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ISMP Adverse Drug Reactions

Pancreatitis-Associated with Riluzole

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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.

PANCREATITIS-ASSOCIATED WITH RILUZOLE

A 79-year-old male was admitted to the hospital with severe upper abdominal pain and vomiting. The patient had no history of alcohol consumption, biliary stones, diabetes, trauma, hypercalcemia, hyperlipidemia, previous acute pancreatitis, or chronic pancreatitis. The patient's medication history only revealed irbesartan, which the patient has been receiving for a number of years for his hypertension, and riluzole (*Rilutek*) 50 mg 3 times daily for amyotrophic lateral sclerosis (ALS). The patient had been receiving riluzole for 3 months.

On admission, the patient's vital signs and physical exam were unremarkable except for a tender abdomen. Lab test results were a serum amylase 1,298 U/L (reference range, ≤100 U/L), lipase 1,650 U/L (reference range, 13-63 U/L), moderate leukocytosis with a white blood cell (WBC) count 15.75 x 10^9/L (reference range, 4.1-10.9 x 10^9/L). Additional laboratory assessments were within normal limits, including total bilirubin, direct bilirubin, c-glutamyl transpeptidase, alkaline phosphatase, serum lipids, and serum calcium. Tests for autoantibodies and possible infectious causes were also negative. The patient received a CT scan 72 hours after the onset of symptoms that revealed mild swelling of the pancreatic body and tail with a focal necrotic area in the distal portion of the tail.

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The patient was diagnosed with acute pancreatitis that was classified as moderately severe according to the revised Atlanta classification of acute pancreatitis. His riluzole was discontinued, and he was managed with fasting, parenteral nutrition, an unspecified carbapenem, and a proton pump inhibitor. The patient's pancreatic enzymes and WBC count returned to normal after 7 days. The patient's irbesartan was continued, because he had received the drug for a significant amount of time without incident; however, riluzole was not reinitiated.

Riluzole is the only drug that is US Food and Drug Administration (FDA) approved for the treatment of ALS. Riluzole possesses the pharmacologic effects of inhibition of glutamate release, inactivation of voltage-dependent sodium channels, and ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors. Common adverse effects of riluzole are nausea, epigastric pain, diarrhea, constipation, and an increase in liver enzymes. Mild acute pancreatic damage has been reported in the literature but is not common. The authors want to alert clinicians that the risk of moderately severe pancreatitis is rare but should be considered in patients receiving riluzole and who become symptomatic.

Ianiro G, Cammarota G, Milani A, et al. Moderately severe acute pancreatitis associated with riluzole. *J Clin Gastroenterol.* 2014;48(6):563.

LINEZOLID-INDUCED HYPOGLYCEMIA

The Center for Drug Evaluation and Research at the FDA conducted a study to review reports of hypoglycemia associated with linezolid (*Zyvox*) use. They searched the FDA Adverse Event Reporting System (FAERS) for reports of hypoglycemia in linezolid patients for a 12-year period. The authors graded the strength of association of each report with the likelihood that linezolid may have caused the hypoglycemia. A total of 41 reports of hypoglycemia were discovered in the FAERS database with 26 of those cases classified as unlikely to be associated with linezolid usage. Of the remaining 15 cases, the relationship between hypoglycemia and linezolid exposure was considered to be highly probable in 7 cases, probable in 4 cases, and possible in 4 cases.

The median age of patients who experienced hypoglycemia was 77 years and 73% of patients were male. Twelve of the 15 patients (80%) had diabetes mellitus; 9 were receiving oral hypoglycemia drugs, 2 patients were receiving insulin, and 1 patient's regimen was not reported. Eight of the 15 patients (53%) received oral linezolid, 6 patients (40%) received intravenous linezolid, and the route of administration was not provided for 1 patient. The median time to the onset of hypoglycemia was 7 days, with a range of 2 to 30 days from the first dose of linezolid. The lowest median blood glucose in patients receiving linezolid was 32 mg/dL, with a range of 12 to 60 mg/dL. In 8 of the 12 diabetic patients (75%), hypoglycemia did not respond to adjustments in the diabetic drug regimen, but it did resolve after discontinuation of linezolid.

The authors sought to develop a possible explanation of how linezolid could cause hypoglycemia. They focused on the weak nonselective monoamine oxidase (MAO) inhibitor effects of linezolid, because hypoglycemia is associated with MAO inhibitors, especially those of the hydrazine type. Therefore, linezolid's activity as an MAO inhibitor may provide a biologic explanation of the possible cause of the hypoglycemia.

