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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) 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.

Allergic Angina Caused by Fluconazole

A 42-year-old female initiated therapy with fluconazole (Diflucan) for a superinfection she contracted after an eczematous flare. Other than a history of eczema, the patient was in good health with no concomitant diseases or cardiac history. The patient administered her first dose of fluconazole, and within 30 minutes, she experienced palpitations and became lightheaded. The patient was taken to her local emergency room, and she was diaphoretic, short of breath, tachycardiac with a pulse rate of 118 beats per minute (bpm), and hypotensive with systolic blood pressure of 90 mm Hg. She began to experience nonpleuritic, nonradiating, retrosternal chest pressure, and an electrocardiogram revealed an ST segment elevation suggestive of an acute inferior wall myocardial infarction. The patient was emergently sent to the catheterization lab and had an urgent coronary angiography. Her angiography did not reveal obstructive disease, and her ejection fraction was >60%. Based on these findings, she did not require percutaneous cardiac intervention.

The patient was admitted to the Coronary Care Unit for observation, and at this time, the results of her initial lab tests were available. Labs tests indicated an elevated troponin and a mild peripheral eosinophilia. The patient's hypotension responded well to normal saline administration, and the patient was stable and discharged to home the next day. Based on this patient's presentation, she was diagnosed with fluconazole-induced Kounis syndrome type 1.

Kounis syndrome is also synonymous with hypersensitivity coronary syndrome or allergic angina. This condition is

associated with mast cell activation and has 3 distinct types. Type I Kounis syndrome occurs in patients with no obvious cardiac risk factors and nonobstructive coronary anatomy. In these patients, an acute allergic insult is thought to trigger a vasospasm leading to an acute coronary event. Type 2 Kounis syndrome is seen in patients with preexisting atherosclerotic coronary disease in which an acute allergic insult triggers plaque destabilization and rupture which in turn leads to a myocardial infarction. Patients with type 3 Kounis syndrome experience an allergic insult and have an in-stent thrombosis. These patients have a history of atopy and baseline elevations in IgE.

Mahal¹ states that drugs that have been associated with causing Kounis syndrome are common antibiotics, corticosteroids, nonsteroidal antiinflammatory drugs, antidepressants, analgesics, and contrast media. The proposed mechanism of Kounis syndrome is that an allergen triggers IgE and mast cell activation and degranulation which releases histamine. The effects of histamine on cardiac function are mediated through H1 and H2 receptors situated on cardiac chambers and coronary arteries. This histamine release causes a coronary

Hospital Pharmacy
2017, Vol. 52(7) 455–458
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sagepub.com/journalsPermissions.nav
DOI: 10.1177/0018578717717621
journals.sagepub.com/home/hpx

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vasospasm which leads to angina or a myocardial infarction. Histamine has also been shown to induce platelet and tissue factor into a hypercoagulable state which also contributes to coronary thrombotic events.

In closing, the author warns that "Cases of Kounis syndrome are more often encountered in clinical practice than expected." The coincidental occurrence of chest pain and allergic reaction accompanied by clinical and laboratory findings of angina should alert the clinician to potential Kounis syndrome.

Rhabdomyolysis Caused by Risperidone

A 57-year-old male with a longtime history of schizophrenia was admitted to the hospital for behavioral changes and agitation because he had missed his medication for the past 2 days. The patient's current medications included aripiprazole 30 mg daily, asenapine 20 mg daily, clonazepam 2 mg daily, and risperidone 2 mg daily which was initiated 2 weeks before the patient's hospital admission. In prior years, the patient had received haloperidol, olanzapine, intramuscular fluphenazine, and intramuscular flupentixol. These medications had all been utilized in the past and had been discontinued due to lack of efficacy in managing the patient's schizophrenia. The patient had tolerated each of these prior antipsychotics without issue except for Ogilvie syndrome which the patient experienced with the use of olanzapine. Ogilvie syndrome is a rare, acquired disorder characterized by abnormalities affecting peristalsis within the colon. In Ogilvie syndrome, the colon is often significantly dilated and the patient experiences symptoms similar to other forms of intestinal pseudo-obstruction and can include nausea, vomiting, abdominal bloating or swelling, and constipation.

