ISMP Adverse Drug Reactions

Deferasirox-Induced Serious Metabolic Abnormalities

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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.

DEFERASIROX-INDUCED SERIOUS METABOLIC ABNORMALITIES

A 3-year-old female patient had been treated with deferasirox 33 mg/kg daily to manage elevated plasma iron levels due to her thalassemia since the age of 2. Thalassemia is a genetic blood disorder in which the body makes an abnormal form of hemoglobin. The disorder results in large numbers of red blood cells being destroyed, which leads to anemia. To treat the anemia, patients receive regular blood transfusions and can develop an elevated iron level that requires treatment with a chelating agent such as deferasirox to remove the iron from the body.

The patient was admitted to the hospital multiple times over a few months for serious metabolic abnormalities. Her symptoms were fever, vomiting, metabolic acidosis, increased azotemia, and dehydration. Her aspartate aminotransferase (AST) was elevated at 472 U/L (normal range, 10-30 U/L) and her alanine aminotransferase (ALT) was elevated at 479 U/L (normal range, 10-40 U/L). She also experienced weight loss and behavioral changes. After 1 month, she was again admitted to the hospital with vomiting, stupor, lockjaw, and myoclonus. Her laboratory analysis revealed serial elevations of her ammonia level at 741 mcg/dL, 744 mcg/dL, and

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536 mcg/dL (normal range, 15-45 mcg/dL); hypoglycemia with a blood glucose of 36 mg/dL (normal range, 70-110 mg/dL); AST 42 U/L; ALT 148 U/L; alkaline phosphatase 396 U/L (normal range, 30-120 U/L); and an international normalized ratio (INR) of 1.36 (normal range, 1-1.3). Her deferasirox treatment was discontinued at that time. The patient was then transferred to the pediatric intensive care unit where her condition was complicated with metabolic acidosis, glucosuria, proteinuria, hemoglobinuria, ketonuria, and leukocyturia. The patient's metabolic acidosis persisted and was complicated by oligoanuria, which necessitated the initiation of continuous venovenous hemodialysis (CVVHD). The patient improved and was discharged after 2 weeks.

Marano et al noted that the use of deferasirox will achieve good iron balance when dosed at ≥ 30 mg/kg/day. However there have recently been reports of increased adverse events when a deferasirox dosage of 30 mg/kg/day is exceeded. The authors investigated a possible pharmacogenetic component of this adverse event for their patient. Marano et al point out that deferasirox is metabolized by uridine diphosphate glucuronosyltransferase (UGT) and eliminated into the bile through multidrug resistance protein 2 (MRP2) and breast cancer resistance protein (BCRP). Defective UGT1A1 alleles and polymorphisms of ABCC2 and ABCG2 coding for MRP2 and BCRP proteins may contribute to the adverse reaction.

The patient was tested and found to be a carrier of UGT1A1 and ABCC2 polymorphisms. These polymorphisms may explain the possible reduction in deferasirox metabolism with a reduction of biliary elimination by MRP2. The authors concluded that the reduced metabolism of deferasirox caused increased deferasirox plasma levels of 186 mg/mL (normal range, 0.16-40 mg/dL). The authors also assume this could have caused the patient's liver and kidney toxicity.

Marano M, Bottaro G, Goffredo B, et al. Deferasirox-induced serious adverse reaction in a pediatric patient: Pharmacokinetic and pharmacogenetic analysis. *Eur J Clin Pharmacol*. 2016;72:247-248.

BICALUTAMIDE-INDUCED HEART FAILURE

An 82-year-old male presented to the emergency department with a 2-week history of shortness of breath with exercise, orthopnea, weakness, and ankle swelling. Laboratory results revealed a B-type natriuretic peptide (BNP) of 3,820 ng/L (normal range, <100 ng/L) and a slightly elevated troponin

I. A chest x-ray revealed cardiomegaly suggestive of congestive heart failure. The patient then had an echocardiogram to evaluate his ejection fraction; it was found to be 18%. The patient was initiated on furosemide, bisoprolol, aspirin, and ramipril for management of his congestive heart failure. He was discharged and was referred to a consultant pharmacist for medication follow-up. The consultant pharmacist discovered that the patient had been receiving bicalutamide 50 mg daily and leuporelin every 4 months for the treatment of prostate cancer. A detailed medication history revealed the patient had received bicalutamide upon initial diagnosis with prostate cancer, however he discontinued it because it made him feel unwell. The patient was then restarted on bicalutamide, and he received it until his admission for congestive heart failure. As a result of this, the patient's bicalutamide was discontinued; however, 21 months later the patient still required heart failure medications and eventually expired due to prostate cancer.

The author reviewed the pharmacology and cardiovascular effects of bicalutamide, a nonsteroidal antiandrogen. He notes that cardiovascular adverse effects have been observed in clinical trials with bicalutamide; specifically, congestive heart failure was twice as likely in patients receiving bicalutamide in clinical trials. This adverse effect was not evaluated, and there were no reports of congestive heart failure during postmarketing surveillance. The author states for this patient, "Heart failure occurred after he commenced bicalutamide; this establishes a temporal relationship. The patient in this case had no previous symptoms suggestive of heart failure, and his cardiovascular health was maintained up until the drug was initiated."

