ISMP Adverse Drug Reactions

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*Joel Shuster, PharmD, BCPP**

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. Shuster at ISMP, 200 Lakeside Drive, Suite 200, Horsham, PA 19044 (phone: 215-947-7797; fax: 215-914-1492; e-mail: joel.shuster@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.

ASPIRIN/CLOPIDOGREL-INDUCED SPONTANEOUS LIVER HEMATOMA

A 76-year-old man presented to his local emergency department (ED) with a day-long complaint of

right upper quadrant pain. He stated that he had not had any trauma. His physical examination was essentially normal except for "mild tenderness in the epigastric area and 2+ pitting edema in both legs."

*Clinical Professor of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, Pennsylvania; Clinical Consultant, Episcopal Hospital, Philadelphia, Pennsylvania; Clinical Advisor, Institute for Safe Medication Practices, Horsham, Pennsylvania.

His medical history included the placement of drug eluting stents after a myocardial infarction 8 years earlier and 3 years after that for unstable angina. One of the stents was coated with heparin and the other was coated with paclitaxel. Other comorbidities included sarcoidosis, pulmonary hypertension, diabetes, and essential hypertension. His medications included aspirin, clopidogrel, glipizide, benazepril, rosuvastatin, allopurinol, prednisone, and omeprazole. He was also using a variety of inhalers for his pulmonary symptoms. He had been taking the clopidogrel and aspirin for 5 years. He did not use nonsteroidal anti-inflammatory drugs.

Laboratory testing revealed the hemoglobin and hematocrit to be slightly below normal, while the platelet count was fine. Abdominal ultrasound and follow-up computed tomography (CT) of the abdomen showed a "large hypodense" mass in the right side of the liver. The patient was admitted to the hospital. Because of a suspected hemorrhage, the aspirin and clopidogrel were discontinued. By the following morning, the patient's hemoglobin had dropped to 8.6 g/dL from 13 g/dL on admission (reference range, 14-18 g/dL), and he was given 2 units of packed red blood cells. The liver transaminases had also increased 5-fold in the first 24 hours. A few days later, a repeat CT scan showed that the first liver lesion had resolved, while a new hypodense lesion had developed. Because of a high white blood cell count, a liver abscess was suspected. "CT-guided aspiration of the lesion revealed 21 mL of dark blood." The patient was treated with an additional unit of whole blood and was discharged a few days later with a "diagnosis of subcapsular liver hematoma while receiving dual antiplatelet therapy." The clopidogrel and aspirin were not restarted upon discharge from the hospital, but the patient was placed back on aspirin alone a month later and had no further problems up to a 1-year follow-up.

The authors state that liver hematoma from antiplatelet therapy is rare, but we must be cautious in using dual therapy for more than the recommended periods of time after stent placements.

Darwish OS, Iqbal E. Dual antiplatelet agent-induced spontaneous liver hematoma. *Ann Pharmacother*. 2012;46(11):e33.

ADENOSINE-INDUCED SEVERE BRONCHOSPASM IN A PATIENT WITHOUT PULMONARY DISEASE

An obese 29-year-old man developed frequent episodes of palpitations that were short and self-limiting. When he developed another episode of palpitations that lasted nearly 2 hours, he presented to his local ED. On physical examination, the patient's heart rate was 210

beats per minute and his blood pressure was 140/90 mm Hg. He complained of "mild chest discomfort" but did not have any difficulty breathing. The electrocardiogram "showed a regular wide QRS tachycardia with a left bundle-branch block morphology, consistent with aberrant supraventricular tachycardia." The patient underwent carotid massage with no effect. The patient was then given a 6 mg intravenous (IV) bolus of adenosine, which also had no effect. A 12 mg bolus was then administered without effect, but the patient developed a mild cough. Another 12 mg IV bolus of adenosine was given, which "cardioverted the patient to sinus tachycardia." The patient immediately developed trouble breathing, and his pulse oximetry showed that he was hypoxic at 83% oxygen saturation on room air. Auscultation revealed "diffuse bronchospasm." An arterial blood gas specimen revealed "hypocapnic respiratory failure," whereas a chest x-ray was normal. He was treated with oxygen and inhaled beclomethasone, along with an IV bolus of methylprednisolone. When this did not help, an IV infusion of aminophylline was started, which relieved the bronchospasm but caused a recurrence of the supraventricular tachycardia (at a rate of 180 beats per minute). Intravenous flecainide halted the new arrhythmia, and the patient had no further problems with bronchospasm or abnormal rhythms. An accessory pathway was later discovered during electrophysiological studies, and the patient was treated with a radiofrequency ablation procedure.

