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.

METFORMIN-INDUCED HEPATITIS

A 41-year-old male presented to his physician with jaundice, fatigue, dark urine, and stool discoloration. The patient reported that his fatigue and yellow sclera had begun approximately 4 days prior to his seeking medical attention. He had stopped his medication based on those symptoms. Four weeks earlier, the patient had been diagnosed with diabetes with a fasting blood glucose of 274 mg/dL (normal range, 65-110 mg/dL), an HbA_{1c} of 11.8% (normal range, 4%-5.9%), and no GAD₂ antibodies. Four weeks earlier, the patient's liver transaminases were normal. The patient's medication regimen was metformin 500 mg 3 times daily and insulin glargine.

The patient's physical exam was unremarkable except for jaundice. His clinical labs revealed the following: total bilirubin 18.1 mg/dL (normal range, 0.3-1 mg/dL), aspartate aminotransferase 419 IU/L (normal range, <35 IU/L), alanine aminotransferase 863 IU/L (normal range, 10-35 IU/L), alkaline phosphatase 479 IU/L (normal range, 44-147 IU/L), and γ -glutamyl transferase 2,181 IU/L (normal range, 7-51 IU/L). The patient's differential blood count was normal except for a mild eosinophilia (5.7%). The patient had no history of gastrointestinal disease, travel, or change of sexual partners. He denied excessive alcohol intake or the use of illicit drugs. An abdominal ultrasound was performed that revealed hepatic steatosis. The following conditions were

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excluded as possible causes of the patient's jaundice: mechanical cholestasis, portal vein thrombosis, Budd-Chiari syndrome, viral hepatitis, hemochromatosis, Wilson disease, and autoimmune hepatitis. Based on these findings, drug-induced hepatitis was suspected.

A lymphocyte activation assay revealed activation (increased CD69 expression) of CD4+ T cells and CD 19+ B cells after incubation with metformin. Antibodies to metformin could not be detected. A review by Ebo et al discusses the use of in vitro testing to diagnose drug allergy. Lymphocyte activation testing explores the involvement of T cells in delayed-type drug hypersensitivity reactions. This type of testing can also identify the etiologic cause in drug fever, drug-induced pancreatitis, interstitial and eosinophilic lung diseases, and drug-induced autoimmune diseases.

Because the patient had discontinued his metformin therapy 4 days earlier and measures of hepatic synthetic function began to improve, a watchful waiting approach was decided on as the best course of action. Treatment for the patient's diabetes was continued with insulin monotherapy. The patient's transaminases were declining as soon as the next day but bilirubin levels increased until 10 days after metformin discontinuation. The patient experienced pruritus and skin eruptions, and treatment with ursodeoxycholic acid was started to accelerate bilirubin clearance. The patient's symptoms subsided within 2 months and his bilirubin and transaminase levels returned to normal. Eosinophils were still slightly elevated (4.1%). Reactivity of CD4+ T cells toward metformin decreased, whereas that of CD19+ B cells still persisted.

The authors point out that only 13 cases of metformin-induced hepatitis have been reported in the literature to date. In these cases, symptoms emerged 2 to 4 weeks after initiation of metformin and subsided 3 to 12 weeks after discontinuation. The authors warn that due to the fact that metformin is a first-line agent in the treatment of diabetes, it is important to be aware of this rare but important adverse effect of metformin treatment.

Hieronimus A, Klein R, Haring HU, et al. Jaundice from diabetes therapy. *Diabetes Care*. 2014;37:e58-e58.

Ebo DG, Leysen J, Mayorga C, et al. The in vitro diagnosis of drug allergy: Status and perspectives. *Allergy*. 2011;66:1275-1286.

