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ISMP Adverse Drug Reactions

Gastrointestinal Nodules and Bleeding with Long-Term Lanthanum Use

DRESS and Hepatotoxicity Due to Rivaroxaban

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Varenicline-Induced Acute Liver Injury

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.

GASTROINTESTINAL NODULES AND BLEEDING WITH LONG-TERM LANTHANUM USE

A 62-year-old male with end stage renal disease (ESRD) developed continuing anemia with guaiac-positive stools. He was subsequently hospitalized for melena and coffee-ground emesis with worsening shortness of breath and a hemoglobin level that had dropped to 5.5 g/dL (normal male range, 13.2-17.5 g/dL).

The patient's history revealed his ESRD was secondary to HIV infection, and he had been undergoing peritoneal dialysis for the last 6.5 years. His adherence to peritoneal dialysis had been exceptional and his viral load was undetectable after dialysis was initiated. The patient's main issue had been hard to control phosphate levels for which he was placed on lanthanum carbonate (*Fosrenol*) 1000 mg 3 times daily, 4 years ago. After the start of lanthanum therapy, the patient's average serum phosphate level ranged from 4.5 to 6 mg/dL (normal range, 2.4-4.1 mg/dL). His chronic anemia had been well controlled with iron infusions and erythropoietin, but recently he required higher doses of erythropoietin and his iron index values were decreasing. The patient's medication history revealed he had also been receiving amlodipine, metoprolol, aspirin, paricalcitol, ritonavir, tenofovir, raltegravir, and a dialysis vitamin product.

The patient had an upper endoscopy performed that revealed, "Active erosive gastroduodenitis with innumerable gastric polypoid nodular lesions and a large 1.2 cm polyp in the duodenal bulb. Further into the duodenum were several flat white patches

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

of mucosa approximately 4 to 5 mm in size. All lesions appeared to be located on top of the mucosal folds." Light microscopy then revealed multinucleated foreign body-type giant cells, all containing a dark brown intracytoplasmic granular material along with extracellular eosinophilic crystalloid substance consistent with foreign material. The patient had a routine colonoscopy 4 years earlier that revealed only 6 nonmalignant polyps. Due to concern of a drug reaction, lanthanum treatment was discontinued. The patient then had a follow-up endoscopy 1.5 years later that revealed nodular lesions were still present but improved. The patient has not had another incidence of bleeding since the discontinuation of lanthanum.

The authors discuss the fact that lanthanum is an alkaline heavy metal that binds phosphate in the stomach and small intestine and forms an insoluble complex that is excreted predominantly in the stool with minimal systemic absorption. They point out, "Newer reports are beginning to emerge of patients treated with long-term lanthanum therapy who either show signs of systemic absorption or have local gastrointestinal complications." Even though the authors did not perform x-ray spectroscopy or crystallography on the foreign body samples, these lesions match the appearance and pathology to prior reports in the literature of lanthanum disposition.

The authors recommend that clinicians be aware of persistent or severe gastrointestinal symptoms in patients with ESRD who receive long-term lanthanum therapy. Since these adverse reactions are uncommon, it is possible that they are overlooked or only occur when a specific set of risk factors are present. The authors recommend stopping lanthanum treatment and follow-up with serial endoscopies, while using an alternative phosphate binding medication.

Valika AK, Jain D, Jaffe PE, et al. A nodular foreign body reaction in a dialysis patient receiving long-term treatment with lanthanum carbonate. *Am J Kidney Dis.* 2016;67(1): 128-132.

DRESS AND HEPATOTOXICITY DUE TO RIVAROXABAN

A 77-year-old male developed fever, malaise, fatigue, and arthralgia approximately 6 weeks after initiating rivaroxaban (*Xarelto*) and discontinuing warfarin after several years of use. The patient was anticoagulated due to the presence of antiphospholipid syndrome and a history of retinal thrombosis. His chronic medications included ezetimibe, valsartan, hydrochlorothiazide, and a daily multivitamin. The patient's initial laboratory results revealed a cholestatic pattern of liver function test elevations with a slightly increased serum creatinine of 1.43 mg/dL. Three days later at a follow-up visit, the patient reported no clinical improvement and further increases in liver function tests and an increase in serum creatinine to 2.02 mg/dL were observed. At this time, the patient's rivaroxaban was discontinued and he was admitted to the hospital for further management.

On admission, the patient's physical exam revealed a painful tenosynovitis in several joints, moderate pitting edema and a faint pink maculopapular rash on his inner arms and extending to his underarms and trunk. His urine analysis revealed occasional red blood cells and granular casts with minimal proteinuria. He had an increased white blood cell (WBC) count that peaked at 28.5 x 10^3/μL with a peak absolute peripheral eosinophil count of 600 eosinophils/μL. A peak absolute peripheral eosinophil count greater than 500 eosinophils/μL represents eosinophilia. A liver biopsy revealed irregular areas of necrosis with no viral inclusion. A skin biopsy demonstrated lymphocytes, eosinophils, and markers consistent with a dermal hypersensitivity reaction. Additional serial laboratory tests demonstrated further increases in liver function tests with a peak total bilirubin of greater than 4 mg/dL (normal range, 0.3-1 mg/dL), a peak alkaline phosphatase of greater than 600 U/L (normal range, 44-147 U/L), and a peak alanine transaminase of greater than 400 U/L (normal range, 10-35 U/L). The patient's serum creatine also peaked at 2.5 mg/dL.