The authors remind us that adenosine is known to cause dyspneic symptoms during cardiac studies, but the symptoms are usually "transient and benign." There are documented cases of severe bronchoconstriction occurring in patients with prior lung disease, but this is apparently the first such case in a patient with normal pulmonary status.

Coli S, Mantovani F, Ferro J, Gonzi G, Zardini M, Ardissino D. Adenosine-induced severe bronchospasm in a patient without pulmonary disease. *Am J Emerg Med*. 2012;30(9):2082.e3-2082.e5.

PACLITAXEL-INDUCED ACRAL ERYTHEMA

A 66-year-old woman was started on paclitaxel as neoadjuvant therapy for ductal breast cancer. After receiving 3 IV doses at 80 mg/m², the patient developed "a nonpruritic, 1-cm confluent erythematous patch over several metacarpophalangeal joints" bilaterally. Continued treatment with the antineoplastic agent caused new areas of discomfort. The new lesions were seen "primarily over her right lateral heel and toes." The erythematous areas became "tender yellow plaques with scaling." Even though there was a reduction in

the dose of paclitaxel, the patient presented with pain and swelling in the right foot after the 11th dose. She had developed multiple lesions and had significant swelling of toes on both feet that caused significant pain. A biopsy of a lesion on the patient's right foot showed "epithelial acanthosis with prominent compact orthokeratotic hyperkeratosis and areas of parakeratosis." She was treated with topical silver sulfadiazine for the open wound areas and received triamcinolone and emollients to the right foot. All lesions and plaques were completely resolved a month after the paclitaxel therapy had been completed.

The authors state that skin rashes are common with paclitaxel, but this type of acral erythema, pertaining to peripheral parts of the body, is not commonly seen. Acral lesions are more commonly seen with other chemotherapeutic agents, such as fluorouracil, cytarabine, or doxorubicin.

Richards KN, Ivan D, Rashid RM, Chon SY. Paclitaxel-induced acral erythema. *Arch Dermatol.* 2012;148(11):1333-1334.

ACUTE LARYNGEAL DYSTONIA ASSOCIATED WITH ARIPIRAZOLE

A 16-year-old girl with a history of rape, sexual molestation, aggressive behaviors, and cutting was admitted to a psychiatric hospital after getting into a fight at school with a female peer. The admitting diagnosis was bipolar disorder not otherwise specified with borderline traits.

Four months before admission, she was given aripiprazole 5 mg daily that had been added to topiramate 25 mg twice daily, which was being used for mood lability. She had been treated in the past with a variety of medications that caused weight gain, oversedation, or other adverse effects that caused her to stop taking the medications. She was also getting naproxen 375 mg twice daily for pain caused by recent cutting attempts. Three days before admission to the hospital, her dose of aripiprazole was increased to 10 mg daily. She was continued on the aripiprazole, topiramate, and naproxen upon admission.

On the third hospital day, 6 days after the increase in dose of the aripiprazole, the woman was found on the floor of the hospital gymnasium "with dyspnea, dysphonia, tongue and throat tightening, cogwheel rigidity, and dizziness." The oxygen saturation varied from 92% to 100%. She was treated with a stat dose of benztropine 2 mg intramuscularly and oral diazepam 5 mg, which caused rapid improvement of her breathing and rigidity. The aripiprazole was halted. Over the next 3 days, benztropine was used orally and there was not a recurrence of symptoms.

The patient had an acute dystonic reaction involving her laryngeal musculature, which was easily treated with the anticholinergic agent, benztropine. The authors state that this is only the second published report of acute laryngeal dystonia occurring with the "newer" or "atypical" antipsychotic agents marketed over the past 20 years or so. It is likely that many such cases have not been reported. With the increased use of some of the antipsychotic agents as adjuncts to antidepressant therapy, we must be aware of such possible episodes of extrapyramidal side effects.

Goga JK, Seidel L, Walters JK, Khushalani S, Kaplan D. Acute laryngeal dystonia associated with aripiprazole. *J Clin Psychopharmacol.* 2012;32(6):837-839.

