ISMP Adverse Drug Reactions

Agranulocytosis Induced by Proton Pump Inhibitors

Bevacizumab-Induced Oral Mucositis in Background of Cutaneous Plaque-Type Psoriasis

Amiodarone-Induced T-U Fusion

Vancomycin-Induced Thrombocytopenia Without Isolation of a Drug-Dependent Antibody

Capecitabine-Induced Chest Pain Relieved by Diltiazem

Fatal Clindamycin-Induced Drug Rash With Eosinophilia and Systemic Symptoms (DRESS) 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.

AGRANULOCYTOSIS INDUCED BY PROTON PUMP INHIBITORS

A 20-year-old man with cystic fibrosis was hospitalized for septic shock. Upon admission, lab tests revealed a white blood cell (WBC) count of $0.7 \times 10^9/L$ and a neutrophil count of $<0.1 \times 10^9/L$. The patient then received multiple antibiotics, meropenem, sulfamethoxazole/trimethoprim, and teicoplanin, which

he had received regularly in the past without hematologic toxicity. For the last 6 years, the patient had received omeprazole for gastroesophageal reflux disease (GERD). Omeprazole was discontinued on admission and ranitidine was initiated. No granulocyte colony-stimulating factors were administered to the patient.

After 9 days, the patient experienced persistent gastroesophageal reflux symptoms; esomeprazole

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40 mg daily was initiated and ranitidine was discontinued. At this time, the neutrophil count had recovered to $13.4 \times 10^9/L$. The patient was discharged and antibiotic therapy was continued for an additional week. Ten days after discharge, the patient was readmitted with a recurrence of fever and agranulocytosis (WBC count $1 \times 10^9/L$; neutrophil count $<0.1 \times 10^9/L$). Esomeprazole was immediately discontinued and antibiotic therapy was initiated. In 3 days, WBC and neutrophil count had improved ($2.3 \times 10^9/L$ and $0.5 \times 10^9/L$, respectively). The patient was not exposed to a proton pump inhibitor (PPI) again.

The authors analyzed the relationship of this patient's PPI exposure and agranulocytosis by utilizing international recommendations. The authors presented the following rationale: "First, the onset of each episode occurred during PPI treatment. Second, we observed a recurrence of agranulocytosis upon exposure to esomeprazole." To date this is the first case report of agranulocytosis due to esomeprazole. Esomeprazole is the S-isomer of omeprazole, and the few published cases of omeprazole-induced agranulocytosis occurred between 3 and 17 days of therapy. However, agranulocytosis may occur after prolonged exposure, resulting in decreased granulocyte production by hypoplastic bone marrow.

The authors tested the patient for a mutation in CYP2C19*17. It was discovered that the patient exhibited a homozygous mutation of CYP2C19*17, which is a novel gene variant associated with faster metabolism of CYP2C19 substrates. The impact of this polymorphism is that the enhanced enzyme activity may have induced an increase of toxic PPI metabolites leading to agranulocytosis. The authors concluded, "Our case suggests that a genetic polymorphism in the PPI metabolism enzymatic system CYP2C19 could play a major role in PPI-induced agranulocytosis."

Dury S, Nardi J, Gozalo C, Lebagry F, et al. Agranulocytosis induced by proton pump inhibitors. *J Clin Gastroenterol*. 2012;46(10):859.

BEVACIZUMAB-INDUCED ORAL MUCOSITIS IN BACKGROUND OF CUTANEOUS PLAQUE-TYPE PSORIASIS

A 29-year-old woman with a long history of cutaneous plaque-type psoriasis and a malignant glioblastoma received treatment with bevacizumab for 2.5 years. The patient initially received multiple cycles of temozolomide, and her tumor remained the same size and symptoms were unchanged. At this time, bevacizumab 10 mg/kg was added to her therapy.

Upon initiation of bevacizumab, the patient reported grade 2 oral mucositis toxicity within 36 hours of treatment. The patient experienced symptoms starting in the dorsum of the tongue with erythematous patches and fissuring. The height of the reaction was seen within 3 to 5 days following treatment, with constant pain and symptoms dissipating in 2 weeks following treatment.

