ISMP Adverse Drug Reactions

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*Michael A. Mancano, PharmD**

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.

CLOZAPINE-INDUCED OBSESSIVE COMPULSIVE SYMPTOMS

This is a report of 2 cases of clozapine (*Clozaril*)-induced obsessive compulsive symptoms with a clear temporal relationship and no history of obsessive compulsive symptoms. Patient 1 is a 52-year-old male with a diagnosis of bipolar disorder since the age of 34 years. At age 38, the patient received clozapine 600 mg daily and experienced full symptom remission with a return to good psychosocial functioning. At age 40, the patient developed disabling checking behaviors indicative of obsessive compulsive disorder. The patient was prescribed sertraline 100 mg daily, and his obsessive compulsive symptoms completely resolved. At age 50, the patient insisted on discontinuing

clozapine and sertraline. While the patient's clozapine dose was being tapered, the patient experienced a complete resolution of obsessive compulsive symptoms while receiving 100 mg daily of clozapine.

Within 2 months of discontinuing clozapine, the patient developed a full manic episode that required hospitalization. He was stabilized on clozapine 300 mg daily and was discharged. Within 4 months, the checking behaviors returned and sertraline was restarted, bringing partial relief. A year later, the patient again insisted on reducing the clozapine dosage, and the cycle of obsessive compulsive symptom remission, mania, response to clozapine, re-emergence of obsessive compulsive symptoms, and improvement with sertraline was observed.

*Chair and Clinical Professor, Department of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, Pennsylvania; Clinical Advisor, Institute for Safe Medication Practices, Horsham, Pennsylvania

The second case occurred in a 42-year-old male with bipolar disorder who was hospitalized several times for mania with psychosis. The patient had started clozapine at the age of 28 years and had achieved symptom resolution, however within 6 months of initiation the patient developed disabling compulsive checking behaviors that responded minimally to selective serotonin reuptake inhibitor (SSRI) therapy. The patient was receiving clozapine 200 mg daily and still exhibited severe compulsive checking behaviors without mania. The patient's clozapine dose was tapered over 6 months with cross-titration to quetiapine. The patient's obsessive compulsive symptoms dramatically improved with a dose of 100 mg daily of clozapine, however the patient experienced a manic episode. The patient's mania eventually resolved with quetiapine 1,200 mg daily. One year after clozapine discontinuation, the patient's obsessive compulsive symptoms remitted and psychosocial functioning improved.

The authors summarize that the first patient experienced the late appearance of obsessive compulsive symptoms after 15 years of therapy with clozapine. The patient experienced complete resolution of symptoms after discontinuation of clozapine and a rapid recurrence of the full syndrome upon restarting clozapine. The second patient illustrates the potential severity of clozapine-induced obsessive compulsive symptoms and the marked improvement with clozapine discontinuation. The authors theorize that because both cases involve bipolar disorder, this suggests that the obsessive compulsive symptoms with clozapine occur independently of schizophrenia. The authors also point out that a limitation of their observations is the fact that clozapine blood levels were not drawn on either patient to quantify the level of patient exposure versus the dosage administered.

Lemke NT, Bustillo JR. Clozapine-induced obsessive-compulsive symptoms in bipolar disorder. *Am J Psychiatry*. 2013;170(8):930.

PLASMA DABIGATRAN ACTIVITY ONE WEEK AFTER DISCONTINUATION IN A PATIENT WITH NORMAL RENAL FUNCTION

A 74-year-old significantly overweight (146 kg [322 lbs]) woman was admitted to the hospital. Four weeks prior to admission, dabigatran (*Pradaxa*) had been initiated in the patient for atrial fibrillation and worsening cardiac failure. On the third day after admission, she experienced an episode of gastrointestinal bleeding; at this time, her hemoglobin was 12.6 g/dL (normal for this patient was 16.5 g/dL). Her renal function was normal on admission (estimated glomerular filtration

rate >90 mL/min) and throughout her hospital stay. The patient's medication regimen was carefully checked for potential drug interactions, and none were identified. The patient's regimen included nifedipine, metoprolol, lisinopril, and intravenous furosemide.

Dabigatran levels were measured using the HEMOCLOT direct thrombin inhibitors assay (HYPHEN BioMed, Andresy, France) at 4 different time points, starting from 24 hours after discontinuation of dabigatran and at 36, 48, and 96 hours. Dabigatran levels were 247 ng/mL, 317 ng/mL, 157 ng/mL, and 10.6 ng/mL, respectively. During this time, coagulation screening including thrombin time was prolonged. The authors present a graphical representation of elevated thrombin values but do not report the numerical values. The graph indicates prothrombin times greater than 100 seconds for 9 days and greater than 50 seconds for 12 days, with initial values approaching 250 seconds for the first 2 days (normal thrombin time, 11-18 seconds) after dabigatran discontinuation. In addition to supportive measures, prothrombin complex concentrate (3,000 units) was administered with no detectable benefit. The patient declined intestinal endoscopy on several occasions, however her melena resolved after 10 days.