INCIDENCE OF THROMBOCYTOPENIA DURING HEPARIN PROPHYLAXIS

This report is a follow-up to a study published in 2008 that showed that patients receiving prolonged unfractionated heparin for a variety of reasons developed thrombocytopenia at an extremely high rate of 33%.¹ In this new report, a total of 1,017 patients were included in the analysis of patients receiving heparin solely for *prophylaxis* of venous thromboembolism. The investigation showed that 190 patients (18.7%) developed thrombocytopenia as a result of being placed on heparin prophylaxis. Thrombocytopenia "was defined as a nadir platelet count $<150 \times 10^9/L$ or a platelet count decrease $\geq 50\%$ from admission levels." Half of the patients had only nadir counts below $150 \times 10^9/L$, while 11% of the patients saw their admitting platelet counts fall below 50% of the first measured values. The other 39% of the patients had platelet counts below the cutoff point, and their counts were more than halved from admission. Forty percent of the cases of thrombocytopenia were caused by low-molecular-weight heparins, although the risk was certainly smaller with these agents.

The authors conclude that almost 1 in 5 patients develop thrombocytopenia during heparin prophylaxis, and this high number still seems to be "under-recognized." They suggest more vigilant platelet monitoring, especially in patients at higher risk.

Wang TY, Honeycutt EF, Tapson VF, Moll S, Granger CB, Ohman EM. Incidence of thrombocytopenia among patients receiving heparin venous thromboembolism prophylaxis. *Am J Med.* 2012;125(12):1214-1221.

ORAL FLUOROQUINOLONES AND THE RISK OF RETINAL DETACHMENT

An article was published in the *JAMA* in early April 2012 that concluded that treatment with oral

fluoroquinolone antibiotics caused an increased risk of retinal detachment.² “The absolute risk in the risk of a retinal detachment was 4 per 10,000 person-years (number needed to harm = 2500 computed for any use of fluoroquinolones).”²² I had not seen that original publication, but I recently found this editorial in the *American Journal of Ophthalmology* that pointed out some potential problems with just a superficial observation of the original analysis.

The authors discuss the fact that tendinitis and/or tendon ruptures may occur in 1 out of 1,000 patients treated with fluoroquinolones, yet we still use the fluoroquinolones in all manner of patients. Is the risk of a rhegmatogenous retinal detachment something to be feared? Please take a look at both of these publications, which may be used for a good discussion in a journal club.

Albini TA, Karakousis PC, Abbey AM, Bartlett JG, Flynn HW. Association between oral fluoroquinolones and retinal detachment. *Am J Ophthalmol*. 2012;154(6):919-921.

PRENATAL EXPOSURE TO ANTIDEPRESSANTS: HOW SAFE ARE THEY?

A prospectively collected database looked at 4 groups of children. Two of the groups included women who took either venlafaxine or selective serotonin reuptake inhibitors (SSRIs) during their pregnancies. Another group included depressed pregnant women who were not treated, and the final group was made up of non-depressed, healthy women. The children of these women were followed to ages 3.5 to 6 years and were given intelligence tests and other tests for neurodevelopment.

The study showed that exposure to antidepressants did not affect the children’s intellectual or behavioral outcomes. Untreated depression certainly led to a much higher risk of postpartum depression. The data also showed “that fetal and childhood exposure to maternal depression were significant predictors of child behavior problems and may represent risk for long-term child psychopathology.”

A well-referenced accompanying editorial in the same issue of the *American Journal of Psychiatry* looks at other reports where prenatal exposure to antidepressants was studied.³

Nulman I, Koren G, Rovet J, et al. Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. *Am J Psychiatry*. 2012;169(11):1165-1174.

PROTON PUMP INHIBITORS: THE GOOD, THE BAD, AND THE UNWANTED

This column has previously reported on uncommon adverse effects associated with proton pump inhibitors (PPIs). Last month (January 2013), we reviewed a case of agranulocytosis brought on by exposure to PPIs.⁴

This report is a 60-reference review of adverse effects associated with PPIs. A good discussion is included about “usage issues” with this class of drugs. Too many hospitalized patients are placed on these agents without good reason. The takeaway lesson from this review is that PPIs should only be used for accepted indications and their long-term use should be evaluated on a regular basis.

Chubineh S, Birk J. Proton pump inhibitors: the good, the bad, and the unwanted. *Southern Med J*. 2012;105(11):613-618.

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2. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. *JAMA*. 2012;307(13):1414-1419.
3. Steiner M. Prenatal exposure to antidepressants: How safe are they? *Am J Psychiatry*. 2012;169(11):1130-1132.
4. Shuster J. ISMP adverse drug reactions. *Hosp Pharm*. 2013;48(1):11-14. ■