The linezolid package labeling was updated to include the possibility of hypoglycemia in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid. The warning also advises that diabetic patients should be counseled regarding the potential for hypoglycemia reactions while receiving linezolid and indicated that an adjustment or discontinuation of hypoglycemia medications or discontinuation of linezolid may be required. Clinicians should be aware of the possibility of hypoglycemia especially in diabetic patients receiving linezolid.

Viswanathan P, Iarikov D, Wassel R, et al. Hypoglycemia in patients treated with linezolid. *Can Infect Dis.* 2014;59(15 Oct):e93-e95.

SORAFENIB-INDUCED ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

A woman in her fifties presented with a history of multifocal hepatocarcinoma previously treated unsuccessfully with radiofrequency, arterial embolization, and selective hepatic radioembolization. She then had the emergence of lung metastases, and treatment was initiated with sorafenib (*Nexavar*) 400 mg orally every 12 hours. Two weeks after treatment with sorafenib was initiated, the patient developed a hand-foot skin reaction (HFSR); treatment was suspended and the skin lesions resolved. At this time, treatment with sorafenib was reinitiated with a dosage reduction to 200 mg orally twice daily, and the patient experienced good results. Based on the patient's response, the dosage of sorafenib was

increased back to 400 mg orally twice daily. Ten days after the dosage increase, the HFSR reappeared and sorafenib treatment was suspended again. After 3 weeks, sorafenib treatment was restated at half the dose (200 mg orally twice daily).

Over the next 4 weeks, the patient continued to receive sorafenib 200 mg orally twice daily and no additional drug was added to her treatment regimen. At 4 weeks, the patient developed an abrupt skin eruption consisting of erythematous and edematous plaques with hundreds of tiny nonfollicular pustules that appeared first in the genital and inguinal areas and subsequently on the legs, abdomen, buttocks, and neck. She had no mucosal lesions, fever, or any other relevant systemic symptoms, however her blood neutrophil and eosinophil counts were elevated. A skin biopsy confirmed the diagnosis of acute generalized exanthematous pustulosis (AGEP). Sorafenib treatment was discontinued immediately, and the patient's skin lesions subsided spontaneously with desquamation occurring a week later.

The patient experienced a classic presentation of AGEP. AGEP typically manifests as a rash that starts on the face or in the armpits and groin and then becomes more widespread. It is characterized by the rapid appearance of areas of red skin studded with small sterile pustules (small blisters filled with white/yellow fluid). There tends to be more disease in skin folds, and facial swelling often arises. AGEP may be associated with a fever and malaise, but generally the patient is not particularly unwell. The rash may last for 1 to 2 weeks and then the skin peels off as the condition resolves. AGEP is usually classified as a severe cutaneous adverse reaction to a prescribed drug.

The most frequent adverse effects of sorafenib are those affecting the skin in up to 60% of patients. Some reports suggest that patients receiving sorafenib for hepatocellular carcinoma who develop skin toxic effects show a longer survival. Several cases of AGEP have been reported in the medical literature in patients receiving imatinib, which shares the same inhibition pathway of platelet-derived growth factor. Sorafenib also inhibits multiple tyrosine kinases, including C-RAF and B-RAF, as well as vascular endothelial growth factor receptors. The authors recommend that the recognition of cutaneous adverse effects early in sorafenib treatment will likely increase medication adherence and administration and minimize dosage reductions and discontinuation of the effective and potentially life-extending drug treatment.

Pretel M, Inarrairaegui M, Lera JM, et al. Acute generalized exanthematous pustulosis induced by sorafenib. *JAMA Derm.* 2014;150(6):664-666.

CREATINE SUPPLEMENTATION–INDUCED THROMBOTIC EVENTS

An 18-year-old active athletic male reported a 1-week history of headache and vomiting. An MRI of the head was ordered, and a thrombosis of the superior sagittal sinus, right transverse sinus, and right internal jugular vein were detected. The patient did not demonstrate any head or neck pathology, and he had no personal or family history of venous thromboembolism. He was not receiving prescription or over-the-counter medication except for creatinine supplementation that he had initiated approximately 3 months prior to his admission. The patient was evaluated for thrombophilia, and all test results were normal, including tests for protein C, protein S, and antithrombin III deficiencies; factor V Leiden and prothrombin gene G20210A mutation; lupus anticoagulant and anticardiolipin antibodies; Janus kinase 2 mutation for myeloproliferative disorders; and paroxysmal nocturnal hemoglobinuria screen.