On admission, the patient's vital signs were stable, and his initial labs including chem-7 and complete blood count were all within normal limits. The patient's current medications were restarted, and he received risperidone 25 mg as an intramuscular depot injection. On the patient's third hospital day, his oral risperidone was increased to 2 mg twice daily. On hospital day 5, the patient was initiated on trihexyphenidyl 2 mg daily because he began to experience extrapyramidal adverse effects from his antipsychotic regimen. The patient then became lethargic and weak and refused to ambulate but he remained afebrile. The patient then experienced tachycardia of 112 bpm with a stable blood pressure of 124/90 mm Hg. On examination, the patient reported mild muscle tenderness, but no muscle rigidity, diminished power, or skin changes. While the patient's laboratory values were normal on admission, his labs on hospital day 5 revealed a sudden worsening of renal function with blood urea nitrogen of 73.65 mg/dL (normal range, 8-23 mg/dL) and serum creatinine of 2.9 mg/dL (normal range, male: 0.9-1.3 mg/dL). Additional abnormal labs included potassium of 5.01 mmol/L (normal range, 3.5-5 mmol/L), alanine transaminase of 43 U/L (normal range, 10-40 U/L), and aspartate transaminase

of 151 U/L (normal range 10-30 U/L). His serum creatine kinase was elevated at 13 735 U/L (normal range, male: ≤ 195 U/L) and peaked at 73 780 U/L the next day. The patient's urine myoglobin was evaluated but was found to be within normal limits.

The patient was diagnosed with acute kidney injury secondary to rhabdomyolysis due to risperidone. The patient was hydrated and all antipsychotic medications were stopped immediately. The patient required intermittent hemodialysis for his renal dysfunction and metabolic abnormalities. The patient's renal function improved and returned to normal function. The patient experienced rhabdomyolysis due to an antipsychotic medication; however, usually this is seen as part of neuroleptic malignant syndrome which the patient did not experience. The patient did not experience an elevated temperature or change in mental status.

In evaluating the patient's rhabdomyolysis, the authors note the patient did not have any other possible causes for his rhabdomyolysis besides the initiation of risperidone. "The fact that he was on two antipsychotics before administration of risperidone, including aripiprazole, which has a long half-life, may have increased the risk for an adverse effect." The authors recommend,

We would like to highlight the importance of being vigilant to the possible development of rhabdomyolysis in patients who are just started on risperidone or has a recent dose increase. This is particularly important because it can lead to severe acute kidney injury with possible life-threatening complications.²

High Incidence of Hyponatremia With High-Dose Trimethoprim-Sulfamethoxazole

Tsapepas et al³ conducted a retrospective cohort study of hospitalized adult patients who received high-dose trimethoprim-sulfamethoxazole (TMP-SMX) over a 2-year period. Patients included in the study had to receive >8 mg/kg/day of trimethoprim for 3 or more consecutive days. Patients who had preexisting hyponatremia at the start of TMP-SMX therapy were excluded as were patients who had decreased renal function or received therapy which could cause hyponatremia. The researchers defined hyponatremia as a serum sodium of less than 136 mEq/L for at least to consecutive calendar days. They categorized patients into 3 groups: normonatremic ($\text{Na} \geq 136$ mEq/L), mild hyponatremia (Na 130-135 mEq/L), and moderate-to-severe hyponatremia ($\text{Na} < 130$ mEq/L).

The authors identified 82 instances of high-dose TMP-SMX use in 76 unique patients. They found that 72.3% of patients treated with high-dose TMP-SMX had hyponatremia. Of the 72.3% of patients with hyponatremia, 32.4% had a nadir sodium level of <130 mEq/L and 40.8% had a nadir sodium level of 130 to 135 mEq/L. Lower sodium levels were associated with a longer duration of therapy and a higher

cumulative dose of TMP-SMX. Patients who were African American were also identified as at an increased risk for hyponatremia. The authors note, “since they excluded patients who had comorbid conditions and those on medications that could lower serum sodium concentrations, therefore the incidence of hyponatremia among hospitalized patients secondary to high-dose TMP-SMX is likely even higher.” Additional findings include an elevated urine osmolality and a relatively low fraction excreted of sodium which suggests volume depletion in patients receiving high-dose TMP-SMX. The authors state that “The findings of a high incidence of hyponatremia upon reexposure suggest the possibility of hyponatremia from TMP-SMX-induced renal salt wasting.”

Tsapepas et al point out that trimethoprim is structurally related to the potassium-sparing diuretic amiloride and has been known to interfere with reabsorption of sodium in the kidney. Trimethoprim blocks the reabsorption of sodium at the epithelial sodium channel in the distal nephron and leads to hyponatremia, hyperkalemia, and metabolic acidosis. While hyperkalemia related to trimethoprim is widely recognized, hyponatremia due to trimethoprim use is often overlooked.

In closing, the authors state,

This study underscores the need for close monitoring of serum sodium levels among patients receiving high doses of TMP-SMX, particularly among African American patients. Strategies such as liberalization of dietary sodium and intravenous saline infusions while on TMP-SMX therapy may be necessary to attenuate the risk of hyponatremia.

Lithium Carbonate-Induced Hypersalivation

A 50-year-old female was admitted to the hospital for symptoms of a manic episode. She had a 4-year history of bipolar disorder and had been receiving outpatient treatment. Prior to her admission, she was receiving escitalopram 10 mg daily, quetiapine 300 mg daily, levothyroxine 100 µg daily, and valsartan 160 mg daily. The patient had stopped all of her medications 2 months before her hospitalization. After admission, the patient received lithium carbonate controlled release 400 mg daily for 3 days and increased to 800 mg daily. Olanzapine and diazepam were also added to her medication regimen. Her levothyroxine and valsartan were also continued, and the patient had been taking these 2 medications for the past 5 years without adverse effect.

