ISMP Adverse Drug Reactions

Vigabatrin-Induced Encephalopathy

Fidaxomicin Hypersensitivity Reactions

Vemurafenib-Induced DRESS

Severe Alkalosis and Hypokalemia With Stanazolol Misuse

Isotretinoin-Associated Lip Abscess

Eltrombopag-Associated Hyperpigmentation

*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.

VIGABATRIN-INDUCED ENCEPHALOPATHY

A 10-month-old female who was diagnosed the month prior with infantile spasms presented with progressive lethargy, followed by a movement disorder and finally left hemiparesis. The child had been receiving vigabatrin (*Sabril*) 150 mg/kg/day and tetracosactide 0.75 mg on alternate days for the prior 14 days. An MRI scan revealed rapidly progressive signal changes within the basal ganglia, brainstem, and cerebellum compared to neuroimaging performed earlier, after the onset of her spasms. All additional neurometabolic investigations were eventually found to be normal. Treatment with vigabatrin was discontinued on day 22 of therapy. The patient started to

make a dramatic recovery within 48 hours of vigabatrin discontinuation and went on to make a full neurological recovery.

In a review of 3 studies evaluating the use of vigabatrin and MRI results, the authors point out that MRI imaging abnormalities within the globus pallidus, thalamus, brainstem, and dentate nuclei are reported in up to 30% of patients with infantile spasms who receive vigabatrin. These abnormalities appear specific to children with infantile spasms, affect younger infants and children, are associated with a higher dosage of vigabatrin (>80 mg/kg/day), and are reversible after the discontinuation of vigabatrin treatment. The inconsistency is that these MRI

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

abnormalities do not consistently correlate with the drowsiness, lethargy, tremor, and abnormal coordination reported in children and adults receiving vigabatrin.

The authors theorize that the potential mechanism of these MRI and clinical observations are largely unknown and may be due to age-specific or disease state-specific conditions. They warn that early recognition of these adverse effects is particularly important, because failure to recognize this condition would have led to palliative management of their patient.

Hernandez V, Kaliakatsos M, U-King-Im JM, et al. Reversible vigabatrin-induced life-threatening encephalopathy. *JAMA Neurol.* 2014;71(1):108-109.

FIDAXOMICIN HYPERSENSITIVITY REACTIONS

Fidaxomicin (*Dificid*) is a macrolide antibiotic that is indicated for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). Fidaxomicin is minimally absorbed with maximal plasma concentrations of fidaxomicin and OP-1118 (primary metabolite) in the nanogram per mL range. Because fidaxomicin is minimally absorbed, systemic adverse reactions are not expected and may not be considered, especially in a patient receiving multiple concomitant medications.

In clinical trials with fidaxomicin, no specific concerns related to hypersensitivity reactions were identified. However, after fidaxomicin's release, reports of hypersensitivity reactions were reported to the US Food and Drug Administration (FDA). Eleven cases of hypersensitivity reactions were reported to the FDA, and one case was reported in the literature. A history of macrolide allergy was documented in 3 of 12 cases.

In all the cases of fidaxomicin hypersensitivity reviewed, 6 patients reported facial, tongue, or throat swelling; 4 reported a diffuse rash; and 1 reported a burning sensation in the throat. A patient described in the literature had a purpuric rash on the lower extremities. The time to onset of the hypersensitivity reactions was between 1 and 7 hours after first receiving fidaxomicin. Ten cases resolved after discontinuation of fidaxomicin; one patient continued fidaxomicin along with diphenhydramine and the itching and rash persisted and one patient had an unknown outcome. Two patients had a positive rechallenge with fidaxomicin.

The fidaxomicin labeling has been changed to reflect the risk of hypersensitivity reactions. The warning in the labeling states that a history of macrolide

allergy should be taken into consideration when initiating fidaxomicin, given that 3 of 12 patients reported a history of macrolide allergy. It is possible that the colonic inflammation caused by *C. difficile* infection can increase the bioavailability of fidaxomicin. It has been hypothesized that in a predisposed patient, a minimal systemic exposure or even contact with inflamed mucosa could be sufficient to cause an allergic reaction.