The patient reported that after he had begun taking creatine supplementation, he frequently felt thirsty and had to drink more fluids. The patient was anticoagulated for 6 months and discontinued taking creatine-containing products. The patient was seen 6 months after anticoagulation had been discontinued, and he had not had a recurrent thrombotic episode.

A 31-year-old male presented with a 5-day history of left lower limb swelling and pain. He was subsequently diagnosed with a left lower limb deep vein thrombosis (DVT) involving his femoral and popliteal veins. The patient had no history of recent surgery or immobilization, however he did travel by air on a 5-hour flight approximately 3 weeks prior to admission. The patient led an active lifestyle and exercised regularly. He had begun taking creatine supplementation for a period prior to his admission. The patient had no personal or family history of DVT, and no other cause of his DVT was evident. The patient received catheter-guided thrombolytic therapy followed by 6 months of anticoagulation. The patient discontinued his creatine supplementation and has not had a recurrence of his DVT to date.

In presenting the 2 cases, the authors warn of this potentially serious adverse effect of a widely utilized sports supplement. Creatine use is generally considered to have minimal adverse health risks. Many people utilize creatine to increase muscle mass, however

creatine supplementation can cause water to be drawn in to the muscles by the osmotic effect produced by an increase in intracellular creatine. This effect can lead to dehydration, especially in a hot environment, and cases of heat stroke have been reported among creatine users. Dehydration is a known precipitating factor for DVT.

The authors state that it is essential that patients are warned of the dehydrating potential of creatine and by extension its thrombotic risk. Creatine's consumption must be accompanied by adequate and continuous rehydration during sporting activities.

Tan CW, Tha MH, Ng HJ. Creatine supplementation and venous thrombotic events. *Am J Med.* 2014;127(8):e7-e8.

ACUTE PANCREATITIS ASSOCIATED WITH QUETIAPINE

A 58-year-old male nursing home resident who had been treated for 20 years for schizophrenia developed abdominal pain, vomiting, fever, and chills. He had no history of diabetes or hyperlipidemia. Upon arrival at the hospital, his laboratory tests revealed normal Chem-7 and liver function tests, lipase 5,482 IU/L (reference value, <160 IU/L), amylase 976 IU/L (reference value, 60-160 IU/L), triglycerides 74 mg/dL (reference value, 70-150 mg/dL), WBC 14.2 x 10^3/µL (reference value, 4.1-10.9 x 10^3/µL), and hematocrit 49.3% (reference value, male 39%-49%). An abdominal ultrasound and CT revealed acute pancreatitis with a gall bladder polyp. Based on the objective findings, a gastroenterologist diagnosed the patient with drug-related acute pancreatitis.

Prior to admission, the patient had received quetiapine (*Seroquel*) 500 mg plus valproic acid 500 mg daily for the last 10 years. Valproic acid was discontinued and the patient received antibiotics and supportive therapy and was discharged after a 12-day hospital stay. Five days after discharge, the patient experienced similar symptoms while receiving monotherapy with quetiapine 500 mg daily. Pertinent laboratory data on this admission were lipase 458 IU/L, WBC 13.6 x 10^3/µL, glucose 102 mg/dL, and hematocrit 41.3%. An abdominal ultrasound revealed acute pancreatitis. The patient was admitted to the hospital and again diagnosed with drug-induced pancreatitis. Quetiapine was discontinued for 14 days and gradually titrated to 100 mg daily. After observation for 6 months, low-dose quetiapine did not induce acute pancreatitis.

In evaluating the patient's pancreatitis, the authors point out that the patient did not have an acute cause or risk factors for acute pancreatitis, such as alcohol abuse or undiagnosed medical conditions, such as diabetes, hyperlipidemia, or metabolic syndrome. All other causes of pancreatitis were excluded with the exception of valproic acid. The authors could not rule out the possibility that the 2 episodes of pancreatitis were separate events related to different drugs or combinations. Although valproic acid-induced pancreatitis is common in children and may occur after a significant length of time of drug administration, the dosage and concentration of valproic acid do not play a role in the development of pancreatitis. The authors evaluated the probability of valproic acid and quetiapine as causes of the patient's pancreatitis; valproic acid scored a 4 on the Naranjo scale while quetiapine scored an 8. The authors believe that it is more likely that quetiapine rather than valproic acid caused the 2 episodes of acute pancreatitis. The authors theorize that the development of pancreatitis may be due to the metabolic effect of quetiapine, such as is seen with the association of quetiapine in hyperglycemia and diabetic ketoacidoses. The authors warn that the accumulation of metabolic effects of quetiapine may cause acute pancreatitis with higher dosages and long-term use.

