ISMP Adverse Drug Reactions

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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.

AMIODARONE-INDUCED TOXIC EPIDERMAL NECROLYSIS

A 74-year-old woman received amiodarone (*Cordarone*) for atrial fibrillation and a rapid ventricular response. Within 72 hours of initiation, the patient developed a diffuse, desquamative rash involving her trunk, limbs, and face, but her mucous membranes were spared. A skin biopsy revealed liquefaction in the basal layer of the epidermis and necrotic keratinocytes, predominantly in the basal layer. Bullous formation was noted, as was a mild inflammatory infiltrate consisting mainly of lymphocytes with occasional neutrophils.

The patient was evaluated by a dermatologist and was observed to have large contiguous patches of epidermal sloughing. The extensive nature of skin involvement favored the more severe diagnosis of toxic epidermal necrolysis; she had contiguous skin lesions over more than 30% of her body. However, the patient did not experience any of the systemic symptoms often associated with toxic epidermal necrolysis, including fever, dysphagia, or lymphadenopathy.

Toxic epidermal necrolysis is a rare but potentially fatal acute epidermolytic dermatopathy. The general consensus is that toxic epidermal necrolysis is related to Stevens-Johnson syndrome but is more severe.

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Mortality associated with toxic epidermal necrolysis is mainly attributed to sepsis and multiorgan system failure. Other conditions that may arise are hypovolemic shock, gastrointestinal hemorrhage, and respiratory failure. The average mortality rate for toxic epidermal necrolysis is 25% to 35%.

Most cases of toxic epidermal necrolysis are related to drug ingestion and typically occur 1 to 3 weeks after initial use of the offending medication. Medications that have been associated with toxic epidermal necrolysis are sulfonamides, antiepileptic drugs, allopurinol, tetracyclines, chemotherapy agents, and nonsteroidal anti-inflammatory agents.

Upon review of the patient's medications, amiodarone was thought to be the cause of the patient's condition. Amiodarone was discontinued, and the patient was transferred to a burn intensive care unit for precautionary measures. The patient remained hemodynamically stable, and her skin lesions improved with supportive care. The patient was discharged in good condition with resolution of her rash and no further recurrences.

Chen A, Sauer W, Nguyen DT. A dire reaction: Rash after amiodarone administration. *Am J Med.* 2013;126(4):301-303.

NILOTINIB-ASSOCIATED CEREBROVASCULAR DISEASE AND STROKE

In November 2012, a 70-year-old female with a past medical history of chronic myelogenous leukemia (CML) experienced acute onset left-sided weakness and dysarthria. Before her CML diagnosis in 1996, she had no history of vascular disease. Her prior treatment included interferon-alpha and low-dose cytarabine followed by imatinib in 2000. After dendritic cell vaccine therapy was unsuccessful, tipifarnib was added in 2004. Due to lack of response and progressive disease, she was switched to nilotinib (*Tasigna*) in 2004 with complete cytogenetic remission.

The patient developed symptoms attributable to progressive peripheral arterial disease (PAD) in 2007. Coronary artery disease was diagnosed in 2008, and she underwent percutaneous transluminal coronary angioplasty (PTCA) and stenting followed by 4-vessel coronary artery bypass grafting. In 2008, there was a strong suspicion that her progressive atheromatous disease was attributable to nilotinib, however the decision was made to continue nilotinib in the context of imatinib-refractory CML. With continued therapy, recurrent claudication symptoms occurred in 2010, and she had a superficial femoral to below-knee popliteal artery bypass. The patient also developed renal artery and mesenteric artery stenosis.

During the patient's nilotinib treatment, she was diagnosed with hypertension, hyperlipidemia, and prediabetes, which were controlled via medication. Her medication regimen included aspirin, clopidogrel, and warfarin.

In 2011, the patient experienced 2 episodes of confusion. Magnetic resonance angiography (MRA) showed multifocal narrowing involving both middle cerebral arteries (MCA) and posterior cerebral artery. There was a 50% to 60% narrowing of the right internal carotid artery (ICA). In November 2012, an MRI showed right MCA distribution ischemic stroke. MRA showed diffuse intracranial atherosclerosis and high-grade stenosis of the extracranial right ICA. The risk of surgical or endovascular carotid intervention was deemed too high due to the diffuse intracranial disease. The patient was maintained on dual antiplatelet therapy and anticoagulation.

Nilotinib has been shown to be superior to imatinib for the treatment of CML; however, follow-up was limited to 24 months. Rapidly progressive PAD has been described as a side effect of nilotinib therapy, however cerebrovascular involvement and stroke have not been previously described. The authors suggest that clinicians should be aware of this serious complication with prolonged therapy.

Coon EA, Zalewski NL, Horrman EM, et al. Nilotinib treatment-associated cerebrovascular disease and stroke. *Am J Hematol.* 2013;88(6):534-535.

PISA SYNDROME CAUSED BY PALIPERIDONE

Pisa syndrome (pleurothotonus) is a condition in which there is sustained involuntary flexion of the body and head to one side and slight rotation of the trunk so the person appears to lean like the Leaning Tower of Pisa. This rare adverse effect is associated with prolonged exposure to antipsychotic medications. Conventional antipsychotic agents have been implicated with Pisa syndrome, and atypical antipsychotics have been reported to be associated with this adverse effect.

A 42-year-old male had been diagnosed with schizophrenia for approximately 10 years. He had received a number of different antipsychotic drugs (flupentixol, sulpiride, and risperidone) to treat his condition without reports of obvious extrapyramidal syndrome. The patient was then placed on quetiapine titrated up to 400 mg daily with limited efficacy. One year later, he was readmitted to the hospital and was found to have been receiving risperidone 4 mg daily, which was prescribed from another practitioner. The patient exhibited central obesity and had hyperlipidemia.