The authors from the Division of Anti-infective Products at the FDA warn that health care providers should be aware of the risk of hypersensitivity reactions with fidaxomicin. It is important to report these events to the FDA MEDWATCH program when they occur.

Iarikov DE, Alexander J, Nambinar S. Hypersensitivity reactions associated with fidaxomicin use. *Clin Infect Dis.* 2014;58(Feb):537-539.

VEMURAFENIB-INDUCED DRESS

A female in her 80s reported a 1-year history of a violet colored growth on her calf. A biopsy revealed a nodular melanoma and 2 suspect lymph nodes. The diagnosis of metastatic melanoma with V600E BRAF mutation was confirmed and vemurafenib (*Zelboraf*) was initiated. The patient's past medical history included hypertension and chronic kidney disease. The patient began treatment with vemurafenib 960 mg twice daily. Three weeks later, she developed scattered pustules and generalized pink, pruritic papules coalescing into plaques on the face, trunk, and extremities with prominent facial edema.

On hospital admission, the patient complained of fevers, chills, and bone pain but was afebrile. However, 3 days prior, a low-grade fever of 37.3°C (99.1°F) was documented during an outpatient visit, and she was advised to begin antipyretic drugs. Her laboratory results revealed the following: WBC 12.4 × 10³/μL (normal value, 4.1-10.9 × 10³/μL), 26% eosinophils (normal value, 1%-3%), AST 107 IU/L (normal value, <35 IU/L), ALT 132 IU/L (normal value, 10-35 IU/L), and serum creatinine 3.3 mg/dL (normal value, female 0.6-1.2 mg/dL) with the patient's normal baseline creatinine of 1.8 mg/dL. The patient's medication history included metoprolol and hydrochlorothiazide, which she had been receiving for at least the last 9 months. Based on the patient's symptoms, a drug eruption was suspected and her vemurafenib treatment was discontinued.

A skin biopsy was performed, and the findings supported the diagnosis of a drug reaction with eosinophilia and systemic symptoms (DRESS). Intra-

venous methylprednisolone was initiated followed by oral prednisone; over the subsequent 6 weeks, the patient experienced desquamation and resolution of her skin eruption and laboratory abnormalities.

The authors point out that DRESS is most commonly associated with the use of aromatic anticonvulsants. A defect in the detoxification of certain drugs is thought to play a role in the development of DRESS, producing toxic metabolites that cause cellular injury and trigger an immune response. Recently, viruses such as human herpesvirus (HHV)-6, HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) have been implicated in the development of DRESS. The patient was found to have an elevated HHV-6 IgG titer (1:160; normal <1:10), which indicates a possible viral reactivation. EBV DNA was also detected, whereas CMV and HHV-7 test results were negative. It is unclear whether these observations are a consequence or cause of the condition.

The authors want to emphasize that the occurrence of DRESS in association with vemurafenib therapy has not been reported. Clinicians should be aware of this possible complication in patients receiving vemurafenib.

Wenk KS, Pichard DC, Nasabzadeh T, et al. Vemurafenib-induced DRESS. *JAMA Dermatol.* 2013;149(10):1242-1243.

SEVERE ALKALOSIS AND HYPOKALEMIA WITH STANZOLOL MISUSE

A 30-year-old man with a history of alcohol and cocaine misuse presented to the emergency department (ED) after a witnessed seizure. Upon arrival, the patient was incoherent, with a Glasgow Coma Scale score of 12/15, a blood pressure of 140/85 mm Hg, and a pulse of 75 bpm. The patient was globally weak on neurologic examination but with no focal deficits, and a CT of his head was normal. The patient's arterial blood gas showed a pH of 7.7 (reference range, 7.34-7.45), PaCO₂ of 6.5 kPa (reference range, 4.4-5.9 kPa), and bicarbonate of 58.9 mEq/L (reference range, 22-26 mEq/L). Chem-7 results were a plasma potassium of 1.7 mEq/L (reference range, 3.5-5 mEq/L), sodium of 124 mEq/L (reference range, 135-147 mEq/L), corrected calcium of 8.6 mg/dL (reference range, 8.5-10.2 mg/dL), magnesium of 3 mg/dL (reference range, 1.8-3 mg/dL), creatinine of 1.83 mg/dL (reference range, male 0.8-1.4 mg/dL), and BUN 44 mg/dL (reference range, 7-20 mg/dL). A urine drug screen was negative for benzodiazepines, opioids, barbiturates, cannabinoids, and cocaine. Additional blood tests, including thyroid and liver

function tests, amylase, glucose, acetaminophen, and salicylate levels were within normal limits.

