

## ***ISMP Adverse Drug Reactions***

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### **Doxycycline-Induced Pseudotumor Cerebri**

### **Excellent Review: Antipsychotic-Induced Hyperprolactinemia**

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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. 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.

#### **ALENDRONATE-INDUCED ASTHMA**

A 45-year-old woman who was a nonsmoker had an 18-year history of mild, persistent asthma. Her symptoms were well controlled with inhaled salmeterol and fluticasone, and she had not had an asthma attack for over 2 years. She was

diagnosed with osteoporosis, and alendronate (*Fosamax* and others) 70 mg once weekly was started. The patient came to the emergency department (ED) 4 hours after her first dose of alendronate with shortness of breath, wheezing, and cough that had lasted for over 30

minutes. Oxygen saturation was 94% (normal, 95% to 99%); respiratory rate was 30 breaths/min (15 to 20 breaths/min); and heart rate was 110 beats/min (70 to 85 beats/min). Blood pressure and temperature were normal. The only abnormal findings during an infec-

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tious disease workup were a slight increase in the eosinophil count and an immunoglobulin E level that was approximately 3 times the upper limit of normal. All other tests were normal, and a diagnosis of “acute asthma attack” was made. The patient’s symptoms were treated with nebulized albuterol and intravenous (IV) hydrocortisone with excellent results, and she was discharged within 12 hours of admission. The woman was told that she might have had an alendronate-induced asthma attack and she was instructed to stop taking that medication.

The patient had no problems with her asthma for the following 2 weeks because she continued on her usual regimen of asthma medications. Although she had been told to avoid the alendronate, the patient decided to take another dose. Within a few hours the dyspnea and wheezing returned, and she went back to the ED. Albuterol and IV hydrocortisone eliminated the symptoms within the first few hours of treatment. This “rechallenge” confirmed the diagnosis of alendronate-induced asthma.

The authors state that this is the first such report, although there are rare prior reports of urticaria and angioedema caused by this agent. They suggest cautious use of alendronate in patients with a history of asthma.

Isik A, Uras I, Uyar ME, Karakurt F, Kafitan O. Alendronate-induced asthma. *Ann Pharmacother*. 2009;43(3):547-548.

### PROTON PUMP INHIBITOR-INDUCED ACUTE INTERSTITIAL NEPHRITIS

A 70-year-old man with a history of well-controlled hypertension occasionally took omeprazole for gastroesophageal reflux disease. He had not taken omeprazole for a month when he began taking lan-

soprazole (*Prevacid*) because of worsening reflux symptoms. Four days after the lansoprazole was started, the patient became nauseous and had 2 loose stools for a single day. He stopped taking the medication. Over the next 2 weeks the patient was fatigued and nauseous without fever, vomiting, or other symptoms. He went to his primary care provider, and the physical examination was unremarkable. The complete blood count with differential was normal, as was the basic chemistry panel, with the exception of the renal function tests. The serum creatinine was 3.8 mg/dL (0.5 to 1.2 mg/dL), and the serum urea nitrogen (BUN) was 45 mg/dL (8 to 23 mg/dL). The patient was given IV fluids for 48 hours, but the BUN and serum creatinine remained elevated. Because the diagnostic workup was negative, it was decided that a kidney biopsy should be done. The test revealed acute interstitial nephritis (AIN). When the patient was last seen, the creatinine was still elevated at 2.8 mg/dL.

The authors point out that this is the fourth report of AIN associated with lansoprazole. The authors also polled the staff at their hospital, and 96% of the physicians did not know that proton pump inhibitors could cause AIN. This editor was also unaware of this adverse affect.

Eken J, Phadke G, Ahmed S, Mahale A. Lansoprazole-induced acute interstitial nephritis. *Southern Med J*. 2009;102(3):335-336.

### MESALAZINE AND HYPEREOSINOPHILIA

Inflammatory bowel disease (IBD) was diagnosed in a 5-year-old boy after he had bloody diarrhea for more than a year. The patient had already had a splenectomy at 15 months of age because

of hereditary spherocytosis, and he also was diagnosed with hyperimmunoglobulin M syndrome a year earlier. The diagnosis of IBD was made after an extensive workup that included colonoscopy, upper endoscopy, and a gastrointestinal barium meal study. None of the findings were stated as pathognomonic for Crohn disease or ulcerative colitis. It was decided that mesalazine be started orally and by daily suppository, along with 15 days of metronidazole therapy. The IBD was partially controlled with this treatment.