PALIPERIDONE-RELATED PERIPHERAL EDEMA

A 50-year-old male who had a 30-year history of paranoid schizophrenia was admitted to a psychiatric

ward with worsening delusions and auditory hallucinations. He had been stabilized on a maintenance dose of haloperidol 10 mg daily prior to admission. Results of laboratory tests, electrocardiogram, and electroencephalogram tests were all normal. Haloperidol was discontinued, and paliperidone (*Invega*) 6 mg daily was initiated. The dose of paliperidone was increased to 9 mg daily over the next 2 weeks. Although the patient's psychotic symptoms improved, he developed a plus 3 pitting edema dorsally in both feet. The edema caused enough pain to interfere with the patient's daily life. The patient's edema tended to worsen when he stood for long periods of time and improved after lying down or wearing compression stockings for a few hours. A repeat lab workup that included complete blood count, chem-7, kidney/liver/thyroid function tests, protein, albumin, C3, C4, IgE/IgM/IgG, urinalysis, and erythrocyte sedimentation rate provided no explanation for the patient's edema.

Three weeks later, a nephrologist and an endocrinologist jointly evaluated the patient's condition and laboratory results. It was decided to initiate amiloride 5 mg daily and hydrochlorothiazide 50 mg daily. Despite diuretic treatment, which caused polyuria, the patient's edema persisted for another 2 weeks. Because the patient was only receiving paliperidone and diuretics, the authors suspected that the edema might have been due to paliperidone. During week 5 of this condition, the dosage of paliperidone was lowered to 6 mg/daily for 3 days and the patient's edema began decreasing. When paliperidone was discontinued, the patient's edema completely subsided within 1 week. Over the next 3 weeks, the patient was gradually reinitiated on haloperidol up to 15 mg daily and his diuretics were also discontinued. The patient did not experience a recurrence of his edema with haloperidol therapy, however his psychotic symptoms resurfaced.

The authors reviewed the available literature identified via MEDLINE searches. In their review of the available cases, they were able to identify some interesting characteristics. The reported cases of antipsychotic-related peripheral edema are more likely to occur in females (72.2%) and in patients with bipolar disorder (33.3%) or schizophrenia (22.2%). The mean age of patients was 44.1 years of age. Risperidone and olanzapine (both 33.3%) were the most likely drugs related to peripheral edema, followed by quetiapine (27.8%) and chlorpromazine (5.6%). The mean time of edema onset after the initiation of antipsychotic treatment was 25.8 days, with a large standard deviation of 28.5 days.

The authors point out that there are 3 hypotheses that might explain the development of peripheral edema with antipsychotic medication: (1) a peripheral vasodilation possibly mediated by antipsychotic antagonism to α -receptors and/or 5-HT₂ receptors, (2) an indirect increase in water retention through activation of the renin-angiotensin-aldosterone system, or (3) a type I and/or type IV allergic response to the antipsychotic. The authors surmise that the peripheral vasodilation theory seems the most plausible.

The authors evaluated the likelihood that the patient's edema was due to paliperidone by utilizing the Naranjo Scale. The edema in this case scored an 8 on the Naranjo Scale, indicating that the patient's edema was probably related to paliperidone. The authors point out that although extensive laboratory testing was conducted, there was no apparent alternative medical cause for the patient's edema. Paliperidone is the 9-hydroxy metabolite of risperidone, so it is likely that these 2 drugs share a common pathway for causing peripheral edema. The authors recommend close monitoring of patients initiated on paliperidone therapy for peripheral edema.

Hsu HC, Cheng KD, Tsang HY. Paliperidone-related peripheral edema. A case report and review of the literature. *J Clin Psychopharm.* 2014;34(2):269-271.

VASOSPASTIC ANGINA INDUCED BY ORAL CAPECITABINE

A 46-year-old female was admitted to the emergency room complaining of a retrosternal pain that started 90 minutes before admission and lasted approximately 10 minutes. The patient also reported 2 additional transient episodes of chest pain during the previous 24 hours that she estimated lasted between 2 and 10 minutes with spontaneous resolution. The patient reported that her symptoms included chest discomfort that radiated to her back as well as malaise, nausea, and sweating. The patient had no prior history of cardiac disease, coagulation disorder, or drug abuse. She only had one cardiovascular risk factor and that was cigarette smoking. The patient's medical history included gastric sarcoma with metastatic peritoneal infiltrates for which she received a subtotal gastrectomy 2 months previously. The patient has started taking capecitabine 1500 mg twice daily 48 hours prior to her current admission.