The patient was treated with parenteral fluid rehydration and potassium replacement. The clinical impression was syndrome of mineralocorticoid excess. The patient's plasma renin and aldosterone concentrations were within normal limits, implying an acute exposure to exogenous steroid. Over the next 48 hours, the patient's electrolyte imbalances and alkalosis were corrected, and his level of consciousness returned to normal. The patient was interviewed, and he revealed he had ingested 50 g of stanozolol (*Winstrol*), as a body-building supplement, during the week before his hospital admission. The patient denied any other concurrent medications or illicit substance use, including diuretics. He also denied a history of vomiting or diarrhea.

The authors point out that stanozolol is known to enhance glucocorticoid in vitro and potentially mineralocorticoid activity, which would account for the patient's electrolyte abnormalities. Typically the dose of stanozolol taken depends on the indication. In patients with hereditary angioedema, doses of 0.5 to 2 mg daily are utilized, whereas body builders and athletes may administer quantities ranging from 50 to 100 mg daily. Even at a 50 to 100 mg daily dose, stanozolol is thought to be safe and side effects are very rarely experienced. The patient admitted to having ingested a weekly dose 1,000 times greater than normally encountered.

Upon review of the patient's blood tests from prior admissions over previous years, it was noted that the patient demonstrated a trend toward hypokalemia. This might imply that he possesses an underlying renal tubular dysfunction that could increase his susceptibility to the mineralocorticoid effects of stanozolol. The patient was discharged from the hospital with an appointment to have follow-up tests to investigate possible renal tubular dysfunction. The patient did not attend his scheduled appointment and was lost to follow-up.

The authors conclude that stanozolol misuse can precipitate profound hypokalemia and metabolic alkalosis. Patients may present with reduced consciousness and therefore may be unable to provide a clear history of substance ingestion. This case is important, because stanozolol misuse is relatively common. Although stanozolol is considered relatively safe when utilized in standard doses, excessive dosing can lead to life-threatening complications.

Maini AN, Maxwell-Scott H, Marks DJ. Severe alkalosis and hypokalemia with stanozolol misuse. *JAMA Dermatol.* 2014;32:196.e3-196.e4.

ISOTRETINOIN-ASSOCIATED LIP ABSCESS

A 15-year-old male with a 2-day history of a lower lip swelling was seen by his doctor. The boy's mother described a rapid onset of edema, erythema, and pain in the lower lip. The boy's condition was initially thought to be allergic angioedema, and corticosteroid therapy was initiated by his pediatrician. Corticosteroid therapy did not lead to a resolution of the lip edema. The patient was then initiated on cephalexin for a presumed infection. Despite 3 doses of cephalexin, the lip swelling continued to progress substantially. The patient was otherwise healthy with no fever or chills. The patient's medical history only included acne vulgaris, for which he was receiving isotretinoin.

The patient returned to his pediatrician and was found to be afebrile and normotensive, however his lower lip was extremely edematous and erythematous. Both sides of his lower lip were very tense and painful. The physician performed a needle aspiration of the lip, which returned frank purulence. The lips were incised and drained with the release of copious amounts of purulence. The abscess pocket extended the full length of the lip. Samples were sent for culture and the patient was admitted to the hospital for empiric intravenous ampicillin-sulbactam and vancomycin. The patient remained afebrile throughout his hospital stay with substantial improvement in lower lip edema, erythema, and pain. Cultures grew methicillin-resistant *Staphylococcus aureus* (MRSA) that was resistant to clindamycin. The patient was discharged with a prescription for trimethoprim-sulfamethoxazole oral therapy.

