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ISMP Adverse Drug Reactions

Metformin-Associated Lactic Acidosis

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Intestinal Necrosis Associated With Calcium Polystyrene Sulfonate

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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.

METFORMIN-ASSOCIATED LACTIC ACIDOSIS

As the authors of this correspondence remind the reader, "metformin is believed to be the most prescribed antidiabetic drug in the world." There were more than 40 million prescriptions for this generic drug filled in the United States in 2008. We chose this simple letter to the editor in the *American Journal of Emergency Medicine* as the lead ADR this month because of

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the point being made by these French authors. They remind us that metformin-associated lactic acidosis (MALA) is rare and some authorities do not believe it is a very real issue. Almost all of the published case reports are in the critical care and emergency medicine literature, and many clinicians have never seen MALA.

Reference is made to a report of metformin overdose that resulted in severe lactic acidosis.[1] This overdose case illuminated the fact that there do not have to be confounding factors that add to the risk of MALA. These authors make a plea that all practitioners should heed "the absolute contraindications of metformin. . .renal dysfunction, congestive heart failure requiring drug treatment, acute or chronic metabolic acidosis, liver disease as shown by abnormal liver function tests, and use of intravenous radiographic contrast agents." The precautionary conditions for the use of metformin should also be well heeded, including age greater than 80 years, dehydration, sepsis, any type of hypoxemia, and the concomitant use of nephrotoxic agents.

The authors also make a plea for practitioners to report all such cases of lactic acidosis in patients using metformin.

Lemyze M, Mallat J, Thevenin D. Metformin-associated lactic acidosis: is it really just an association? *Am J Emerg Med*. 2011;29(3):349-350.

ESCITALOPRAM-RELATED RHABDOMYOLYSIS

A 27-year-old man with suicidal ideation and many classic symptoms of major depressive disorder was started on escitalopram (*Lexapro*) 10 mg daily. He had baseline laboratory testing that showed a normal hemogram, liver function studies, and creatine kinase. The patient's total cholesterol and low-density lipoprotein levels were slightly elevated.

Twelve days after starting the antidepressant therapy, a follow-up laboratory examination showed a greatly increased creatine kinase (CK) level of 24,346 units/L (reference range, 0-190 units/L). The patient's renal function was normal, and he had no physical trauma or excess exercise that may have contributed to the apparent rhabdomyolysis. The only other lab values that were abnormal were the liver transaminases. The aspartate aminotransferase (AST; referred to as the GOT in this report) was 550 units/L (20-40 units/L), and the alanine aminotransferase (ALT or GPT) was 153 units/L (10-40 units/L). The hepatitis serologies were negative, as they had been at baseline. An escitalopram level was obtained and reported as "within therapeutic range." Nevertheless, the escitalopram was discontinued and copious oral hydration was given. The CK levels dropped dramatically to near normal within 8 days. The authors concluded that the transaminase elevations were probably due to myocyte destruction rather than to any liver damage. They based this on the AST/ALT ratio being larger than 1, no alcoholism, and negative hepatitis serologies.

The authors believe that this is the first published case of rhabdomyolysis associated with escitalopram. There have been reported cases of serotonin syndrome with concomitant increases in CK levels and other cases where multiple drugs were on board beside the antidepressant.

Lewien A, Kranaster L, Hoyer C, Elkin H, Sartorius A. Escitalopram-related rhabdomyolysis. *J Clin Psychopharmacol*. 2011;31(2):251-253.

ADALIMUMAB-INDUCED DISSEMINATED SUPERFICIAL POROKERATOSIS

A 55-year-old man with a 10-year history of debilitating chronic psoriatic arthritis had been treated unsuccessfully with corticosteroids, cyclosporine, and methotrexate. He was started on adalimumab (*Humira*) 40 mg subcutaneously every other week along with weekly doses of methotrexate 15 mg by mouth. He had an excellent response within 12 weeks with a significant reduction in his arthritic symptoms. The methotrexate was stopped about 2 months later, and the patient did well for 2 more years on just the adalimumab.

At the 2-year mark, the patient complained of multiple porokeratotic lesions on his upper and lower limbs. He stated that these lesions had started a year earlier. (Porokeratosis is defined as "a rare dermatosis in which there is a thickening of the stratum corneum with an annular keratotic rim or cornoid lamella surrounding progressive centrifugal atrophy."[2])

The dermatologic examination revealed "well-demarcated, small (0.5-1 cm in diameter), horny papules with a palpable raised border" on the arms and legs. There had been no history of drug reactions, sun sensitivity, or alternative medication use. A biopsy confirmed the diagnosis of disseminated superficial porokeratosis. A complete workup eliminated any other causative agent. The patient actually refused to stop the adalimumab treatments and also refused symptomatic treatment of the skin lesions.

