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ISMP Adverse Drug Reactions

Rivaroxaban-Induced DRESS

Serotonin Syndrome Induced by Paliperidone

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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.

RIVAROXABAN-INDUCED DRESS

A 65-year-old male underwent hip replacement surgery and received deep vein thrombosis (DVT) prophylaxis with rivaroxaban (*Xarelto*) 10 mg daily beginning on the day of his discharge from the hospital. The patient was discharged 1 week after his surgery. Ten days after discharge, the patient began to experience chills and fever that persisted and peaked at 104.9°F (40.5°C). By day 15 after discharge, the patient reported generalized skin erythema with pruritus. The patient was admitted to the hospital on day 18 after discharge for evaluation. A chest x-ray revealed discreet bilateral pulmonary infiltrates, however blood cultures were negative. The patient received an antihistamine and was discharged. He continued to receive rivaroxaban until day 20 after his initial surgical discharge.

Forty-eight hours after the discontinuation of rivaroxaban, the patient was admitted to the intensive care unit (ICU) with hypotension and bradycardia. Laboratory tests revealed the patient had anemia, elevated white blood cell count with increased neutrophils and eosinophils, acute renal failure with a GFR of 45 mL/min, and mild cholestasis. The patient was also hypoxic with an elevated alanine aminotransferase, gamma-glutamyl transpeptidase, elevated direct bilirubin, and a prolonged prothrombin time. The following day, the patient exhibited peripheral eosinophilia that peaked at 1,065 cells/mcL (>500 mcL is considered eosinophilia). CT scans discovered bilateral pulmonary infiltrates, bilateral perirenal infiltrates, and

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multiple mediastinal lymphadenopathies. He continued with a low-grade fever of 100.8°F (38.2°C) and a rash over his lower limbs for several days.

An exhaustive battery of tests was conducted to discover the cause of the patient's condition, including viral, bacterial, and immunologic causes; however, all tests were negative. Based on the severity of the patient's clinical presentation and associated unexplained prolonged high fever, rash, eosinophilia, pulmonary infiltrates, acute renal failure, multiple lymphadenopathies, and abnormal liver function, the authors arrived at a diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS). Scoring of the patient's condition revealed a 6 on the Kardaun scale (Kardaun, 2007), indicating that DRESS was present with a high degree of certainty. The authors then applied the RegiSCAR criteria (Kardaun, 2013), which requires the patient to have 3 out of 4 of the following symptoms: fever, lymphadenopathy, internal organ involvement, and hematological abnormalities. It was confirmed that the patient had all 4 symptoms and was likely to have DRESS.

The patient continued to receive his other chronic medication throughout his bout with DRESS. His chronic medications were atorvastatin and saw palmetto. The patient's DRESS was treated with oral corticosteroids with subsequent tapering over the next 3 months. The patient did not have a recurrence of his DRESS symptoms upon completion of his steroid regimen. The authors state, "Identification and prompt withdrawal of the offending drug is the mainstay of treatment for patients with DRESS. Although optimum treatment remains controversial, patients are usually treated with corticosteroids."

Radu C, Baring C, de Blay F. Rivaroxaban-induced drug reaction with eosinophilia and systemic symptoms. *J Investig Allergol Clin Immunol*. 2016;26(2):111-143.

Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist? *Br J Dermatol*. 2007;156:609-611.

Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): An original multisystem adverse drug reaction. Results from a prospective RegiSCAR study. *Br J Dermatol*. 2013;169:1071-1080.

SEROTONIN SYNDROME INDUCED BY PALIPERIDONE

A 17-year-old female was admitted to the hospital for acute psychosis with auditory hallucinations and disorganized behavior. She was evaluated for alternate causes of her change in mental status, and none were found. After 1 week in the hospital, the patient was initiated on paliperidone extended release (*Invega*) 9 mg daily and was discharged the next day. The patient was readmitted 10 days later with persistent psychosis due to poor medication adherence. On admission the patient was reinitiated on paliperidone-ER 9 mg daily and estazolam 2 mg at bedtime was started.

On the second day of the patent's admission, she had tachycardia of 131 bpm. On the fifth day of her admission, the paliperidone dosage was increased to 12 mg daily due to a lack of improvement in her symptoms; lithium 900 mg daily was added to her regimen for augmentation therapy. The patient's heart rate then increased to 140 bpm and her temperature rose to 99.9°F (37.7°C). The patient also exhibited additional symptoms of severe drooling, restlessness, sweating, whole-body tremor, rhythmic foot contractions, bilateral pupil dilation, increased bowel sounds with watery diarrhea, lower limb joint rigidity, and muscle hypertonicity. After the development of these symptoms, the patient became extremely agitated and confused. She was treated with anticholinergic medications and lorazepam, but her symptoms did not subside.