The mucocutaneous effects of isotretinoin include xerostomia and lip swelling (cheilitis). Since these effects are common, the absence of mucocutaneous symptoms implies medication nonadherence. The fissuring and cracking of the lips with cheilitis leads to the breakdown of an important mucocutaneous barrier and can predispose patients to bacterial or viral infections. In addition to causing breakdown of mucosal barriers, isotretinoin also leads to increased colonization with *S. aureus*, which increases the incidence of folliculitis and furunculosis (boils).

The authors theorize that the use of isotretinoin leading to cheilitis, decreased mucocutaneous barriers, and staphylococcal colonization likely caused the severe lip abscess in the patient. In addition, both of the patient's parents were health care providers and presumably exposed the patient to carriage of MRSA. The authors hope to raise awareness of the development of severe lip abscesses related to isotretinoin use

and to prevent delayed diagnosis of this serious complication of a commonly utilized acne treatment.

Huoh KC, Chang KW. Lip abscess associated with isotretinoin treatment of acne vulgaris. *JAMA Dermatol.* 2013;149(8):960-961.

ELTROMBOPAG-ASSOCIATED HYPERPIGMENTATION

A 69-year-old White female with refractory acute myelogenous leukemia (AML) was noted to have a graying of her skin. The patient had been receiving eltrombopag (*Promacta*) 300 mg/day as part of a clinical trial for 3 months. The patient's husband and clinical team noted gray hyperpigmentation predominantly affecting the face. The patient had received cytarabine and daunorubicin for 10 weeks prior to eltrombopag and sirolimus and mitoxantrone 5 weeks prior to eltrombopag. The patient's hands, nails, sclera, and mucosa were uninvolved. The patient's hyperpigmentation remained stable over the subsequent 8 months during eltrombopag treatment.

A second case was encountered in a 66-year-old female of mixed White, African, and Native American descent with refractory AML. She developed darkening of her skin during treatment with eltrombopag. The patient had received cytarabine and daunorubicin 3 months prior to initiating a clinical trial with eltrombopag. Two months after starting eltrombopag, the patient had a diffuse dusky complexion involving her face, arms, and legs. The patient's pigmentation remained stable 3 months into eltrombopag therapy. The patient, her husband, and the oncology team believed that she was notably darker than before beginning eltrombopag treatment. On comparison with a family photograph, the patient's skin was believed to be darker than baseline according to her dermatologist.

Eltrombopag is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy and for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It should be noted that the patients received eltrombopag 300 mg daily as part of a clinical trial protocol. The currently recommended dosages of eltrombopag range from 25 mg to 50 mg daily with a maximum daily dosage of 75 mg daily.

The authors state that although some of the chemotherapeutic agents used previously in these patients have been associated with hyperpigmentation, the onset of the clinical graying in their patients occurred more than 10 weeks after discontinuing treatment with those agents. They recommend that

further investigation is needed to determine the etiology of the hyperpigmentation.

Braunstein I, Wanat KA, Elenitsas R, et al. Eltrombopag-associated hyperpigmentation. *JAMA Dermatol.* 2013;149(9):112-114. ■

(Continued from page 413)

REFERENCES

1. White SJ. Leadership: Successful alchemy. *Am J Health Syst Pharm.* 2006;63:1497-1503.
2. Weber RJ, Stevenson J, Ng C, White S. Measuring change in health-system pharmacy over 50 years: "Reflecting" on the Mirror, Part I. *Hosp Pharm.* 2013;48(11):966-969.
3. Weber RJ, Stevenson J, White S. Measuring Change in Health-System Pharmacy Over 50 Years: "Reflecting" on the Mirror, Part II. *Hosp Pharm.* 2014;49(1):97-100.
4. Francke DE, Latiolais CJ, Francke GN, Ho NF. *Mirror to Hospital Pharmacy*. Washington, DC: American Society of Hospital Pharmacists; 1963:46.
5. Conversations with Health-Systems Pharmacy's Most Influential Leaders [video collection series]. <http://www.ashpfoundation.org/MainMenuCategories/CenterforPharmacyLeadership/LeadershipVideos>. Accessed February 24, 2014. ■