The authors state that an evidence-based reversal strategy for dabigatran is not available for management of a bleeding patient, however expert consensus is that such an intervention is less likely because of the relatively short half-life of dabigatran (12-14 hours). For this reason, supportive therapy is the mainstay until thrombin time, a surrogate measure for dabigatran levels, is within normal range. In this report, the authors identified a high plasma level of dabigatran for at least 5 days and a prolongation of thrombin time for 1 week after its discontinuation despite normal renal function. They theorize that the only possible explanations for the prolonged plasma dabigatran level are a drug interaction not previously described, prolonged clearance in a patient with cardiac failure, redistribution of the drug in the adipose tissue, or the patient being significantly overweight.

Thachil J, Pike G, Keighly-Jones L, et al. Plasma dabigatran activity one week after discontinuation in a patient with normal renal function. *Am J Med*. 2013;126(8):e5-e6.

ANTABUSE REACTION DUE TO OCCUPATIONAL SOLVENT EXPOSURE

This report describes a painter who experienced a disulfiram reaction due to occupational exposure of alcohol-containing solvents. A 45-year-old industrial painter developed vomiting, intense shivering, and

delirium while he was painting in a factory. The patient was transported to a hospital. At admission, he was still delirious, dyspneic, and febrile and had diffuse erythema over his forearm and face. His heart rate was 120 bpm, his blood pressure was 60/40 mmHg, he had an oxygen saturation of 92% on room air, and his arterial blood gas revealed metabolic acidosis (pH 7.24). The patient was started on broad-spectrum intravenous antibiotics, and he received fluid resuscitation with the addition of norepinephrine to stabilize his central venous pressure. The patient's complete blood count (CBC), metabolic profile, liver function tests, lipid profile, electrolytes, chest x-ray, and ultrasound of the abdomen were all within normal limits. The patient's sensorium and hemodynamic status dramatically improved within 3 hours of admission. The patient's cultures remained sterile, and his antibiotic coverage was stopped.

The patient was able to provide a detailed history that revealed he was an alcoholic of 5 years and had started on disulfiram 100 mg daily approximately 9 months earlier. His recent medical history included frequent reports of palpitations, chest discomfort, paresthesia, and easy fatigability. The patient's old medical records did not indicate a detectable blood alcohol level while receiving disulfiram. Detailed questioning revealed that due to his occupation the patient was exposed to a variety of solvents such as metal paints, thinners, varnish removers, and polish containing methanol, ethanol, isopropyl alcohol, and toluene for about 8 to 12 hours a day for 6 days a week. After complete resolution of symptoms, he was discharged with directions to use a cartridge respirator and wear gloves while painting. The patient reported feeling much better after adopting the recommended exposure precautions.

The authors theorize that inhalation or transcutaneous absorption of alcohols and/or solvents might have caused accumulation of aldehyde and interacted with disulfiram, resulting in the patient's recurring symptoms and frequent medical consultations. Disulfiram decreases the metabolism of solvents such as toluene and xylene, which are commonly found in thinners by inhibiting CYP450 enzymes. The authors recommend that when disulfiram is initiated, an occupational history should be investigated. Consideration should be given to incidental, intentional, occupational inhalation, or transcutaneous absorption of alcohol and/or solvents.

Senthilkumaran S, Menezes RG, Ravindra G, et al. Antabuse reaction due to occupational exposure – another road on the map? *Am J Emerg Med.* 2013;31:1286.

WITHDRAWAL SYMPTOMS WITH DRONABINOL

A 71-year-old woman with a history of anxiety and postmyocardial infarction depression was hospitalized for ischemic bowel and failure to thrive. She was treated with duloxetine, methylphenidate, and supportive therapy, and her depressive symptoms gradually improved. Weeks later, she developed acute worsening of her mood, anxiety, appetite, nausea, and stomach pain, as well as visual hallucinations, tremors, and diaphoresis. Dronabinol (*Marinol*) 10 mg twice daily, which she had been taking for 3 months, and methylphenidate 5 mg daily had been abruptly stopped 3 days earlier for their perceived ineffectiveness in improving appetite. Metoclopramide had also been discontinued, because of its potential for tardive dyskinesia. Based on the patient's symptoms, dronabinol withdrawal was suspected and dronabinol was reinstated at 5 mg twice daily along with quetiapine 25 mg twice daily for hallucinations and possible delirium. Over the next 2 to 6 days, all of the symptoms returned to recent baseline measurements and the quetiapine was quickly tapered and discontinued without recurrent of symptoms.