While in the emergency department, the patient received an echocardiogram that was normal with an ejection fraction of 72%, heart rate of 62 bpm, normal diastolic function, normal valve flow, and an absence

of pericardial effusion. The patient's physiological hemodynamic parameters were unremarkable, and there were negative biochemical markers for myocardial necrosis (cardiac troponin, creatinine phosphokinase, CK-MB, lactate dehydrogenase, and serum glutamic oxaloacetic transaminase). The patient's thrombolysis in myocardial infarction (TIMI) score for unstable angina was very low, and she continued to receive capecitabine while receiving continuous telemetry monitoring. The patient's cardiac enzymes for the next 24 hours continued to be negative for cardiac necrosis, and consecutive echocardiogram readings showed no repolarization abnormalities.

Thirty-six hours after the last episode of chest discomfort, the patient had a witnessed episode of heavy retrosternal chest discomfort while on telemetry. A new echocardiogram was taken immediately and revealed sinus bradycardia (50 bpm) with diffuse ST-segment elevation in the anterior leads (V3 to V6) and inferolateral leads (I, II, III, aVL and aVF) and peaked T-waves in the same leads, suggestive of transmural ischemia. Her blood pressure was 150/90 mm Hg. Her pain subsided after continuous infusion of nitroglycerine was started and a 5 mg capsule of nifedipine was administered sublingually. The patient had a resolution of symptoms within 10 minutes. An echocardiogram taken 40 minutes after the event showed progressive recovery of ventricular repolarization abnormalities. Daily echocardiograms confirmed a normal repolarization pattern. The patient was discharged without cardiovascular therapy, and her capecitabine therapy was discontinued. The patient was initiated on intravenous cisplatin therapy.

Capecitabine is an oral prodrug of 5-fluorouracil and is not a cytotoxic drug itself, but it is converted by a 3-step enzymatic cascade to 5-fluorouracil within human cancer cells. Cardiotoxic effects of 5-fluorouracil are well known, however capecitabine-induced cardiotoxicity has been rarely reported. 5-fluorouracil had been known to induce acute coronary syndrome (ACS), heart failure, hypertension, hypotension, cardiomyopathy, and arrhythmias. Myocardial injury, thrombogenic effects, immuno-allergic reaction, and coronary vasospasm have all been implicated in the mechanism underlying 5-fluorouracil cardiotoxicity.

The authors warn that capecitabine should be considered to be a drug with cardiotoxic potential, even in the absence of prior cardiac history because it can induce coronary spasm at the macro- or microvascular level. Clinicians should be aware of its potential cardiac hazard, which might be manifested

by coronary angiospasm, especially in patients with cardiovascular risk factors. Because of the increased usage of capecitabine, patients should be warned and informed about the possibility of chest pain and other possible emergent anginal symptoms, particularly during the first few days of treatment. Most importantly, patients who develop ACS should not be retreated with capecitabine.

Golias C, Dimitriadis G, Dimitriadis D, et al. Acute presentation of vasospastic angina induced by oral capecitabine: A case report. *J Med Case Rep.* 2014;8:18.

SKIN HYPERPIGMENTATION DUE TO LONG-TERM VORICONAZOLE THERAPY

A male in his 40s with mixed African American and White race/ethnicity and a history of pulmonary sarcoidosis and secondary pulmonary aspergillomas presented for a follow-up dermatologic examination. The patient was also being evaluated for a lung transplant. The patient had been evaluated 3 years prior, and his dermatologic exam was unremarkable. The patient was noted to have Fitzpatrick type IV skin. The Fitzpatrick Scale is a method to classify the response of different types of skin to ultraviolet (UV) light. The scale ranges from I to VI, with class I always burning from the sun and class VI tanning easily and never burning. Since the patient was classified as Fitzpatrick Scale type IV, his skin is best described as moderate brown with typical Mediterranean skin tone. With sun exposure, the patient rarely burns and always tans well.

On examination, the patient was noted to have new hyperpigmented lesions on his forearms that he stated had been present for a few months. The patient had been receiving voriconazole (*Vfend*) 200 mg twice daily for the last 32 months for treatment of his fungal disease. Additionally, the patient had a history of long-term prednisone usage (varying doses of up to 60 mg daily) since 2008 to manage his pulmonary sarcoidosis. The patient had no history of atypical melanocytic lesions, and there was no family history of melanoma. The patient reported sun exposure with no history of increased occupational exposure or sunburns.