The author evaluated the patient's adverse effect utilizing the Naranjo scale; it scored a 7/10, which indicates that bicalutamide was the probable cause of the patient's congestive heart failure. He also asserts that due to bicalutamide's effect on the androgen-androgen receptor system, it may negate the protective role the androgen-androgen receptor system has against angiotensin II-induced vascular remodeling. Vascular remodeling is an underlying mechanism in the vasodilatory failure that contributes significantly to left ventricular dysfunction. Therefore, bicalutamide does not simply increase the risk of cardiovascular disease due to hormonal changes, but it also seems to directly injure the cardiovascular system.

The author states, "Further studies are required to ascertain the underlying processes that mediate such

pathogenesis, but evidence thus far points to possible direct cardiotoxic effects. The risk of developing or exacerbating heart failure should be considered in patients on bicalutamide.”

Guirguis K. Bicalutamide causes heart failure in an elderly patient with prostate cancer. *Exp Opin Drug Safety*. 2016; 15(3):297-302.

COMBINATION IPILIMUMAB AND NIVOLUMAB–INDUCED LETHAL MYOCARDITIS

Johnson et al reported on 2 patients who received the combination therapy of ipilimumab (*Yervoy*) and nivolumab (*Opdivo*) for the treatment of metastatic melanoma and who both experienced deadly cardiotoxicity.

The first patient was a 65-year-old female who reported atypical chest pain, dyspnea, and fatigue 12 days after receiving her first doses of ipilimumab/nivolumab. Her lab data were remarkable for a markedly elevated creatine phosphokinase (CPK) of 17,720 U/L (normal range, 29-168 U/L), creatine kinase-myocardial band (CK-MB) >600 ng/mL (normal range, <5.99 ng/mL), and a troponin I level of 4.7 ng/mL that increased to 51.3 ng/mL (normal range, <0.03 ng/mL). The patient was diagnosed with myocarditis and myositis with rhabdomyolysis. She experienced a number of conduction defects culminating with complete heart block. She was treated with intravenous methylprednisolone 1 mg/kg daily for 24 hours and expired after clinical deterioration and multiorgan failure.

The second patient was a 63-year-old male who reported fatigue and myalgias 15 days after receiving his initial dose of ipilimumab/nivolumab. He had ST segment depression, a new ventricular conduction delay, and myocarditis. His troponin I was 47 ng/mL, CK-MB 451 ng/mL, and CPK level 20,270 U/L. He received methylprednisolone 1 mg/kg daily for 4 days and infliximab 5 mg/kg. The patient also developed complete heart block and received a temporary pacemaker. He subsequently had 2 cardiac arrests, after which supportive care was withdrawn and he expired.

Ipilimumab is a recombinant human IgG1 immunoglobulin monoclonal antibody that binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4). CTLA-4 is a down-regulator of T-cell activation pathways. Blocking CTLA-4 allows for enhanced T-cell activation and proliferation. In melanoma, ipilimumab may indirectly mediate T-cell immune responses against tumors. Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits

programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding. The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted. This releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Combining nivolumab (anti-PD-1) with ipilimumab (anti-CTLA-4) results in enhanced T-cell function that is greater than that of either antibody alone, resulting in improved antitumor responses in metastatic melanoma.

The authors sought to identify the pathology for the patients' conditions, and they performed gross and microscopic evaluations of both patients. Immunofluorescence studies were performed to identify the cell types in the infiltrates that were found in the myocardium, skeletal muscle, and tumors. Patient 1 revealed an intense, patchy lymphocytic infiltrate within the myocardium that also involved the cardiac sinus and atrioventricular nodes. Likewise, skeletal muscle showed lymphocytic destruction of isolated myocytes. Patient 2 showed similar T-cell and macrophage infiltrates in the myocardium, the cardiac conduction system, and skeletal muscle that were indicative of lymphocytic myocarditis and myositis. In both patients, immune infiltration was restricted to cardiac and skeletal muscle; no other tissues were affected, including adjacent smooth muscle.

Johnson et al proposed 3 possible mechanisms for the adverse effects experienced by these patients: “T cells could be targeting an antigen shared by the tumor, skeletal muscle, and the heart, or the same T-cell receptor may be targeting a tumor antigen and a different but homologous muscle antigen. Alternatively, it is possible that clonal, high-frequency, T-cell-receptor sequences across tumor and muscle samples are misleading and that distinct T-cell receptors are targeting dissimilar antigens.”

The authors highlight that although myocarditis is rare, occurring in less than 1% of patients, myocarditis is more frequent and severe with the combination of ipilimumab and nivolumab than with nivolumab monotherapy. The authors warn that clinicians should be vigilant for immune-mediated myocarditis, particularly because of its early onset, nonspecific symptomatology, and fulminant progression.

Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375(18):1749-1755.

POLYMYXIN B-TRIMETHOPRIM EYE DROP-INDUCED ANAPHYLAXIS

A 2-year-old male was brought to the emergency department with severe eye swelling and erythema of the cheeks. His symptoms worsened to lip swelling and pulmonary symptoms including stridor while at rest. It was reported that the patient's symptoms began immediately after the first administration of polymyxin B-trimethoprim eye drops (*Polytrim*) for the treatment of his bacterial conjunctivitis. A medication history revealed that the patient had an episode of bacterial conjunctivitis 5 months earlier and received polymyxin B-trimethoprim drops without incident.

The patient's anaphylactic reaction was treated with intramuscular epinephrine, nebulized racemic epinephrine, and methylprednisolone. He was admitted to the hospital for observation, and his symptoms slowly resolved after 24 hours with continued corticosteroid and antihistamine therapy. The patient's medical history was negative for prior allergic reactions or atopic dermatitis.

The patient was allergy tested 3 months after his anaphylactic reaction. He underwent a skin prick test for each of the components of the eye drop he had received, trimethoprim and polymyxin-B. The patient tested positive to polymyxin-B but negative to trimethoprim. Henao and Ghaffari concluded that the patient's reaction was consistent with an IgE-mediated hypersensitivity to polymyxin-B. They theorize that the patient was sensitized to polymyxin-B when he had received his first prescription for the eye drops. The authors state, "Although the eye is considered an immune privileged site as a result of poorly understood mechanisms that limit immune response within the eye to preserve vision, in this case the eye drops may have caused a systemic reaction by coming in contact with oral and nasal mucosa." The authors recommended that the patient avoid all polymyxin-containing products such as over-the-counter antibacterial creams and ointments and certain vaccines including inactivated polio vaccine and certain brands of influenza vaccine. The authors warn that even though systemic allergic reactions to eye drops are expected to be rare, health care professionals should be aware of the potential for anaphylaxis after ocular administration of an antibiotic eye drop.

Henao MP, Ghaffari G. Anaphylaxis to polymyxin B-trimethoprim eye drops. *Ann Allergy Asthma Immunol.* 2016; 116:366-379.

METHYLPHENIDATE-INDUCED DIFFUSE MACULOPAPULAR RASH

An 11-year-old male with no known drug allergies experienced a few episodes of skin eruptions possibly related to food. He also experienced several episodes of itching and mild and local skin eruptions on his arms and chest. These episodes were considered psychological by his dermatologist and pediatrician due to his history of social and generalized anxiety. The patient was initiated on sertraline 25 mg daily for his anxiety; he received this dosage for 3 months without any significant side effects. His sertraline dosage was subsequently increased to 50 mg daily, and it was tolerated well by the patient except for itching and mild skin eruptions on his arms and upper chest. His sertraline was discontinued at this time. For the next month, the patient did not experience skin eruptions.

It was reported that the patient was having trouble in school mainly related to attention issues. The patient's most recent episode of itching and mild local skin eruptions was considered to be stress related. Therefore sertraline 50 mg daily was restarted and methylphenidate 27 mg daily was also initiated for his attention deficit disorder. Over the next 4 months, the patient's anxiety and attention problems had moderate improvement and he did not experience any significant adverse effects. His methylphenidate dosage was increased to 54 mg daily. After 1 week at this new dosage, the patient developed a nonpruritic maculopapular skin rash on his face and chest and then the rash spread all over his body within 1 day. The patient's sertraline and methylphenidate were discontinued at this time. The patient's rash was treated with a short-term antihistamine and steroid and resolved within 10 days.

Kaya and Coskun conducted a literature search to investigate the types of skin eruptions that have been reported with the use of methylphenidate. They note that case reports have included pruritic maculopapular, pruritic raised edematous circular shaped, fixed drug eruption, exanthematous pustulosis, and exfoliative dermatitis. By comparison, their patient developed a nonpruritic diffuse rash that included the face, neck, trunk, back, arms, and legs. The authors also completed a Naranjo scale to assess the probability that methylphenidate caused the rash; the case scored a 7 out of 10, which indicates probable causality. During the course of their literature search, they uncovered one case report (Coskun et al) that

noted a patient who did not experience a skin rash with immediate release methylphenidate, however the patient experienced a rash with an extended-release formulation. The extended-release formulation was an osmotic controlled release oral delivery system (OROS) formulation, such as the one utilized by Concerta. They note that the OROS formulation contains more than 10 excipients that are not present

in the immediate release formulation, and these may be the cause of the adverse reaction.

Coskun M, Tutkunkardas MD, Zoroglu S. OROS methylphenidate-induced skin eruptions. *J Child Adolesc Psychopharmacol.* 2009;19:593-594.

Kaya I, Coskun M. Diffuse maculopapular rash with increasing dosage of methylphenidate. *J Clin Psychopharmacol.* 2016;36(1):106-107. ■