Chang TG, Chiu NY, Hsu WY. Acute pancreatitis associated with quetiapine use in schizophrenia. *J Clin Psychopharm.* 2014;34(3):382-383.

HYPOMAGNESEMIA AND SEIZURE ASSOCIATED WITH RABEPRAZOLE

A 51-year-old woman presented with a witnessed seizure, tongue biting, muscle stiffness, and urinary incontinence. He past medical history was significant for diabetes, hypertension, and gastroesophageal reflux disease (GERD). The patient had been receiving rabeprazole (*Aciphex*) for the past 5 years with no history of diuretic use. Her laboratory results on admission were sodium 140 mEq/L (reference range, 135-145 mEq/L), potassium 3.2 mEq/L (reference range, 3.5-5 mEq/L), chloride 101 mEq/L (reference range, 95-107 mEq/L), bicarbonate 27 mEq/L (reference range, 22-26 mEq/L), creatinine 1.7 mg/dL (reference range, female 0.6-1.2 mg/dL), calcium 5.6 mg/dL (reference range, 8.5-10.2 mg/dL), magnesium 0.4 mEq/L (reference range,1.8-3.0 mEq/L), glucose 318 mg/dL (reference range, 65-110 mg/dL), and albumin 3.1 mg/dL (reference range, 3.5-5.5 mg/dL). The patient's EKG revealed a prolonged QTc interval. Additional laboratory results revealed an inappropriately low PTH 17 pg/mL (reference range,10-65 pg/mL), low ionized calcium 0.87 mmol/L (reference range,1.1-1.4 mmol/L), phosphorous 3.3 mg/dL (reference range, 2.4-4.1 mg/dL), 1,25 dihydroxyvitamin

D of 86.2 pg/mL (reference range, 25-65 pg/mL), aldosterone 1.8 ng/dL (reference range,4.5-35.4 ng/dL), renin 1.7 µg/L/h (reference range,0.8-5.8 µg/L/h), and a random urine magnesium of 14 mg/dL (reference range, female ≥40 years of age, 0.4-15 mg/dL).

The authors point out that proton pump inhibitors (PPIs) can induce hypomagnesemia, which can lead to seizures, arrhythmias, hypotension, tetany, and death. Magnesium is excreted via the renal and gastrointestinal route, so the prime culprit in PPI-induced hypomagnesemia is impaired intestinal absorption of magnesium. The authors recommend that in patients with gastrointestinal malabsorption of magnesium, H_2 blockers should be the first-line therapy; if PPI therapy is required, then close monitoring of magnesium is necessary especially in cardiac patients who might have a propensity for arrhythmia.

Nand B, Bhagat M. Serious and commonly overlooked side effect of prolonged use of PPI. *Am J Med*. 2014;127(9):e5. ■

(continued from page 1003)

led to the diluent being identified as a ready-to-use product, and it was dispensed without reconstituting the actual antibiotic. At the time, ISMP called upon the US Food and Drug Administration (FDA) and the manufacturer to improve label clarity, and the diluent container labels were then revised to state, "diluent for Cipro Oral Suspension." Similarly, the new vancomycin product diluent bottle should be prominently labeled, "diluent for vancomycin 25" or "diluent for vancomycin 50."

We also received reports in which the powder alone was dispensed without dilution for oral antibiotic products. This can happen with this product, because the powder container is marked with an icon that states, "Oral Solution." Another issue with this product is that the bottle of vancomycin powder, which acts as the dispensing container after reconstitution, is not prominently labeled with the expected final concentration or the total volume after reconstitution. This information may not be available unless the bottle happens to be relabeled with that information once reconstituted.

The powder container should state, "Vancomycin 25 Powder—Must be Diluted." Until this change is made by the company, hospitals and pharmacies using this product are advised to label containers appropriately so the grape diluent is not administered as the drug itself or the powder is not administered or dispensed without dilution. We also recommend labeling the reconstituted powder containers with the final concentration per mL and total volume, along with the notation, "Reconstitution Completed."

We have contacted both FDA and CutisPharma to request improvements to the way the product carton and containers are labeled. ■