The authors remind us that adalimumab is a tumor necrosis factor-alfa (TNF-alfa) antagonist and many of these agents cause adverse skin reactions. Severe skin reactions to adalimumab appear less commonly than

with the other agents in this class like etanercept and infliximab.

Guarnieri C, Cannavò SP, Polimeni G. Adalimumab-induced disseminated superficial porokeratosis. *Ann Pharmacother*. 2011;45(2):280-281.

NEPHROTIC SYNDROME ASSOCIATED WITH ADALIMUMAB

This is the second ADR this month caused by adalimumab. A 60-year-old man with a long history of Crohn disease had been treated intermittently with prednsione for flare-ups of his gastointestinal disorder. A recent colonoscopy and biopsy showed mild chronic inflammation in the lamina propria. After another exacerbation of the Crohn disease, he was given mercaptopurine and prednisone but could not be tapered off of the corticosteroid. The decision was made to start adalimumab with one dose of 160 mg subcutaneously, followed by 80 mg subcutaneously every 2 weeks.

The patient showed an excellent response with a decrease in stool frequency from a baseline of 4 to 6 bowel movements per day down to 1 to 2 per day. After 4 months or so, the patient's serum creatinine became slightly elevated from his baseline. The serum creatinine had risen to 2.6 mg/dL (patient's baseline, 1.4 mg/dL; reference range, 0.5-1.5 mg/dL) by the 7th month of treatment. At this time, the patient had increased leg edema and proteinuria. He underwent a nephrology workup with many negative tests, but the renal biopsy showed stage 2 to 3 membranous glomerulonephritis with tubular injury and interstitial fibrosis. The adalimumab was discontinued, and corticosteroids were reintroduced. The proteinuria lessened, and the patient continued on prednsione with the addition of mycophenolic acid.

The authors give an extensive, well-referenced review of the nephrotic syndrome caused by anti-TNF-alfa agents. This is not a common effect of this class of agents, but one that has to be considered as these agents gain use against various immune diseases and neoplasms.

Gupta A, Pendyala P, Arora P, Sitrin MD. Development of the nephrotic syndrome during treatment of Crohn's disease with adalimumab. *J Clin Gastroenterol*. 2011;45(3):e30-e33.

METHOTREXATE-INDUCED PERIORBITAL RADIATION RECALL

A 63-year-old man developed primary retinal diffuse large B-cell lymphoma. He was given radiation to both orbits of the eyes. Six weeks later, high-dose methotrexate with folinic acid rescue was given. The dose of methotrexate was 3.5 g/m^2. Two days after this first dose of methotrexate, the patient "developed severe erythema with desquamation in the periorbital region around both orbits where he received radiation." The patient was treated with prednisolone eye drops, topical bacitracin, and systemic prednisone for 1 week. The patient continued to receive the chemotherapy treatments every 4 weeks, and each time he developed a slight rash around his eyes without dermatitis. The reactions lessened over time.

The authors offer a brief discussion of radiation recall, which is a rare occurrence seen with various antineoplastic agents whereby an area of skin "recalls" radiation exposure following administration of the response-inducing medication. The mechanism of this reaction is not well understood.

Kiel PJ, Jones KL. Methotrexate-induced periorbital radiation recall. *Ann Pharmacother*. 2011;45(1):133.

MICTURITION DIFFICULTY ASSOCIATED WITH ARIPIPRAZOLE

A 20-year-old male presented to a psychiatry clinic with symptoms suggesting a new-onset psychosis. He was suspicious, displayed ideas of reference, showed a cognitive decline, and had become socially withdrawn. A tentative diagnosis of prodromal schizophrenia was made, and he was started on aripiprazole (*Abilify*) 7.5 mg daily. Within a little more than 1 month, most of the patient's symptoms improved, but he complained of restlessness and difficulty in urination. The patient complained of it taking a long time to complete micturition. He sometimes had to sit down just to wait until the urinary flow ensued. There was no urinary pain. Because of continued complaints, the aripiprazole was discontinued and another second-generation agent was initiated. His urinary symptoms stopped within a few days of discontinuing the original agent.

A 25-year-old with a 1-year history of psychosis and "prominent low mood" was started on aripiprazole 7.5 mg daily and sertraline 25 mg daily. Within 1 week, the patient complained of restlessness, "general uneasiness," and striking urinary hesitancy. He was free of any signs of urinary infection. The sertraline was stopped, and low-dose lorazepam and propranolol were added to treat the apparent akathisia. The motor restlessness remitted over the next few weeks, but the urinary hesitancy continued. The aripiprazole was then discontinued, and the urinary symptoms completely cleared within several days. The new antipsychotic agent did not cause any urinary symptomatology.

