ISMP Adverse Drug Reactions

Sildenafil-Induced Erythema Multiforme

Acute Liver Injury Due to Febuxostat

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Lidocaine-Induced Hoigne Syndrome

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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.

SILDENAFIL-INDUCED ERYTHEMA MULTIFORME

A 49-year-old male experienced pruritus and mild erythema for approximately 12 hours. The patient had no other abnormalities on physical exam. The patient's medical history included HIV, which was diagnosed 4 years earlier. On diagnosis, his CD4 count was very low at 53 cells/mm³ (normal value, 400-1400 cells/mm³), and he received highly effective antiretroviral therapy with tenofovir plus emtricitabine, atazanavir, and ritonavir. After 4 years, the patient was receiving the same antiretroviral therapy and his CD4 count was stable at 620 cells/mm³ with an undetectable HIV viral load. The patient had received a dose of ceftriaxone 2 months earlier for the treatment of syphilis. The patient reported that he had applied a new body lotion, so he was suspected

of having contact dermatitis. He was started on cetirizine 10 mg daily and was told to stop using his new body lotion.

The next day the patient experienced intense pruritus and an extensive maculopapular rash, covering his extremities, abdomen, thorax, and gluteal region with less extension to his back and neck. He had a single target-lesion in his right palm and oral mucosal lesions that caused a tingling sensation. His diagnosis was changed to erythema multiforme (EM) and a CBC, Chem-7, ESR, and HSV 1 & 2 serology were ordered, which were all normal. The patient then reported that he had used a tablet of sildenafil (*Viagra*) 100 mg 5 days prior to his initial symptoms.

The patient's cetirizine dosage was increased to 10 mg twice daily for 7 days. Three days after

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this dosage increase, the patient was examined; the improvement in his skin was obvious and his pruritus was lessened. The total duration of the lesions was less than 2 weeks. Six months later, the patient had a skin patch test for sildenafil, which was positive. This positive test confirmed a cell-mediated drug allergy.

The author analyzed the patient's case and stated, "The initial appearance of symmetrical maculopapular and target lesions on the extremities is typical in EM, usually spreading from acral to proximal areas and finally to the trunk." He also noted that HIV-infected patients have a higher risk of developing cutaneous reactions, presumably as a result of immune dysregulation and altered drug metabolism.

Pitsios C. Erythema multiforme caused by sildenafil in an HIV (+) subject. *Eur Ann Allergy Clin Immunol.* 2016;48(2):58-60.

ACUTE LIVER INJURY DUE TO FEBUXOSTAT

A 34-year-old male with severe gout began to experience nausea, fatigue, abdominal pain, dark urine, jaundice, and itching. These symptoms began 2 months after initiating febuxostat (*Uloric*) 40 mg daily that was added to his antigout regimen of colchicine 1.2 mg and allopurinol 300 mg daily. A medication history revealed the patient was also taking simvastatin, lisinopril, hydrochlorothiazide, ranitidine, amitriptyline, and acetaminophen with codeine 1 to 2 tablets daily. The patient denied ingesting any over-the-counter medications as well as herbal products.

The patient's physical exam revealed a severely obese patient with a body mass index (BMI) of 63.3 kg/m² and jaundice, however there was no fever or signs of chronic liver disease. Lab tests revealed a serum total bilirubin of 8.3 mg/dL (normal value, 0.3-1 mg/dL), alkaline phosphatase 201 U/L (normal value, 44-147 IU/L), alanine transaminase 148 U/L (normal value, 10-35 U/L), and serum amylase 779 U/L (normal value, 60-160 U/L). His complete blood count was normal except for 5% eosinophils (normal value, 1%-4%) and his international normalized ratio (INR) was 1.09. Hepatitis A, B, C, and E tests were all negative as well as smooth muscle antibodies. An abdominal ultrasound and CT scan of the patient's abdomen revealed gallstones but no evidence of biliary obstruction; this result was confirmed by endoscopic retrograde cholangiopancreatography (ERCP). The patient's allopurinol, hydrochlorothiazide, and lisinopril were discontinued at this time, however febuxostat was continued. The patient's liver function tests minimally improved over the next 40 days but

still remained abnormal. The patient also remained symptomatic. A liver biopsy revealed intrahepatic cholestasis and mild inflammation necrosis.

The patient's febuxostat was discontinued 40 days after his initial symptoms, and he experienced a prompt resolution of symptoms and normalization of liver function tests. The patient's allopurinol, lisinopril, and hydrochlorothiazide were then reinitiated and his symptoms as well as his liver functions tests remained normal at his 6-month follow-up visit.

The authors elaborate that febuxostat is a xanthine oxidase inhibitor that has a higher specificity for xanthine oxydase than allopurinol. Febuxostat is considered to be safer than allopurinol; it was not linked to cases of clinically apparent liver injury in pre-licensure studies, but it was associated with elevated serum enzyme levels. The authors state, "The latency of 2 months, cholestatic pattern of serum enzyme elevations, and liver histology of cholestatic hepatitis were typical of drug-induced liver injury, but somewhat atypical of allopurinol hepatotoxicity, which usually causes hepatocellular injury features of hypersensitivity (fever, rash and eosinophilia) and acute hepatitis with eosinophils and granulomas on liver biopsy."