During a flare-up of the IBD 2 years later, laboratory tests showed an increased white blood cell (WBC) count of 63,000 cells/mm<sup>3</sup> (5,000 to 10,500 cells/mm<sup>3</sup>), with an eosinophil count of 35,000/mm<sup>3</sup> (0% to 5% of WBC; at 56% of the WBC here). The peripheral smear and bone marrow examination showed increased levels of eosinophils at 74% and 16%, respectively. Hypereosinophilic leukemia was ruled out, and a full workup did not reveal the cause of the hypereosinophilia. Therefore, it was suspected that the mesalazine might be the culprit because the patient was not taking any other medications. Soon after the mesalazine was stopped, the eosinophilia resolved. It did not recur during 2 years of follow-up. This is the first case report describing this rare adverse effect.

Usta Y, Ozen H, Gurakan F, et al. Hypereosinophilia due to mesalazine treatment. *J Clin Gastroenterol*. 2009;43(4):382.

### TARDIVE DYSKINESIA ASSOCIATED WITH ARIPIPRAZOLE

Tardive dyskinesia (TD) is the most serious involuntary movement disorder associated with the conventional or older antipsychotic agents. One of the primary benefits of the newer or atypical antipsy-

chotic drugs is that TD and other disorders of the extrapyramidal system occur much less frequently. However, TD has been reported with all of the atypical drugs. Following is a review of 2 case reports of newly diagnosed TD in 2 separate patients who had never taken antipsychotic drugs and developed TD after exposure to aripiprazole (*Abilify*).

The first patient is a 19-year-old woman who had taken aripiprazole for 2 years before she developed dystonia. The woman was born with fragile X syndrome, and the medication was being used to control “anxiety and violent outbursts.” On presentation the patient displayed leftward trunk deviation and extensor posturing of her upper extremities. She also showed anterocollis and left laterocollis. The patient had had these dystonic movements for about a year and was brought in for evaluation when they worsened after an increase in aripiprazole dosing from 7.5 to 15 mg daily, which had occurred 3 months earlier. The drug was tapered off, and the dystonia improved dramatically over the next 3 months and was completely resolved in approximately 9 months.

The second patient is a 62-year-old man who was prescribed aripiprazole 15 mg daily for treatment of symptoms related to posttraumatic stress disorder. After 18 months of therapy, the patient developed classic signs of TD, including involuntary movements of the mouth and tongue that progressed to include his neck and trunk. The physical examination demonstrated right-sided torticollis, jaw and lingual dystonia, and “truncal dystonia with arching of the back and lateral flexion of the trunk.” The symptoms persisted after the aripiprazole was stopped, and multiple therapies over 18

months were unsuccessful. The patient eventually had surgery for bilateral globus pallidus internus deep brain stimulation and within 3 months had “considerable benefit.”

The authors believe that their report is the first that illustrates TD caused by aripiprazole in patients who are naïve to antipsychotics. They offer a brief but excellent discussion of TD rates in patients taking conventional antipsychotic drugs as compared with the atypical antipsychotics. The report is well referenced and bears review because of the atypical antipsychotic agents being used for new indications. Health care professionals must be forewarned of the importance of counseling patients to quickly report any dyskinetic movements so that the offending agent can be removed as soon as possible.

Lungu C, Aia PG, Shih LC, Esper CD, Factor SA, Tarsy D. Tardive dyskinesia due to aripiprazole: report of 2 cases. *J Clin Psychopharmacol.* 2009;29(2):185-186.

