Dapsone Gel

Renal Tubular Acidosis After Topiramate Administration

Diabetic Ketoacidosis Following Epidural Steroid Injection in a Nondiabetic Patient

Galactorrhea Associated with Bupropion Therapy

Telaprevir-Induced Acquired Perforating Dermatitis

Manic Episodes Associated with Tramadol Use

*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.

METHEMOGLOBINEMIA CAUSED BY TOPICAL DAPSONE GEL

A 19-year-old female came to an emergency room after she noticed that her lips and fingers were blue. She reported a medical history of depression and acne vulgaris. Her medication history included a daily dose of citalopram and an oral contraceptive product. She reported that she did not ingest any supplements or herbal products. On examination, the patient's vital signs were a heart rate of 109 beats per minute (bpm), blood pressure of 129/80 mm Hg, respiratory rate of 18 breaths per minute, temperature of 98.4°F, and a pulse oximetry of 85% while

on room air. She complained of a mild headache and dyspnea, but she exhibited no signs of respiratory distress while having periorbital and acral cyanosis.

Laboratory evaluations revealed normal electrolyte levels and a normal complete blood cell count (CBC) with hemoglobin of 12.4 g/dL (reference range female, 11-16 g/dL). An arterial blood gas obtained while she was breathing room air showed a pH of 7.40 (reference range, 7.35-7.45), PaCO₂ 35.2 mm Hg (reference range, 33-45 mm Hg), PaO₂ 84.6 mm Hg (reference range, 75-105 mm Hg), carboxyhemoglobin 0% (reference range, <2%), and a methemoglobin 20.3% (reference range, ≤1%).

*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 received a single 100 mg dose of intravenous methylene blue, which represents a 1.9 mg/kg dose. Her cyanosis and symptoms completely resolved within 30 minutes of receiving methylene blue. A follow-up methemoglobin level was drawn 2 hours after the methylene blue dose was administered and revealed a methemoglobin level of 1.9%. A comprehensive urine drug screen utilizing gas chromatography-mass spectrometry revealed the presence of citalopram and dapson. The patient was then asked if she could identify the source of the dapson; she reported that she used an acne medicine, dapson topical 5% gel (*Aczone*). An additional methemoglobin level obtained 10 hours after methylene administration was 7.2%. The patient did not exhibit any signs of hemolysis and remained asymptomatic. She was discharged on hospital day 2.

Swartzentruber et al stated that the patient reported only applying a pea-sized amount of dapson gel to her face, twice daily for the past 7 days. She had no known explanation for the enhanced absorption of dapson. The patient did not have any open wounds on her face, nor had she undergone any dermatologic procedures that could potentially enhance absorption. The authors also mention that a plasma level of dapson is detectable within 2 hours of application and has a half-life of 48 hours. While dapson-induced methemoglobinemia has been noted with the systemic administration of dapson, this case is the first documented occurrence of methemoglobinemia from topical dapson administration.

Allergan, the manufacturer of *Aczone*, also commented on this rare adverse event. Watton et al stated that, "Methemoglobinemia was not reported in clinical trials owing possibly to the substantially lower systemic concentration associated with the use of topical dapson, as compared to the oral formulation." They also mentioned that methemoglobinemia has been added as a possible adverse event to all reference safety material for *Aczone*.

Swartzentruber GS, Yanta JH, Pizon AF. Methemoglobinemia as a complication of topical dapson. *N Engl J Med*. 2015;372(5):491-492.

Watton C, Smith K, Carter E. Allergan, the manufacturer of *Aczone* replies. *N Engl J Med*. 2015; 372(5):492.

RENAL TUBULAR ACIDOSIS AFTER TOPIRAMATE ADMINISTRATION

A 20-year-old female was treated for an anaphylactic rash following the administration of clarithromycin. The patient was in overall good health and did

not have any prior medication allergies. Her medication history included topiramate (*Topamax*) for cluster headaches, as well as sertraline and amitriptyline for the management of depression. She did not report a history of alcohol or any other substance abuse.