Treatment with fluconazole 100 mg daily was initiated for presumed oral candidiasis but was switched to nystatin liquid after the patient developed diarrhea while receiving fluconazole. The patient experienced limited improvement, and the likelihood of a fungal infection was considered low. Valacyclovir was then initiated to combat a possible viral etiology, however the oral lesions persisted.

Temozolomide therapy was discontinued after 1.5 years, and bevacizumab was continued as monotherapy. The mucositis remained unchanged with bevacizumab monotherapy. To date, oral mucositis has not been reported in the literature with bevacizumab. The authors report that the Naranjo scale revealed a probable association between bevacizumab and the mucositis observed in this case. The only other medications the patient had received were lisinopril and ondansetron, which were only administered during temozolomide therapy. The authors noted that "the patient's symptoms have been reproducible for 2.5 years while receiving bevacizumab monotherapy much of the time." The patient's lesions were found to be consistent with oral psoriasis. The reasons the psoriatic exacerbations have been confined to the oral mucosa are unknown.

Popa AM, Valla K, Radhakrishnan L, et al. Bevacizumab-induced oral mucositis in background of cutaneous plaque-type psoriasis. *Ann Pharmacother*. 2012;46(11):e32.

AMIODARONE-INDUCED T-U FUSION

An 80-year-old woman with a history of paroxysmal atrial fibrillation was admitted to the hospital with a chief complaint of light-headedness. The patient was initiated on amiodarone 2 months earlier for maintenance of normal sinus rhythm and was currently maintained on 200 mg daily. The patient had received appropriate amiodarone loading when therapy was initiated. An electrocardiogram was performed upon admission, and the phenomenon of amiodarone-induced T-U fusion was documented. T-U fusion is the fusion between the T wave and U wave and is evident as notched T waves. The patient also experienced a prolongation of the QT interval, which is a marker for increased risk of serious ventricular arrhythmias and torsade de pointes.

It was determined that the patient's light-headedness was due to volume depletion, which was treated and resolved. Other causes of T-U fusion and QT prolongation were ruled out, for example, electrolyte abnormalities and the presence of QT prolonging medications other than amiodarone and amiodarone-interacting medications. The patient was stabilized and discharged with a dosage reduction of amiodarone to 100 mg daily. Studies have shown that there is a significant correlation between the plasma and myocardial concentrations of amiodarone and the QTc interval. There is also a strong correlation between the dosage of amiodarone and the plasma and myocardial concentrations of the drug.

The authors caution that amiodarone-induced T-U fusion and QT prolongation should be warning signs for proarrhythmic events, especially the development of torsades de pointes, and a marker for increased plasma amiodarone concentrations. They also state that it should be mandatory to review patients for possible amiodarone drug interactions that might synergize and cause cardiac conduction abnormalities. Awareness of the phenomenon of T-U fusion and measurement of the QTc interval are critical to avoid potentially fatal outcomes in patients receiving amiodarone.

Omar HR. Amiodarone-induced T-U fusion. *Am J Emerg Med*. 2012;30(9):2081.e1-.e2.

VANCOMYCIN-INDUCED THROMBOCYTOPENIA WITHOUT ISOLATION OF A DRUG-DEPENDENT ANTIBODY

A 41-year-old male was admitted to the hospital for replacement of a dislodged gastrojejunal tube. The patient had been transferred from an extended-care facility prior to admission. He had a history of developmental delays, generalized tonic-clonic seizures, and esophageal dysmotility. On hospital day 9, the patient spiked a 103°F fever with productive sputum; vancomycin 500 mg IV every 12 hours was initiated with piperacillin/tazobactam 4.5 g IV every 8 hours. The patient had normal renal function and a platelet count at the initiation of therapy of $449 \times 10^3/\text{mm}^3$ (reference range, $150\text{--}350 \times 10^3/\text{mm}^3$).