The authors had this adverse reaction adjudicated by the Drug-Induced Liver Injury Network and the case was scored as "highly likely" that it resulted from the use of febuxostat. Clinicians should be aware that although it is a rare occurrence, febuxostat can cause a clinically apparent liver injury with a cholestatic pattern of liver abnormalities without evidence of hypersensitivity or autoimmune features. Abrupt discontinuation of febuxostat will result in rapid improvement of symptoms and laboratory abnormalities.

Bohm M, Vappalanchi R, Chalasani N, et al. Febuxostat-induced acute liver injury. *Hepatology.* 2016;63(3):1047-1049.

INTRAVENOUS ACETAMINOPHEN-INDUCED ACUTE HEPATOTOXICITY

A 92-year-old female was admitted to the hospital for a bowel obstruction. On hospital day 3, she underwent a laparoscopic reduction of internal hernias. Her medications prior to admission included aspirin, amlodipine, carvedilol, levothyroxine, memantine, celecoxib, paroxetine, quetiapine, and probiotics. On hospital days 1 and 2, she received oral doses of metoclopramide and intravenous ondansetron as well as intravenous fluids. During surgery, she received general anesthesia with sevoflurane, as well

as succinylcholine, etomidate, rocuronium, fentanyl, esmolol, neostigmine, glycopyrrolate, bupivacaine, and lidocaine.

The patient's operation was uncomplicated. Postoperatively she was treated with intravenous acetaminophen 1 g every 6 hours for analgesia; this was continued until hospital day 6 for a total acetaminophen dosage of 13 g. Additional postoperative medication included subcutaneous heparin, intravenous potassium chloride and ondansetron, and oral famotidine and metoclopramide. The patient experienced nausea and vomiting for 2 days postoperatively; when the patient resumed oral intake, the intravenous acetaminophen order was not changed to oral acetaminophen. The original intravenous acetaminophen order did not include a stop date.

On hospital day 5, the patient experienced epigastric pain. Liver function tests taken on day 5 revealed a serum total bilirubin of 1.8 mg/dL (normal value, 0.3-1 mg/dL), alanine transaminase (ALT) 3,914 U/L (normal value, 10-35 U/L), aspartate transaminase (AST) 4,698 U/L (normal value, < 35 U/L), INR 1.68 (normal value, 0.9-1.2), and ammonia 60 mcg/dL (normal value, 15-45 mcg/dL). The patient's AST and ALT were within normal limits at the initiation of acetaminophen therapy. The patient's serum acetaminophen level was 15.3 mcg/mL (reference range, <10-20 mcg/mL) at 26 hours after her last intravenous acetaminophen dose. The patient did not experience acidosis or encephalopathy, and all other serum chemistries were within normal limits. The patient's serum creatinine was normal at 1.3 mg/dL on admission and 0.7 mg/dL on discharge.

Based on the patient's symptoms and laboratory results, her acetaminophen was discontinued and intravenous acetylcysteine was started by standard protocol over a 21-hour period. The protocol called for the patient to receive acetylcysteine 150 mg/kg intravenously over 1 hour, followed by 50 mg/kg intravenously over 4 hours, and then followed by 100 mg/kg over the next 16 hours. The patient had a 9.5-hour interruption of her acetylcysteine after which it was restarted at the 100 mg/kg, but it was discontinued after only 14.5 hours. The patient received a total of 35.5 hours of intravenous acetylcysteine therapy. At the time of discontinuation of acetylcysteine, her transaminases showed consistent improvement and her INR was 1.3, ammonia 36 mcg/dL, and total bilirubin 1.7 mg/dL. The patient's mental status remained normal throughout her admission. The patient was discharged 2 days

after acetylcysteine was discontinued with an AST/ALT of 333/1,024 U/L.

Seifert et al measured acetaminophen-protein adducts (APAP-CYS) in the patient's serum samples. APAP-CYS are considered a specific biomarker of acetaminophen exposure, and APAP-CYS concentrations have been found to correlate with acetaminophen-induced hepatotoxicity. The expected range of APAP-CYS during therapeutic dosing is less than 1.1 μ M. On day 3 of intravenous acetaminophen therapy, the patient's APAP-CYS concentration was 1.79 μ M; day 5 = 4.81 μ M; and day 6 = 2.92 μ M. The patient did not have a medication error or additional source of acetaminophen. No other hepatotoxic medications were utilized in this patient, and the patient had no history of shock, alcohol usage, malnutrition, or viral hepatitis. A hepatic ultrasound, which was performed prior to the initiation of intravenous acetaminophen, showed hepatic steatosis, normal vascular function, and possible cirrhosis.

Seifert et al noted that higher than expected serum APAP-CYS concentrations occurred with standard intravenous acetaminophen dosing versus expected APAP-CYS concentrations with therapeutic oral dosing. The elevated APAP-CYS levels are consistent with cases of hepatotoxicity following repeated supratherapeutic acetaminophen ingestion (>4 g daily). The fact that the patient had a measurable acetaminophen concentration a full 26 hours after her last intravenous acetaminophen dosage clearly indicated a prolonged acetaminophen clearance.