After her treatment for anaphylaxis, the patient reported that she did not feel well with nausea, palpitations, and headache. The patient was afebrile and lab tests revealed a normal white blood cell (WBC) count, plasma C reactive protein, and normal liver function tests. Additional blood tests revealed metabolic acidosis and hyperlactatemia. Her arterial pH was 7.29 (reference range, 7.35-7.45), lactate of 4.8 mmol/L (reference range, 0.5-2 mmol/L), and serum bicarbonate of 12.5 mmol/L (reference range, 22-26 mmol/L). The patient was immediately treated with supportive care and fluid resuscitation, after which her lactate level decreased but only by a very small amount. The patient's topiramate was titrated downward, and her acid-base values slowly returned toward normal over the following 14-day hospital stay.

Renal tubular acidosis (RTA) is a condition that manifests by the accumulation of acid in the body due to a failure of the kidneys to properly acidify the urine therefore leading to metabolic acidosis. The authors report that prior case reports have outlined cases of topiramate-induced metabolic acidosis. It is thought that topiramate impairs both the reabsorption of filtered bicarbonate by the proximal renal tubule and the excretion of hydrogen ions by the distal renal tubule. RTA can make patients acutely ill and can chronically lead to nephrolithiasis and osteoporosis.

The authors concluded that this patient was most likely experiencing topiramate-induced RTA that led to severe metabolic acidosis. The authors believe the causative agent was topiramate, because the other possible etiological factors for the cause of RTA, which include diabetes, tissue ischemia, pancreatitis, HIV, and systemic lupus erythematosus, had been excluded.

Tan HK, Rudrappa S, Tang CH. Renal tubular acidosis following topiramate. *J Med Case*. 2014;5(12):634-635.

DIABETIC KETOACIDOSIS FOLLOWING EPIDURAL STEROID INJECTION IN A NONDIABETIC PATIENT

A 56-year-old African American female was seen by her primary care physician with a chief complaint of neck pain and right arm pain that radiated down her arm. Her medical history included hypertension, hyperlipidemia, and a prior cerebrovascular accident

with no residual neurologic deficits. The patient had a recent fasting glucose level of 87 mg/dL and a negative family history of diabetes. To treat her neck and arm pain, the patient was given a trapezius trigger point injection of 4 mg/1 mL of dexamethasone with 1 mL of bupivacaine 0.5%. She was also initiated on tramadol, meloxicam, and methocarbamol. The patient then received a repeat injection 3 weeks later. X-ray and MRI results revealed moderate to severe degenerative disc disease at C6-C7 as well as severe narrowing of the left C4-C5 neuro-foramen. Approximately 1 week after the second dexamethasone injection, the patient received an injection of 40 mg triamcinolone and 2 mL of 0.9% normal saline solution at the C6-C7 cervical inter-vertebral space under fluoroscopy. She received this injection from a pain management specialist.

One week after the epidural triamcinolone injection, the patient was seen at the emergency department complaining of a 3-day history of xerostomia, polydipsia, polyuria, generalized weakness, and diarrhea. Fingerstick glucose was 410 mg/dL, and urinalysis revealed a glucose greater than 1,000 mg/dL, ketones 15 mg/dL, and positive nitrites. Her urine was negative for leukocyte esterase, and a urine culture was positive for more than 100,000 cfu/mL of *Escherichia coli*. Her anion gap was calculated as 15 mmol/L (reference range, 8-16 mmol/L), acetone of 1.2 mmol/L (reference value, <0.6 mmol/L), and potassium of 3.1 mEq/L (reference range, 3.5-5 mEq/L). Based on the objective data, the patient was diagnosed with diabetic ketoacidosis (DKA) and was admitted to the intensive care unit.

The authors discuss that epidural steroids have been documented to cause DKA in patients who are diagnosed diabetics. They also point out that upon their review of the literature, cases of DKA have occurred in nondiabetic individuals following epidural injections, but these patients had concurrent infections or were pregnant. The authors also took into consideration the patient's positive urine culture; they did not believe it was an active infection but instead was a colonization from asymptomatic bacteruria. They based their opinion on the fact that the patient had no history of recurrent urinary tract infections and did not complain of urinary tract infection symptoms.