These 2 case reports of urinary difficulty with aripiprazole are the first such published accounts of

micturition problems associated with this second-generation antipsychotic agent. Urinary difficulty caused by older antipsychotics is easily explainable due to the anticholinergic or alpha-adrenergic effects of many of those drugs. Also, psychotic patients are commonly given anticholinergic therapies to counteract the extrapyramidal side effects often seen with the class of antipsychotic drugs, and these agents give rise to urinary complaints. The 2 patients in these case reports were only receiving the agent, aripiprazole, that is not expected to cause such difficulty. This report and the one following are examples of new cases or second reports of ADRs associated with a medication that has been marketed for more than 8 years.

Chiang C-L, Liu C-C. Micturition difficulty associated with aripiprazole – report of 2 cases. *J Clin Psychopharmacol.* 2011;31(1):128-129.

ARIPIPRAZOLE-RELATED ACUTE TRANSIENT MYOPIA AND DIPLOPIA

A 19-year-old woman with a history of obsessive compulsive symptoms was admitted to a psychiatric clinic. She had no history of drug abuse and had never had any problems with her eyes or any neurological diseases. She was started on sertraline. Over the course of 8 weeks, she had been titrated up to a daily dose of 200 mg. At that point, her symptoms had decreased by less than 35%. Aripiprazole was then added to her regimen as an adjunctive therapy. This new medication was dosed at 10 mg daily. Two weeks later, the young woman complained of the acute development of blurred vision and diplopia. She underwent an ophthalmologic exam, and she was determined to have an acute myopia "in the order of 4.0 diopters in the right eye and 4.5 diopters in the left eye." She was given glasses that helped the myopia, but she still complained of the double vision. Two weeks later, the aripiprazole was discontinued. An eye examination 10 days after that revealed that her vision was back to 20/20 and the diplopia had resolved.

The authors of this report state that it is the second report of myopia related to aripiprazole therapy. Ocular side effects with this agent are rare.

Selvi Y, Atli A, Aydin A, Yener HI. Aripiprazole-related acute transient myopia and diplopia. *J Clin Psychopharmacol.* 2011;31(2):249-250.

INTESTINAL NECROSIS ASSOCIATED WITH CALCIUM POLYSTYRENE SULFONATE

A 73-year-old woman was admitted to a hospital with severe abdominal pain. She had a history of chronic obstructive pulmonary disease that had been treated with 2 mg oral methylprednisolone daily. A computed tomography (CT) scan of the abdomen "showed widespread dilatation of the bowel." The diagnosis of acute colonic pseudo-obstruction was made. This is also referred to as Ogilvie syndrome. She underwent an endoscopic procedure that described healthy colonic mucosa. On the third hospital day, the patient's serum potassium level rose to 5.6 mEq/L (3.5 to 5 mEq/L). The belief was that adrenal insufficiency was to blame. Calcium polystyrene sulfonate (*Resonium Calcium,* not available in the United States) was given at 15 g daily from days 3 to 6 as was hydrocortisone 100 mg. These agents were given via a nasogastric tube. The calcium polystyrene sulfonate is an ion-exchange resin like the sodium polystyrene sulfonate resin (*Kayexalate* and others) used commonly throughout the world.

On day 6 of the woman's hospitalization, she developed severe pain once again with signs of early shock. After another CT scan of the abdomen that showed a peritoneal effusion and pneumoperitoneum, she underwent an emergency laparotomy. A large area of necrotic bowel was resected. There were many aphthous erosions on the serosal surface along with the later finding of microscopic crystals embedded in cecal and jejunal mucosal ulcers. There also was a white, fibrinous coating of the serosal surface. Five days later, the patient suffered a second round of shock; a second surgery was performed because peritonitis had set in following rupture of the colonic anastomosis performed during the first operation. The surgeon resected another 19 cm of small bowel and noted a white "deposition" along the serosal surface. Again, crystals were found in ulcerated portions of the removed section of bowel upon pathologic examination.

The woman required a third laparotomy on day 17 because of a mesenteric infarction that destroyed an extensive area of the small intestine. She died 2 days later of multiple organ failure.

The authors discuss the fact that sodium polystyrene sulfonate ion-exchange resin has been implicated in the past as a cause of colonic necrosis, especially when used with sorbitol or in patients with uremia or postoperative ileus. In 2009, this column reviewed 2 published articles discussing multiple deaths due to the use of sodium polystyrene sulfonate.[3,4] This is the first published case report of fatal intestinal necrosis associated with calcium polystyrene sulfonate.

Goutorbe P, Montcriol A, Lacroix G, Bordes J, Meaudre E, Sourad J-B. Intestinal necrosis associated with orally administered

calcium polystyrene sulfonate without sorbitol. *Ann Pharmacother*. 2011;45:e13.

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3. Shuster J. ISMP adverse drug reactions. *Hosp Pharm*. 2009;44(8):660-661.

4. Shuster J. ISMP adverse drug reactions. *Hosp Pharm*. 2009;44(10):856-857. ■