The authors point out that withdrawal has only been described in animals and oral cannabinoid users in research studies. Like cannabis, dronabinol's tolerance, withdrawal, and psychoactive properties are mediated through the CB₁ receptor. Common symptoms of cannabinoid withdrawal include irritability, anxiety, decreased appetite or weight loss, restlessness, and sleep difficulties, including strange dreams. Less common symptoms include chills, depressed mood, stomach pain, shakiness, and sweating. The onset of withdrawal is within 24 hours of abstinence, peaks within 2 to 3 days, and last approximately 1 to 2 weeks.

The authors attribute the onset and resolution of symptoms to the removal and addition of dronabinol, because of their quick disappearance after reinitiation and their continued absence after discontinuation of quetiapine. The authors recommend that potential withdrawal symptoms be considered during dronabinol use; tapering during discontinuation could prevent their occurrence.

Muramatsu RS, Silva N, Ahmed I. Suspected dronabinol withdrawal in an elderly cannabis-naïve medically ill patient. *Am J Psychiatry.* 2013;170(7):804.

PSEUDOLITHIASIS DUE TO CEFTRIAXONE

A 14-year-old boy (1.7 m [5 ft, 7 in.]; 60 kg [132 lbs]) presented to an emergency department with attacks of severe nocturnal abdominal pain. He had

been treated successfully in the same hospital for Lyme arthritis of his right knee with 2 weeks of high-dose ceftriaxone (4 g daily). The patient's symptoms had started 4 days after completion of ceftriaxone therapy, and the symptoms had persisted for 7 consecutive nights. The pain was localized in the epigastric region and the right hypochondrium of the abdomen and radiated to the back. The patient felt ill and had vomited several times, but he had no fever.

Laboratory tests were indicative of cholestasis (reference values in parentheses): alkaline phosphatase 398 U/L (<350 U/L), gamma-glutamyl transpeptidase 291 U/L (<45 U/L), total bilirubin 72 $\mu\text{mol/L}$ (<17 $\mu\text{mol/L}$), direct bilirubin 63 $\mu\text{mol/L}$ (<5 $\mu\text{mol/L}$), aspartate transaminase 161 U/L (<40 U/L), alanine transaminase 187 U/L (<45 U/L), C-reactive protein 13 mg/L (<10 mg/L), and leukocytes $10.4 \times 10^9/\text{L}$ ($4\text{--}10 \times 10^9/\text{L}$). An abdominal ultrasound revealed multiple biliary concretions and sludge localized both inside the gallbladder and in the neck of the gallbladder. A diffuse dilation of intrahepatic bile ducts was also noted. Based on the patient's presentation and laboratory results, a diagnosis of cholecystolithiasis with cholestasis was suspected.

Gallstones in children are very rare, but the medical literature indicates that ceftriaxone is associated with the development of reversible cholelithiasis, also known as pseudolithiasis. Because of the recent use of ceftriaxone in this patient, this was likely to have played an important role in the pathogenesis. The patient was managed conservatively, and his pain

decreased. After a few days, the young man was discharged in good condition. The patient had a follow-up ultrasound 4 months after discharge, and it indicated a complete disappearance of the abnormal findings observed on admission.

The authors indicate the proposed mechanism by which ceftriaxone induces cholelithiasis is the capacity of ceftriaxone to precipitate with calcium ions. This process is facilitated by the relatively high concentration of ceftriaxone in bile. As a result, an insoluble calcium-ceftriaxone complex is formed. In addition to the increased risk for the development of pseudolithiasis during ceftriaxone therapy, there are also some rare cases described in the literature of nephrolithiasis associated with ceftriaxone use.

The authors emphasize that besides stopping or converting the ceftriaxone therapy, no other treatment is recommended. This "wait and see" policy can prevent overdiagnoses and unnecessary treatment, especially cholecystectomy and its possible complications. Although it is known that ceftriaxone therapy in children can cause the side effect of sonographic biliary abnormalities, only a minority of these cases will be accompanied with the clinically relevant symptoms and biochemical deviations seen in gallbladder disease. Awareness of this phenomenon is important in preventing unnecessary treatment.

von Martels JZH, van de Meeberg EK, Holman M, et al. Pseudolithiasis after recent use of ceftriaxone: An unexpected diagnosis in a child with abdominal pain. *Am J Emerg Med*. 2013;31:1294.e5-1294.e6. ■