Physical examination revealed numerous hyperpigmented macules clinically consistent with lentigines on his face, with darker and multicolored macules on his sun-exposed forearms. Lentigines are benign, acquired brown macules resembling a freckle except that the border is usually regular and microscopic elongation of rete ridges is present,

with increased melanocytes and melanin pigment in the basal cell layer. Biopsies were taken of the most clinically suspicious hyperpigmented lesions, and they were remarkable for epidermal hyperplasia with pigmentation along the basal layer consistent with a lentiginous growth pattern. The patient's atypical lesions were excised, and the patient was counseled on appropriate sun protection measures and self-skin examination, with close dermatologic follow-up.

The authors point out that there are multiple cutaneous adverse effects, including UV-A photosensitivity manifesting as erythema, blistering, pruritus, cheilosis, eczema, and lentigo formation. Malignant skin conditions associated with chronic voriconazole use, including melanoma in situ and squamous cell carcinoma, have been reported in patients with Fitzpatrick skin types III and below and are more common in patients with some degree of immune compromise. Possible mechanisms for voriconazole-induced photosensitivity and phototoxicity currently remain unknown. One current theory includes a potentially phototoxic UV-B-absorbing N-oxide metabolite of voriconazole. Alternatively, inhibition of CYP450 with voriconazole therapy is thought to possibly increase serum retinol levels, a known photosensitizer.

The authors warn that cutaneous adverse effects of long-term voriconazole therapy are not only burdensome but also lead to morbidity and mortality. Voriconazole product labeling recommends discontinuation of voriconazole therapy if a squamous cell carcinoma or melanoma develops. In patients awaiting transplant, the development of melanoma could compromise their ability to receive an organ transplant. This report highlights the development of atypical melanocytic lesions in a dark-skinned individual receiving concurrent voriconazole and immunosuppression therapy and reinforces the importance of counseling patients on appropriate sun protection and sun avoidance. Patients, regardless of skin type, require frequent dermatologic follow-up and surveillance for the development of lesions.

Massey PR, Wanat KA, Elenitsas R, et al. Atypical lentigines in a man with mixed African American and white race/ethnicity receiving long-term voriconazole therapy. *JAMA Dermatol.* 2014;150(3):334-335.

VACCINE-ASSOCIATED MEASLES

A 23-year-old healthy male was given measles vaccine, without a rubella or mumps vaccine at

the same time. Eighteen days post vaccination, the patient presented with a high fever 40°C (104°F). At 20 days post vaccination, a rash appeared on his trunk, legs, and arms. Koplik's spots, a runny nose, and red eyes were also noted. Koplik's spots are small, white spots (often on a reddened background) that occur on the inside of the cheeks early in the course of measles. Two days after disease onset, blood samples, a throat swab, and a urine sample were collected and tested for measles virus by reverse transcription-polymerase chain reaction. A sequence corresponding to the measles protein (533 bp) was amplified from the serum, peripheral mononuclear cells, and throat swab and was identical to that of the genotype A virus (DQ345721). The patient had no history of travel before vaccination or contact with patients with measles. Before vaccination, he tested negative for serum antibodies against measles virus. Therefore the patient was diagnosed with vaccine-associated measles.

The authors stated that vaccine-associated measles can occur in children and immunocompromised individuals. Little is known about the occurrence of vaccine-associated measles in healthy adults because preschool children are usually vaccinated. The Centers for Disease Control and Prevention reported that complications after measles infection are more common among children aged less than 5 years and adults older than 20 years. Analysis of 57 vaccine-associated cases revealed that the average time of disease onset was 8.8 days post vaccination. The majority (94.7%) developed clinical signs within 2 weeks post vaccination. The patient reported in this case developed symptoms at 18 days post vaccination, which is longer than anticipated. Clinicians should be aware of the possibility of vaccine-associated measles in both children and adults.

Kurata T, Kanbayashi D, Kinoshita H, et al. Late onset of vaccine-associated measles in an adult with severe clinical symptoms: A case report. *Am J Med.* 2014;127(4):e3-e4. ■