Seifert et al point out that the patient had several factors that may have contributed to her acetaminophen-induced liver injury. First, she was elderly; these patients may have a smaller volume of distribution and prolonged half-life with acetaminophen. Also there is limited experience with intravenous acetaminophen in patients older than 75 years. Second, she was postoperative and likely catabolic due to her nothing by mouth status. Third, she had multiple intravenous acetaminophen doses administered over several days. Seifert et al point out that in Australia it is recommended to switch a patient to oral acetaminophen therapy or another pain reliever once the patient is capable of oral intake. Fourth, there was no monitoring of hepatic transaminases or INR, which is recommended if intravenous acetaminophen is continued beyond 48 hours. Fifth, the patient has some evidence of prior hepatic disease by ultrasound prior to intravenous acetaminophen initiation. Seifert et al point out that these uncommon circumstances

limit the generalizability of risk to a small number of patients and therefore this case has little impact on the overall safety profile of acetaminophen. The authors reported this case to illustrate a potential hazard of intravenous acetaminophen and a potential utility of APAP-CYS adducts to evaluate acute liver injury due to acetaminophen.

Seifert SA, Kovnat D, Anderson VE, et al. Acute hepatotoxicity associated with therapeutic doses of intravenous acetaminophen. *Clin Toxicol*. 2016;54(3):282-285.

ACUTE TRANSIENT MYOPIA INDUCED BY ZANAMIVIR

Weng et al report a 31-year-old female who experienced acute blurred vision, especially at a distance, in both eyes after zanamivir (*Relenza*) treatment for influenza. Her complaints of blurred vision began one day after initiating zanamivir. In addition to the blurred vision, the patient also had periocular edema and skin rashes over her face, trunk, and extremities. An eye exam revealed a visual acuity of 6/30 in her right eye and 6/20 in her left eye, however her intraocular pressure was not elevated.

Because an acute allergic reaction was suspected, treatment was initiated with intravenous antihistamines and oral steroids and zanamivir was discontinued. Gradually her skin rash and periocular edema resolved and her visual acuity improved. Weng et al offered the following 3 mechanisms by which zanamivir could cause acute myopia: ciliary spasm, lens edema, and ciliary body and/or choroidal effusion. The authors note that acute myopic changes have not been reported with the use of zanamivir, however a recent case report details a case of bilateral acute angle-closure glaucoma and acute transient myopia associated with oseltamivir, which is another marketed antiviral neuraminidase inhibitor used to combat influenza.

Weng et al note that this patient's ocular symptoms resolved spontaneously after discontinuation of zanamivir and antihistamine treatment, however devastating consequences such as angle-closure glaucoma could have occurred if the patient had been left untreated.

Weng TH, Lin SM, Chiang SY. Relenza-induced acute myopia change. *Optom Vis Sci*. 2016;93:307-309.

LIDOCAINE-INDUCED HOIGNE SYNDROME

Thompson and Theobald report a 22-year-old female who was to receive a local lidocaine injection

prior to a bone marrow biopsy. The patient had a history of anxiety, but she displayed no anxiety symptoms when the procedure started. The patient received 5 mL of 2% lidocaine (100 mg) locally over her right iliac crest. The patient was still experiencing pain and received 2 more injections of lidocaine, one subcutaneously and one periosteal, that totaled 18 mL of lidocaine. The patient's total lidocaine dose was 360 mg (5 mg/kg).

After the injections, the patient developed tingling in her right leg and right ear. She developed lightheadedness, profound anxiety, restlessness, and a feeling like "her brain is burning." The patient began screaming for her fiancé, and had anxiety so severe she ran from the procedure room to the waiting area where her fiancé was waiting. The patient was transported to the emergency department where she said she was seeing graveyards and exclaimed, "I can see my tomb!" Her fiancé observed that during this whole event the patient was oriented and not confused. The patient received lorazepam 1 mg intravenously, which improved her symptoms. A CT scan and blood tests revealed no abnormalities.

Thompson and Theobald evaluated the patient's adverse reaction; it is best described as Hoigne syndrome. They explain that, "Hoigne syndrome is an acute, nonallergic reaction manifesting as 'doom anxiety'." Hoigne syndrome can produce symptoms within minutes of receiving a local anesthetic injection. Patients often feel intense anxiety and impending death. Patients can also have perceptual disturbances that can affect any of the sensory systems. Importantly, patients will recognize that these perceptions are not real."

Thompson and Theobald note that Hoigne syndrome has been reported in patients receiving procaine penicillin injections, intravenous lidocaine infusions, and nail bed and intramuscular injections of local anesthetics. They describe the current theory that local anesthetics may cause Hoigne syndrome through local anesthetic-induced limbic sensitization in the brain. The authors point out that the preferred management is prompt recognition, patient reassurance, and the administration of benzodiazepines.

Thompson TM, Theobald JL. Hoigne syndrome: A little-known adverse effect of lidocaine. *Am J Emerg Med*. 2016;34:679.e3-679.e4. ■