Serotonin syndrome was suspected, and the patient's lithium and paliperidone were discontinued. Quetiapine 200 mg daily was initiated with supportive care for the serotonin syndrome. Over the next 3 days, the patient's heart rate decreased to 100 bpm and her mental status, autonomic hyperactivity, and neuromuscular abnormalities improved. After the initiation of quetiapine, the patient's psychotic symptoms recurred. Paliperidone-ER 9 mg was reinitiated and quetiapine was stopped, however the same adverse effects returned with the reinitiation of paliperidone. The patient then became agitated with a mild temperature of 99°F (37.3°C) and tachycardic with a heart rate of 146 bpm. Following the recurrence of symptoms, paliperidone was discontinued and quetiapine 200 mg daily was restarted. The patient regained clear consciousness and had complete improvement of her symptoms within 3 days. The patient was stabilized and discharged; she remained stable without signs of psychosis for 20 days after discharge while receiving quetiapine 200 mg daily.

The authors emphasize that since serotonin syndrome is associated with serotonergic agents, it is important to review the pharmacology of paliperidone. Paliperidone is an atypical antipsychotic agent with 5-HT_{2A}, 5-HT_7, and D_2 receptor antagonism. 5-HT_7 receptor inhibition produces the same behavioral effects as antidepressants that increase

serotonergic transmission. The authors theorize, "Like the 5-HT_{1a} receptors, which they share functional and morphological characteristics, the 5-HT_7 receptors may have opposite effects on serotonergic transmission. Perhaps this is the possible cause of paliperidone-induced serotonin syndrome."

Yang CH, Juang KD, Chou PH, et al. A case report of probable paliperidone ER-induced serotonin syndrome in a 17-year-old Taiwanese female with new onset psychosis. *Medicine*. 2016;95(9):1-2.

PIPERACILLIN-TAZOBACTAM–INDUCED NEPHRITIS AND HEPATITIS

A 30-year-old diabetic female had a recent hospitalization for osteomyelitis of her right foot with a partial amputation of 2 toes. She was discharged to complete a 6-week course of intravenous vancomycin and metronidazole. She came to the emergency department with significant symptoms of persistent nausea and vomiting, a temperature of 102°F, and hypoxia with variable pulse oximetry readings between 50% and 60%. Her initial arterial blood gas revealed a pH 7.38 (normal range, 7.33-7.45), pCO2 33 mm Hg (normal range, 33-45 mm Hg), pO2 54 mm Hg (normal range, 75-105 mm Hg), and HCO3 20 mEq/L (normal range, 22-26 mEq/L) while receiving 4 liters of oxygen. A chest x-ray revealed possible interstitial infiltrates but no obvious pneumonia. Empiric piperacillin-tazobactam was initiated for hospital-acquired pneumonia due to the patient's recent hospitalization, and therapeutic enoxaparin was initiated for possible pulmonary embolism.

A CT scan indicated that the patient had bilateral scattered opacities consistent with pneumonia as well as bilateral pleural effusions. The patient also had a nasal swab that was positive for influenza A. The patient was continued on piperacillin-tazobactam for hospital-acquired pneumonia, and doxycycline and oseltamivir were added to her regimen. The patient's home intravenous vancomycin was continued. The patient's clinical course included intubation with mechanical ventilation for 4 days due to septic shock. The patient improved by the fifth hospital day and was extubated and transferred to the floor. After 2 days on the floor, the patient developed multiple organ dysfunction including worsening renal failure, liver failure, and leukocytosis. By day 7 of her hospital stay, the patient's piperacillin-tazobactam was discontinued. On hospital day 8, the patient was moved back to the ICU due to multiorgan failure that lasted 2 days.

The patient's creatinine peaked at 5.4 mg/dL (normal range, female 0.6-1.1 mg/dL) and required hemodialysis. Her WBC increased to 39.04 $x10^3$ cells/μL (normal range, 4-11 $x10^3$ cells/μL), and she developed daily fevers up to 104°F with a rash. Her liver function tests revealed an increased bilirubin of 2.3 mg/dL (normal range, 0.3-1.2 mg/dL), AST 368 IU/L (normal range, 10-30 IU/L), ALT 180 IU/L (normal range, 10-40 IU/L), GGT 128 IU/L (normal range, 2-30 IU/L), lactate dehydrogenase 1356 IU/L (normal range, 100-300 IU/L), and an international normalized ratio of 2.5 (normal range, 1-1.3). All blood cultures were negative, but the patient had an elevated absolute eosinophil count with leukocytosis. A renal biopsy demonstrated acute interstitial nephritis.

The patient developed a rash and eosinophilia that was suggestive of an allergic reaction, and she was diagnosed with a piperacillin-tazobactam–induced leukemoid reaction. Additionally, based on the time course, piperacillin-tazobactam was thought to be the cause of her acute interstitial nephritis. On hospital day 17, the patient was started on intravenous methylprednisone 125 mg daily for 3 days followed by oral prednisone 60 mg daily. The patient's fever, rash and leukocytosis improved. The patient began to produce urine and was removed from dialysis.