The patient described having hypersalivation on the third day of inpatient lithium carbonate therapy along with a constant salty taste and polyuria. The patient's symptoms increased when the lithium carbonate dosage was increased to 800 mg daily. A trough lithium serum level was drawn 12 hours after a dose of lithium carbonate extended release and the level was 0.9 mEq/L (normal range, 0.6-1.2 mEq/L). One week later, a subsequent lithium trough level was 0.7 mEq/L, and her physical and laboratory findings were normal. The patient's

hypersalivation continued, and she described excessive saliva on her lower lip which she constantly had to hold a tissue to wipe the excess saliva from her lip. She did not describe nocturnal hypersalivation. The patient did not manifest any signs or symptoms of lithium toxicity during her admission.

The patient was discharged on a regimen of lithium carbonate extended release 800 mg daily, olanzapine 5 mg daily, levothyroxine 100 µg daily, and valsartan 160 mg daily. After discharge, the patient was scheduled for a follow-up appointment in 10 days. A few days before her scheduled appointment, the patient acutely had nausea and vomiting and went to her family physician. Her physician asked her to stop all of her medications and have her laboratory parameters evaluated at her scheduled 10-day follow-up appointment. Her lithium serum level was 0.4 mEq/L at her scheduled appointment. The patient had not taken any of her psychotropic medications since her visit to her family physician a few days prior to her scheduled appointment. During the time when she was not taking her lithium, the patient noticed that her hypersalivation was progressively decreasing. Upon further questioning, the patient reported that she had hypersalivation 1 year ago when she was receiving lithium 600 mg daily which resolved after discontinuation. She reported she had not had any other episodes of hypersalivation.

Khalil et al⁴ speculate, “low aldosterone/angiotensin II due to angiotensin receptor blocker intake along with lithium carbonate could have induced lithium accumulation in the intracellular compartment and in the saliva of our patient, manifesting clinically with hypersalivation along with salty taste.” The authors also note that case reports have been published of patients manifesting with signs and symptoms of lithium toxicity without a high lithium serum level. They suggest that intra-red blood cell concentration of lithium may better reflect lithium intoxication when lithium serum levels are in the therapeutic range. In closing, Khalil et al warn that

lithium toxicity should be considered even with lithium serum levels within the normal range. Potential interacting drugs that are being concomitantly taken such as ARBs or ACE inhibitors should warrant particular attention because of their ability to increase lithium serum levels.

Persistent Hemorrhage After Idarucizumab Administration

Alhasham et al⁵ report a 65-year-old male who was seen in an emergency department with complaints of generalized weakness and shortness of breath. The patient reported a 3-day history of black stools, and he had recently initiated treatment with dabigatran (Pradaxa) due to atrial fibrillation. The patient had no prior history of gastrointestinal hemorrhage. His initial vital signs included a blood pressure of 74/52 mm Hg, an irregular heart rate of 122 bpm, and a respiratory rate of 22 bpm. A nasogastric tube was placed and yielded an immediate return of 300 mL of bright red blood which failed to clear

after the administration of 700 mL of 0.9% normal saline. The patient was given packed red blood cells (PRBCs) and a pantoprazole infusion was initiated. The patient's thrombin time was 120 seconds (normal range, 13-16 seconds) which suggested significant dabigatran activity. Based on the fact that the patient remained critically ill with his extended thrombin time, idarucizumab (Praxbind) 5 grams was administered to reverse dabigatran's anticoagulant effect.

One hour after administration of idarucizumab, the patient's thrombin time had decreased to 20.4 seconds; however, the patient remained critically ill. Various interventions were performed to assess his clinical situation which included esophagogastroduodenoscopy which revealed a hemorrhaging vessel in the duodenum. The patient was given factor VIII inhibitor bypass activity along with additional units of PRBCs. The patient then underwent emergency angiography, and embolization of the bleeding artery was performed which stopped the bleeding. Overall, the patient had received a total of 8 units of PRBCs over a period of 6 hours.

Alhasham et al point out that idarucizumab reverses dabigatran in a dose-dependent fashion. While their patient's thrombin time improved significantly in less than 1 hour after idarucizumab administration, the patient's activated partial thromboplastin time (aPTT), thromboelastography

(TEG), and fibrinogen activity did not normalize. The patient did not have any other possible cause for his coagulopathy other than his use of dabigatran. In closing, Alhasham et al make an excellent point with regard to the fact that in clinical trials with idarucizumab the reversal of dabigatran occurred within minutes; however, the median time to achieve homeostasis was 11.4 hours. The authors conclude that this may not lead to timely hemostasis in a patient with a life-threatening hemorrhage.

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