The patient was diagnosed with drug-induced liver and skin injury with probable drug rash with eosinophilia and systemic symptoms (DRESS) from rivaroxaban. The patient was started on a tapering dose of methylprednisolone. Within the first week of methylprednisolone treatment, the patient's liver enzymes and creatinine both decreased by 50%. The patient's fatigue and arthralgia also improved with a complete resolution of his rash. The patient's methylprednisolone was gradually tapered over one month. Since the patient needed continuing anticoagulation, warfarin was reinitiated as the patient had tolerated warfarin therapy in the past.

The authors point out, "This case of drug induced liver disease with DRESS due to rivaroxaban raises the possibility of human leukocyte antigen-mediated injury." Their theory is further supported by the fact that the patient promptly responded to methylprednisolone. They state, "There is no consensus on the role of glucocorticoids in drug induced liver disease,

but their role in the treatment of DRESS is well established and in this case, along with withdrawal of the offending drug, seemed to attenuate many of the systemic features of immuno-allergic drug induced liver disease."

Barrett P, Vappalanchi R, Masuoka H, et al. Severe drug-induced skin and liver injury from rivaroxaban. *Dig Dis Sci.* 2015;60:1856-1858.

THROMBOCYTOPENIA INDUCED BY PENTOXIFYLLINE

A 72-year-old Chinese male was admitted to the hospital for pneumonia. His medication history included warfarin 1.5 mg daily, atorvastatin 20 mg daily, gliclazide sustained-release 160 mg twice daily (a sulfonylurea for diabetes), omeprazole 20 mg daily, isosorbide dinitrate 10 mg twice daily, acarbose 100 mg twice daily, carvedilol 6.25 mg twice daily, a multivitamin daily, ferrous fumarate 400 mg twice daily, nitroglycerine 0.5 mg as needed, furosemide 80 mg twice daily, and lactulose 10 mL 3 times daily. On day 10 of his hospital stay, the patient was started on pentoxifylline sustained release for treatment of his lower limb ischemia due to peripheral artery disease. The patient was started on a renally adjusted dose of pentoxifylline 400 mg twice daily due to an estimated creatinine clearance of 27 mL/min. The patient had an ultrasound 4 days earlier that ruled out a lower limb deep vein thrombosis.

When pentoxifylline was started, the patient was already receiving concomitant digoxin, atorvastatin, omeprazole, a multivitamin, gliclazide, promethazine with codeine syrup, aspirin, lactulose syrup, and parenteral piperacillin-tazobactam 2.25 g every 6 hours (day 10 of therapy for pneumonia). Carvedilol, acetaminophen, nitroglycerine, and parenteral furosemide were all initiated on the same day as pentoxifylline. The patient's warfarin was discontinued when pentoxifylline was initiated because the patient was experiencing hematuria, however the patient's international normalized ratio (INR) was 1.65. The patient's hematuria was investigated and found to be due to catheter-related cystitis and mild benign prostatic hyperplasia; after cystoscopy, he did not experience further hematuria.

Seventy-two hours after pentoxifylline was initiated, the patient's platelets dropped from 252 x 10^3/µL to 105 x 10^3/µL. On the fourth day of pentoxifylline, the patient's platelets reached the lowest value of 68 x 10^3/µL. On this day, aspirin was discontinued; the next day, pentoxifylline was discontinued. A screen for disseminated intravascular coagulation (DIC) was sent that revealed a serum prothrombin time of 16.3 seconds (reference range, 12-14.5 seconds), activated partial thromboplastin time of 38.8 seconds (reference range, 27-35.6 seconds), thrombin clotting time of 20.2 seconds (reference range, 15.1-17.9 seconds), d-dimer of 1.8 µg/mL (reference range, <0.5 µg/mL), and fibrinogen of 515 mg/dL (reference range, 147-391 mg/dL). Based on these results, it was concluded the patient did not have overt DIC.

Forty-eight hours after pentoxifylline discontinuation, the platelet level rose to 106 x 10^3/µL on the 16th day of his hospital admission. Aspirin 100 mg daily was restarted and the patient's platelet level continued to rise and normalized by hospital day 17 at 145 x 10^3/µL. The patient did not receive any further doses of pentoxifylline. However 15 days after pentoxifylline was discontinued, the patient developed a second episode of thrombocytopenia that was determined to be secondary to DIC. The patient's DIC was precipitated by *Escherichia coli* urosepsis complicated by shock. He was treated with 4 days of piperacillin-tazobactam followed by 8 days of meropenem. The patient subsequently deteriorated and died due to congestive heart failure with severe ischemic cardiomyopathy with an ejection fraction of 25%, resulting in cardiorenal syndrome on the 45th day of hospitalization.