The authors recommend that if a patient experiences DKA after an epidural steroid injection, this should warrant halting any further epidural steroid injections until a fasting glucose can be performed in 3 to 4 weeks following the last epidural steroid injection to confirm the patient's nondiabetic status.

Berry AC, Tick ME, Patel BB, et al. Diabetic ketoacidosis following administration of a cervical epidural steroid injection in a non-diabetic. *J Med Cases*. 2014;5(9):495-497.

GALACTORRHEA ASSOCIATED WITH BUPROPION THERAPY

A 34-year-old female was seen in an outpatient psychiatry clinic with complaints of demoralization, malaise, loss of interest, and increased sleep and appetite for the past 3 years. The patient had been treated with sertraline 100 mg daily for 2 months approximately 2 years earlier, and she did not derive benefit from sertraline therapy. The patient did not have an organic etiology for her depression and had not used alcohol or narcotics. She reported that her menstrual cycle was regular and she was not pregnant, did not use oral contraceptives, and was not sexually active. She was diagnosed with major depressive disorder and treatment with bupropion (*Wellbutrin*) 150 mg daily was prescribed.

The patient returned to the outpatient clinic 2 weeks after initiating bupropion and complained of galactorrhea. A CBC, fasting blood glucose, lipid profile, and thyroid function test were drawn, and all were within normal limits. The patient had a blood prolactin level of 98 ng/mL (reference range female, 3-27 ng/mL). Additional organic causes for her galactorrhea and hyperprolactinemia were investigated via a head MRI; no space-occupying mass in the pituitary gland was identified. A gynecologic consultation was completed and no pathology was identified. Treatment with bupropion was discontinued, and the patient's galactorrhea ceased 2 days after bupropion discontinuation. A week later, the patient's blood prolactin level had dropped to 3 ng/mL. The patient was started on fluoxetine 20 mg daily and responded to therapy. She has not had galactorrhea during a 4-month observation period.

The authors concluded that the galactorrhea and hyperprolactinemia were due to the bupropion, because the temporal relationship of the start of galactorrhea coincided with the initiation of bupropion. Additionally, the patient's galactorrhea ceased within 48 hours of bupropion discontinuation. The patient's galactorrhea occurred in the absence of other drug usage or organic cause. In reviewing the literature, the authors point out that women are suggested to be more prone to antidepressant-related increases in prolactin. Usually hyperprolactinemia and galactorrhea are adverse effects seen during treatment with antipsychotic medications, and they have not been reported with the use of bupropion.

Bupropion increases the extracellular concentration of dopamine and norepinephrine by blocking their reuptake. It therefore increases norepinephrine and dopamine levels in the prefrontal cortex by blocking norepinephrine and dopamine carriers. Bupropion has no effect on serotonin transmission. In closing, the authors state that although bupropion is considered prolactin neutral, a clear mechanism for the adverse effect is not evident. They urge further investigation to clarify the mechanism and receptor effects of this adverse effect.

Cam B, Bilgin AA. Bupropion-associated galactorrhea: A case report. *J Clin Psychopharmacol*. 2015;35(1):113-114.

TELAPREVIR-INDUCED ACQUIRED PERFORATING DERMATOSIS

A male in his fifties who had been diagnosed with hepatitis C virus (HCV) infection presented to a dermatologist with complaints of pruritic ulcerated papules on his lower legs. Three weeks prior, the patient had begun treatment with telaprevir (*Incivek*) 2250 mg orally daily in combination with ribavirin 1200 mg orally daily and pegylated interferon alfa-2a 180 mcg/week subcutaneously. The patient's medication history revealed that he was not receiving any concomitant medications, and he had previously received a course of ribavirin and peginterferon without incident.

The patient was suspected of having acquired perforating dermatitis (APD; also known as Kyrle disease), which has a prevalence of approximately 10% in dialysis populations and occurs predominantly in African Americans and patients with diabetes mellitus. APD is also associated with other conditions such as hepatic disease, thyroid illnesses, malignancies, scabies, and AIDS. The patient's blood test was negative for HIV; he was also negative for liver malignancy based on an alpha-fetoprotein test and an abdominal CT scan. The patient reported no history of diabetes or chronic kidney disease or failure.