After 24 hours of vancomycin and piperacillin/tazobactam therapy, the patient's platelet count declined to $138 \times 10^3/\text{mm}^3$. Piperacillin/tazobactam was discontinued and ceftazidime was administered for 1 day. On day 5, the platelet count continued to decline to $15 \times 10^3/\text{mm}^3$, and vancomycin was discontinued. The next day the platelet count increased to $27 \times 10^3/\text{mm}^3$, and the platelet count rebounded to

$229 \times 10^3/\text{mm}^3$ by day 6 after vancomycin discontinuation and remained normal until discharge on hospital day 29. The patient had not received any additional drugs known to cause thrombocytopenia.

While investigating the thrombocytopenia, many factors were ruled out. The patient had received a 7-day course of vancomycin 3 months before this admission and 2 doses on days 4 and 5 of the current admission. Even though the patient had not received heparin, a heparin-mediated platelet antibody assay was ordered and was negative. The patient did receive dalteparin later during his hospitalization, and it was tolerated without incidence and the platelet count did not decline. Disseminated intravascular coagulation was also ruled out as a possible cause for the thrombocytopenia. Drug-dependent antibody assays for ceftazidime, piperacillin/tazobactam, and vancomycin were performed and were negative.

Two months later, the patient was readmitted for gastrostomy tube placement. On day 3 of his hospital stay, he developed fever, leukocytosis, and a change in mental status. The patient was then empirically covered for possible nosocomial pneumonia with vancomycin and piperacillin/tazobactam at the same doses he had received during his prior admission. At the initiation of therapy, the patient's renal function was normal and his platelet count was to $131 \times 10^3/\text{mm}^3$. After 2 doses of vancomycin, the patient's platelet count declined to $81 \times 10^3/\text{mm}^3$. Vancomycin and piperacillin/tazobactam were discontinued and daptomycin was initiated. After vancomycin discontinuation, the platelet count rebounded from a nadir of $80 \times 10^3/\text{mm}^3$ to $243 \times 10^3/\text{mm}^3$ over 5 days. While assessing the platelet decline, the following lab tests were negative: serotonin release assay, heparin-induced thrombocytopenia antibody, and vancomycin-dependent platelet-reactive antibody. On discharge, the patient's platelet count was $315 \times 10^3/\text{mm}^3$.

The authors concluded that "the patient's vancomycin-induced immune thrombocytopenia may have occurred by an alternative mechanism that has yet to be elucidated." The authors suggest that "even in the absence of the positive antibody test and other physiologic processes that could explain the thrombocytopenia, vancomycin-induced immune thrombocytopenia should remain on the differential diagnosis as a cause for drug-induced thrombocytopenia."

Ruggero MA, Abdelghany O, Topal JE. Vancomycin-induced thrombocytopenia without isolation of a drug-dependent antibody. *Pharmacotherapy*. 2012;32(11):e321-e325.

CAPECITABINE-INDUCED CHEST PAIN RELIEVED BY DILTIAZEM

The authors report a case series of 5 patients with primary colorectal adenocarcinoma or anal squamous cell carcinoma who were started on a 2-weeks-on, 1-week-off capecitabine dosing regimen in addition to other chemotherapeutic agents and/or radiation. Within the first few doses, patients experienced chest pain and/or dyspnea at rest or with exertion. These patients did not have histories of clinically significant coronary artery disease. All 5 patients experienced immediate and sustained chest pain relief after discontinuing capecitabine and were able to successfully tolerate retreatment with capecitabine after initiating diltiazem. This intervention allowed these patients to continue their indicated chemotherapeutic regimen.

Capecitabine is a 5-fluorouracil prodrug that was not associated with cardiac side effects during clinical trials, but an increasing number of case reports and small case series have been published describing a spectrum of cardiac toxicities ranging from typical angina at rest or exertion to myocardial infarction and death. Several factors are important about this cohort: They were relatively young, with no histories of coronary artery disease and normal results on exercise stress imaging. All 5 patients experienced chest pain within a few days of initiation of capecitabine treatment, suggesting a cumulative-dose effect versus a peak-dose effect.