The authors point out that, "Early identification of drugs causing thrombocytopenia is key to prevent worsening of thrombocytopenia and avoid clinical complications, such as life-threatening gastrointestinal or cerebral hemorrhages. Hospitalized patients may be on multiple medications, which could all be related to drug-induced thrombocytopenia. Hence, a pharmacist plays an essential role by assessing the temporal relationship and literature to determine drugs with a higher likelihood of inducing thrombocytopenia. Unnecessary discontinuation of all suspected drugs regardless of its risk could deprive the patient of essential medications needed."

Tan MW, Sklar GE. Pentoxifylline-induced thrombocytopenia: A case report. *J Pharm Pract.* 2015:1-5.

AMLODIPINE-INDUCED SCHAMBERG'S DISEASE

A 31-year-old male was treated for hypertension with lisinopril 20 mg daily; however after 5 weeks, his blood pressure was still elevated. Amlodipine 10 mg daily was added to his lisinopril 20 mg daily and his blood pressure was effectively lowered. After 3 months of treatment, the patient developed purpuric

skin eruptions around his ankle region accompanied by ankle edema. The patient's skin lesions progressively worsened. After 2 months asymptomatic, Schamberg's disease-like irregularly distributed rust-colored spots were located on the outer side of his tibia from his ankles to his knees. The patient's amlodipine treatment was discontinued. For the next 3 months, his skin changes were still visible, but became brown and the intensity was slightly reduced. Four months after amlodipine discontinuation, the patient's lesions completely disappeared.

The authors state that Schamberg's disease is a rare dermatosis characterized by progressive, nonpalpable pigmentary changes. Typically the lesions occur in patches with "cayenne pepper spots" with pigmentation as a prominent feature. The lesions do not exceed 3 cm in diameter and manifest themselves as reddish-brown macules. Macules are located especially on the lower extremities and have a vasculitic appearance, although this skin disorder is not associated with hematologic disease. Schamberg's disease is asymptomatic, may occur at any age, and affects males more often than females. The skin symptoms are caused by erythrocytes breaking down outside the capillary with hemosiderin deposits.

At a later date, the patient's lisinopril was discontinued; 6 months later, amlodipine was again started. The patient manifested symptoms of the same adverse skin reaction after one month of amlodipine therapy. A skin biopsy was performed, which revealed perivascular inflammatory T-cell lymphocytic infiltrate and extravasation of blood cells. Based on the patient's clinical symptoms and biopsy findings, Schamberg's disease induced by amlodipine was diagnosed.

The authors' note that the pathological mechanism of this condition remains unknown, but this patient's condition was probably caused by drug-induced erythrocytes breaking down outside the capillary with hemosiderin deposits.

Schetz D, Kocic I. A new adverse drug reaction – Schamberg's disease caused by amlodipine administration – a case report. *Br J Clin Pharmacol.* 2015;80(6):1477-1478.

VARENICLINE-INDUCED ACUTE LIVER INJURY

A 50-year-old female initiated varenicline (*Chantix*) 0.5 mg once daily for 3 days, 0.5 mg twice daily for 4 days, and then 1 mg twice daily for smoking cessation. After 3 weeks of varenicline therapy, the patient developed nausea and fatigue. She stopped taking varenicline but continued to develop pruritus, dark urine, and jaundice. The patient sought medical care one week after stopping varenicline. Blood tests were drawn and revealed a total bilirubin 5.61 mg/dL (normal range, 0.3-1 mg/dL), alanine aminotransferase (AST) 207 U/L (normal range, <35 U/L), alkaline phosphatase 249 U/L (normal range, 44-147 U/L), and gamma-glutamyl transpeptidase 976 U/L (normal range, 7-51 U/L). The patient's physical exam was unremarkable except for jaundice.

Hepatitis serologies against hepatitis A, B, C, and E were negative as were immunoglobulin M antibodies to Epstein-Barr, cytomegalovirus, antinuclear and smooth muscle antibodies, and no peripheral eosinophilia. The patient's symptoms gradually disappeared over the next 1 to 2 weeks and returned to normal. The patient was not hospitalized and did not receive any specific therapy. The patient had no history of chronic liver disease, alcohol, or illegal substance abuse. The patient's medication history revealed atenolol 50 mg daily, amlodipine 5 mg daily, and bendroflumethiazide daily. The patient reported she did not take over-the-counter or herbal medications and had no drug allergies. During her jaundice and elevated liver function tests, she did not stop taking her chronic medications.

The authors state that the mechanism of how varenicline might cause liver injury is not known. Varenicline undergoes minimal hepatic metabolism and is excreted largely unchanged in the urine. They note that this fact does not mean that the drug cannot cause hepatotoxicity. They state that varenicline appeared to cause a mild acute hepatitis with jaundice after a latency of 2 to 3 weeks. Thus, varenicline should be listed as a potential, but rare, cause of acute, clinically apparent drug-induced liver injury.

Mogensen H, Bjornsson ES, Varenicline-induced acute liver injury with jaundice. *Hepatology.* 2015;61(6):2110-2111. ■