The patient's physical exam revealed extensive xerosis and ulcerated papular and nodular lesions on the lower legs, each with an inflammatory border and a central keratotic plug. At this time, telaprevir therapy was discontinued and the patient was treated with betamethasone dipropionate and petroleum jelly both applied once daily. He experienced a slow but progressive improvement over the following 2 weeks with no new lesions. All of his lesions resolved within 2 months, however pigmented and atrophic scars remained.

The authors point out that ADP is a cutaneous response to superficial trauma caused by scratching. Telaprevir has been shown to cause cutaneous eruption, mostly pruritic eczematous dermatitis, in up to 56% of patients. They warn that ADP is a potential severe cutaneous adverse effect of telaprevir therapy brought on by itching and repeated scratching, which is often caused by this protease inhibitor.

Pernet C, Pageaux GP, Guillot B, et al. Telaprevir-induced acquired perforating dermatosis. *JAMA Derm*. 2014;150(12):1371-1372.

MANIC EPISODES ASSOCIATED WITH TRAMADOL USE

A 28-year-old male was seen in an emergency department for treatment of a spontaneous pneumothorax. The patient received tramadol (*Ultram*) 100 mg daily for pain after he received a tube thoracostomy. While the patient was receiving tramadol, he experienced agitation, pressured speech, racing thoughts, insomnia, increased energy, and aberrant sexual behavior. All of these symptoms disappeared within 5 days after the end of tramadol treatment. A week later, the patient presented to the same emergency department with a second spontaneous pneumothorax and was again treated with tramadol 100 mg daily for pain. On this occasion, the patient's symptoms included insomnia, grandiosity, irritability, pressured speech, increased energy, and sexual behavior. Although tramadol had been discontinued at the time of his initial discharge from the hospital, his symptoms had become more severe; new symptoms including catalepsy, psychomotor agitation, and hostility had appeared 3 days before his second hospital admission.

The patient was hospitalized in a psychiatric inpatient facility after psychiatric assessment in the emergency department. Physical examination, laboratory analyses, and an MRI scan of the brain were unremarkable. The patient had no personal or family history of psychiatric disorders. Given the patient's history, onset of symptoms, and lack of physical findings, the authors concluded that tramadol treatment was the probable cause of the patient's manic episodes. The patient's symptoms disappeared within a week after treatment with quetiapine 300 mg daily and divalproex 1000 mg daily were initiated. After 3 months of treatment, the patient stopped taking his quetiapine and divalproex due to increased sedation. In the 2-year follow-up, the patient neither displayed mood disturbances nor any psychiatric symptoms.

The authors point out that tramadol is a centrally acting opioid analgesic that binds weakly to the mu receptor and enhances the action of serotonin and norepinephrine by interfering in their reuptake and release mechanisms. In animal models, tramadol has been shown to induce antidepressant-like effects similar to monoaminergic system drugs. It has been demonstrated that the molecular structure of tramadol is similar to that of the antidepressant venlafaxine. In the clinical setting, tramadol has been reported to be effective in the treatment of obsessive-compulsive disorder as well as depression. It is reported that 13.3% to 25% of the bipolar patients who received venlafaxine therapy had manic switch, and this rate is significantly higher than that in bipolar patients receiving other antidepressants. The authors reinforce

that antidepressants that act on both serotonergic and noradrenergic mechanisms are associated with higher risks of manic switch. The authors hypothesized that this patient's manic episodes were triggered by tramadol's monoaminergic system effects.

The authors warn that tramadol can cause serotonergic syndrome or manic switch by interacting with the selective serotonin reuptake inhibitors. In patients with diagnosed bipolar disorder and now in those without a history of mental health issues, the antidepressant effects of tramadol need to be taken into account when it is used for analgesic purposes.

Ceylan D, Kacar M, Ulas H. Manic episodes associated with tramadol, a case report. *J Clin Psychopharmacol.* 2015;35(1):111-112. ■