The authors present the Stanford algorithm for managing suspected capecitabine-induced coronary vasospasm. The algorithm outlines complete recommendations from baseline testing through the management of cardiac adverse effects as well as the initiation of diltiazem. The authors recommend “in patients without ongoing ischemia, in whom capecitabine is clinically indicated, initiate diltiazem, sublingual nitroglycerin as needed for acute events and continue capecitabine therapy with close follow-up.”

Ambrosy AP, Kunz PL, Fisher GA, et al. Capecitabine-induced chest pain relieved by diltiazem. *Am J Cardiol.* 2012;110(11):1623-1626.

FATAL CLINDAMYCIN-INDUCED DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) SYNDROME

A 63-year-old, obese, Caucasian female presented to the emergency department (ED) with a 4-day history of generalized, diffuse, erythematous, raised, and mildly pruritic rash; nausea and vomiting; and complaints of decreased urine output. The patient had begun clindamycin therapy 4 days earlier for a

methicillin-sensitive *Staphylococcus aureus* (MSSA) prosthetic hip infection, and she reported that a rash began on her face and spread to her trunk and extremities. On examination, it was noted that the rash covered approximately 90% of her body surface area. Laboratory testing revealed a WBC count of $30 \times 10^3/\text{mm}^3$ (reference range, $4.5\text{--}11 \times 10^3/\text{mm}^3$), blood urea nitrogen 31 mg/dL (10–20 mg/dL), serum creatinine 2 mg/dL (0.4–1.5 mg/dL), C-reactive protein 36.3 mg/L (0.08–3.1 mg/L), aspartate aminotransferase (AST) 55 U/L (8–42 U/L), alanine aminotransferase (ALT) 67 U/L (3–30 U/L), total bilirubin 4.3 mg/dL (0.3–1 mg/dL), and alkaline phosphatase 1010 U/L (44–147 U/L). Clindamycin was discontinued and a continuous intravenous nafcillin infusion was started for continued MSSA treatment.

Further laboratory tests revealed mildly elevated liver function tests, serum creatinine 3.5 mg/dL, and a complete blood count with differential identified peripheral eosinophilia as high as 24% (0%–4%), corresponding to an absolute eosinophil count of 5,232 cells/ mm^3 (<350 cells/ mm^3). By day 4, pancreatic enzymes were elevated with an amylase 118 U/L and lipase level of 50 U/L. DRESS represents a type of hypersensitivity syndrome characterized by severe cutaneous rash and accompanied by systemic toxicities. Toxicities can include lymphadenopathy and organ toxicities such as hepatic and renal failure. DRESS syndrome is more frequently associated with anticonvulsants but has been reported with antimicrobial agents. Based on the patient's findings of rash, eosinophilia, elevated liver enzymes, enlarged lymph nodes, possible pancreatitis, and acute kidney injury, along with recent clindamycin use, the hypersensitivity reaction was classified as DRESS syndrome secondary to clindamycin therapy.

The patient's clinical status continued to decline and she was transferred to the intensive care unit on hospital day 11. The patient had progression of multisystem organ failure, and mechanical ventilation was initiated due to worsening hypoxemia on hospital day 13. The patient's serum creatinine peaked at 4.6 mg/dL and blood urea nitrogen 75 mg/dL. On hospital day 14, continuous renal replacement therapy was started. The patient's liver function worsened with increasing coagulation parameters, including an international normalized ratio (INR) of 13.4 (0.8–1.1). The patient expired on hospital day 16.

The authors evaluated the patient's symptoms and objective data utilizing the registry on severe cutaneous adverse drug reactions scale (RegiSCAR), which revealed a score indicating a definite diagnosis

of DRESS. The authors also utilized the Naranjo scale for adverse reactions, which indicated a probable relationship between the reaction and clindamycin therapy.

The authors noted, “To our knowledge, this is the first case report of fatal clindamycin-induced DRESS

syndrome and only the second case report of DRESS attributable to clindamycin therapy.”

Quidley AM, Bookstaver PB, Gainey AB, et al. Fatal clindamycin-induced drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. *Pharmacotherapy*. 2012;32(12):e387-e392. ■