#### **ATRIAL FIBRILLATION AND CORONARY VASOSPASM CAUSED BY ONDANSETRON**

A 51-year-old man underwent 2 elective surgical procedures: one for hernia repair and a septoplasty for a deviated nasal septum. His only cardiovascular risk was hyperlipidemia, which was treated with atorvastatin. No problems presented during the surgeries, and the patient’s heart was in normal sinus rhythm throughout the procedures. The patient received IV doses of ondansetron (*Zofran* and others) 4 mg and glycopyrrolate 0.3 mg at the end of surgery. In the recovery room 3 hours later, the patient became nauseous and diaphoretic. He was given another dose of IV ondansetron, and he immediately complained of chest pain and vom-

ited. Because he was being continuously monitored, the electrocardiogram revealed “inferolateral ST segment elevation, with ST segment alternans and new-onset atrial fibrillation.” The systolic blood pressure fell from 162 mm Hg to 90 mm Hg. Heparin therapy was initiated, along with aspirin. The patient’s condition was stabilized, and he was sent to the cardiac catheterization laboratory, where an angiography was normal. The troponin level was also normal. Electrical cardioversion was performed 16 hours after the onset of the atrial fibrillation, and the patient’s heart converted to normal sinus rhythm. Holter monitoring for 24 hours showed no other evidence of recurrent atrial fibrillation. The patient has done well for 3 years of follow-up.

The authors point out that there are a number of case reports of apparent coronary artery vasospasm and arrhythmias associated with ondansetron and dolasetron. It has not been reported that the other 5-HT<sub>3</sub> receptor antagonists used for controlling nausea and vomiting, granisetron and palonosetron, cause these rare cardiovascular events.

Havrilla PL, Kane-Gill SL, Verrico MM, Seybert AL, Reis SE. Coronary vasospasm and atrial fibrillation associated with ondansetron therapy. *Ann Pharmacother.* 2009;43(3):532-536.

#### **DOXYCYCLINE-INDUCED PSEUDOTUMOR CEREBRI**

A 23-year-old woman was prescribed doxycycline 100 mg twice daily for the treatment of acne vulgaris. She also was given topical tretinoin microsphere gel. The patient came to the ED 2 months later with severe headaches that had been getting worse over the previous 3 weeks. She described the pain as 9 out of 10 and stated that the

headaches were “diffuse, throbbing, worse when lying down, and associated with occasional nausea as well as blurry vision.” Laboratory tests and the physical examination were unremarkable with the exception of bilateral papilledema. A lumbar puncture was performed, which was normal except for a mildly elevated opening pressure. The cerebrospinal fluid was normal, as was a magnetic resonance imaging study of the brain. The patient reported “substantial symptomatic improvement” after the lumbar puncture; and she was sent home for recommended rest, given acetaminophen treatment for the headaches, and prescribed outpatient follow-up.

When the patient came back to the neurology department 3 days later, she complained of the return of the headache and still had papilledema. The neurologist suspected pseudotumor cerebri (PTC),

also known as benign intracranial hypertension, which is a known adverse effect of the tetracycline class of antibiotics. The doxycycline was stopped and a tapering dose of oral methylprednisolone was prescribed. Within 1 week the patient had no more complaints of headache, nausea, or blurred vision.

The authors point out that PTC has been reported with tetracyclines, oral retinoids, nalidixic acid, and amiodarone. In 2004 a series of 7 case reports of PTC associated with doxycycline was reviewed in this column.<sup>1</sup>

Tabibian JH, Gutierrez MA. Doxycycline-induced pseudotumor cerebri. *South Med J.* 2009;102(3):310-311.

#### **EXCELLENT REVIEW: ANTIPSYCHOTIC-INDUCED HYPERPROLACTINEMIA**

In the March issue of *Hospital Pharmacy*, an interesting cross-

sectional survey of hyperprolactinemia in patients taking antipsychotic drugs in Norway was mentioned.<sup>2</sup> Following is the citation for an excellent review of antipsychotic-induced hyperprolactinemia that uses over 60 references to enable full understanding by the reader of the extent of this adverse effect.

Bostwick JR, Guthrie SK, Ellingrod VL. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy.* 2009;29(1):64-73.

#### **REFERENCES**

1. Shuster J. ISMP adverse drug reactions: doxycycline and intracranial hypertension. *Hosp Pharm.* 2004;39(9):827-830, 856.
2. Shuster J. ISMP adverse drug reactions: three reviews: antipsychotic-induced hyperprolactinemia, cephalosporin-induced neurotoxicity, adverse drug reactions with therapy for latent tuberculosis. *Hosp Pharm.* 2009;44(3):214-220. ■