Kraleti and colleagues state, "The timeline of events in our patient including acute renal failure, hepatic failure along with fever, eosinophilia and rash were suggestive of a drug-induced reaction. Out of all her medications piperacillin-tazobactam was thought to be the most likely contributor and her rapid improvement after discontinuation of the drug proved the causal relationship." They also warn, "Although piperacillin-tazobactam is considered to be relatively safe and serious adverse effects are rare, these reactions should always be kept in mind in a patient who presents with organ failure and hypersensitivity reaction."

Kraleti S, Khatri N, Jarrett D. Piperacillin-tazobactam induced interstitial nephritis, hepatitis and serum sickness-like illness. *J Ark Med Soc*. 2016;112:278-280.

BRENTUXIMAB-INDUCED HAND-FOOT SYNDROME

A 51-year-old male had received successful treatment for stage IV B Hodgkin's lymphoma and then relapsed 3 years later and received a bone marrow transplant. The patient relapsed 6 months after bone marrow transplantation and was treated with brentuximab (*Adcetris*). After initiation of brentuximab, the patient experienced severe pain, itching, and a

maculopapular rash on his hands and feet. This reaction started 2 days after a second cycle of brentuximab monotherapy. The patient was diagnosed with severe hand and foot syndrome. He had a maculopapular rash with cracking of the skin with fissure formation below the ring and middle finger. The sole of the patient's feet had a maculopapular rash with cracking of the skin with a fissure formation below the big toe. The patient's lesions improved after the discontinuation of brentuximab and the initiation of systemic and local corticosteroids with an antihistamine and strong analgesics.

Hand and foot syndrome is also known as acral erythema, palmar-plantar erythema, or Bergdorf's reaction. This syndrome is characterized by well-demarcated painful erythema, edema, numbness, and desquamation over the palms and soles that may develop following treatment with a variety of chemotherapeutic agents including bleomycin, cisplatin, cyclophosphamide, hydroxyurea, idarubicin, methotrexate, sorafenib, sunitinib, and other agents. Tenderness involving the skin overlying the fingers and toes, followed by bulla formation and subsequent desquamation, often occurs. This adverse effect results when a small amount of the responsible drug leaks out of the blood vessels, damaging tissues. The reaction predominates over the palms and soles, where eccrine glands are more numerous, and also is a result of the increased friction and heat that extremities are exposed to through daily activities.

There are many ways to manage and prevent worsening of hand and foot syndrome symptoms. Prevention methods include using cold compresses, avoiding hot baths, applying emollient creams, and avoiding walking barefoot. Treatment of hand and foot syndrome includes the use of systemic and topical corticosteroids, pain medications, and anesthetics. Finally, a reduction in dosage or a temporary stoppage of the suspected chemotherapeutic agents is warranted.

Rehman JU, Kelta M, AlBeirouti B, et al. Brentuximab-induced hand-foot syndrome in a Hodgkin lymphoma patient. *Ann Hematol*. 2016;95:509-510.

VALPROIC ACID–INDUCED HYPERKALEMIA

A 76-year-old female with no psychiatric history was admitted to a psychiatric unit for displaying symptoms of mania that included an elevated mood, decreased need for sleep, talkativeness, and grandiose thoughts. During her first week of hospitalization, the patient received valproic acid 500 mg daily for treatment of her mania and did not receive any concomitant mediations. All of her meals were standard meals as provided from the hospital. Her admission labs did not exhibit abnormalities; however on the patient's fifth day of valproic acid therapy, her serum potassium level was 6 mEq/L (normal range, 3.5-5 mEq/L) and she had a mild hyponatremia of 133 mEq/L (normal range, 135-145 mEq/L). The patient had an EKG that exhibited tented T-waves indicative of hyperkalemia.

The patient was evaluated for possible causes of her hyperkalemia, and the following tests were conducted: glomerular filtration rate, urine microalbinuria, and a renal ultrasound. Results of all these tests were normal. After 1 week of valproic acid therapy, the drug was discontinued. The patient's potassium and sodium levels returned to normal at 3.8 mEq/L and 136 mEq/L, respectively. A follow-up EKG was normal with the disappearance of tented T-waves. The patient was discharged 3 weeks later after being stabilized on olanzapine 5 mg daily for her mania.

Kuo and colleagues state that the patient's hyperkalemia emerged only after valproic acid was initiated and her hyperkalemia resolved after discontinuation of valproic acid. It is notable that the patient did not receive any other medications before hyperkalemia occurred, and she also took only the meals offered by the hospital. This case is important because the observations on the chronological association between hyperkalemia and valproic acid were not confounded by concomitant medications or an unhealthy diet.

The mechanism by which valproic acid may cause hyperkalemia is unclear. Two possible mechanisms include the impairment of potassium excretion caused by decreased mineralocorticoid function or abnormal potassium reabsorption in the renal tubules. The authors conclude, "The observations from this case highly suggest that, in addition to the hyponatremia that has been reported previously, clinicians should also be very careful to monitor serum potassium levels in older patients taking valproic acid."

Kuo YC, Lin YC. Emerging hyperkalemia following valproic acid use in an elderly patient with late-onset mania. *J Clin Psychopharmacol*. 2016;36(4):394. ■