Although the patient's positive symptoms improved, he still had obvious negative symptoms and metabolic syndrome. The patient was then switched to aripiprazole titrated to 30 mg daily for 9 months. The patient exhibited psychotic symptoms, vivid delusions, and auditory hallucinations, and mild hepatic function impairment was noted. Aripiprazole was replaced with paliperidone (*Invega*) extended release 3 mg daily for 2 months, which was increased to 9 mg daily within 3 days of exacerbation of his positive symptoms.

After 1 month of treatment with paliperidone, the patient exhibited a walking tilt toward his right side. Physical examination revealed tonic flexion of the spine toward the right, along with a slightly backward axial rotation. The patient had no family history of dystonia or secondary dystonia resulting from metabolic disorders or organic disorders. Based on these observations, paliperidone was discontinued and replaced with olanzapine 10 mg daily.

Throughout the course, the patient's concomitant medications included trihexyphenidyl, clonazepam, and estazolam. Without increasing the dosage of antiparkinsonism agents, the Pisa syndrome gradually subsided after 2 weeks of olanzapine treatment. Three months after discontinuation of paliperidone and continued olanzapine treatment, there was no recurrence of Pisa syndrome.

Pisa syndrome has occurred in patients mostly after prolonged treatment with stable doses of antipsychotic agents or after changes in antipsychotic therapy. The pathophysiology of Pisa syndrome is not well understood; it has been suggested that dopaminergic-cholinergic imbalance or serotonergic or noradrenergic dysfunction may be implicated. Approximately 40% of patients with Pisa syndrome are therapeutically responsive to anticholinergics, and a reduction in dose or discontinuation of the offending antipsychotic agent remains the first-line treatment option.

Teng PRT, Lai TJ. Paliperidone-related Pisa syndrome. *J Clin Psychopharm.* 2013;33(1):129-130.

MACROGLOSSIA ASSOCIATED WITH METHYLPREDNISOLONE

A 35-year-old female with a past medical history of myasthenia gravis and a gastric follicular dendritic sarcoma was admitted to the hospital for difficulty clearing secretions and slurred speech. Prior to admission, the patient was receiving prednisone 40 mg every other day in addition to pyridostigmine, mycophenolate mofetil, levonorgestrel/ethinyl estradiol, and omeprazole. The patient was intubated, and

myasthenic crisis was suspected. The patient received one dose of intravenous (IV) methylprednisolone sodium succinate 30 mg (*Solu-Medrol*), and plasmapheresis was initiated. The patient then received methylprednisolone sodium succinate 250 mg IV every 6 hours, pyridostigmine bromide 2 mg IV every 3 hours, and mycophenolate mofetil 1,000 mg by feeding tube every 12 hours. Other drugs administered on day 1 were heparin, propofol, famotidine, fentanyl, and inhaled albuterol.

On day 2 of her hospital stay, the patient developed macroglossia (enlarged tongue) that significantly impaired her ability to close her mouth by day 3. During this time, diphenhydramine 25 mg every 6 hours via feeding tube was initiated and methylprednisolone was continued. On day 5, the patient's steroid therapy was switched to prednisone 50 mg daily administered by feeding tube. By hospital day 7, the patient's tongue swelling was improved; by day 10, the tongue edema was resolved completely, which allowed the patient to be extubated. Shortly after the patient was extubated, she developed shortness of breath and stridor due to vocal cord edema and required reintubation. The patient then had a tracheotomy on hospital day 12 and was weaned off mechanical ventilation by day 15. She was eventually discharged on hospital day 28 and continued on prednisone 50 mg daily by mouth.

The authors give an excellent overview of steroid-induced hypersensitivity reactions and possible mechanisms. The authors point out that the frequency of hypersensitivity reactions is likely underestimated, as corticosteroids are used for their anti-inflammatory and immunomodulatory effects. It is imperative to recognize the manifestations of these hypersensitivity reactions, because they can rapidly evolve into life-threatening situations. Based on the fact that the patient tolerated oral prednisone, the authors conclude that the hypersensitivity reaction was likely due to the succinate ester present in the IV methylprednisolone formulation.

Igneri LA, Czosnowski QA, Whitman CB. Methylprednisolone sodium succinate – associated macroglossia in a critically ill patient. *Pharmacotherapy.* 2013;33(2):e14-e18.

AROMATASE INHIBITOR-INDUCED "MALE PATTERN BALDNESS" IN WOMEN?

The authors studied 15 menopausal women with hormone receptor-positive breast cancer who were between the ages of 50 and 65 and were receiving the aromatase inhibitors anastrozole (*Arimidex*) or letrozole (*Femara*). The authors state that female androgenic

alopecia (FAGA) is a common and distressing cause of hair loss caused when dihydrotestosterone (DHT) binds to androgen receptors, leading to miniaturization of scalp hair follicles in genetically susceptible women. FAGA is characterized by a specific diffuse loss of hair of the parietal or frontovertical regions (“in the crown”) where 5- α reductase is expressed and maintains the frontal hairline. Aromatase is also localized in the frontal and occipital hair follicles, with higher levels in women as compared to men.

The authors observed the 15 patients after 12 and 24 months of aromatase inhibitor therapy. The patients demonstrated recession of frontal and parietal hairlines, mimicking a typically FAGA with male patterns; this is not a “real” FAGA, but is an alopecia induced by the aromatase inhibitors.

Aromatase inhibitors block the synthesis of estrogens and induce a relative enhancement in the activity of 5- α reductase. This enhancement leads to a relative increase in the amount of testosterone available for conversion to DHT, causing a male pattern hair loss that mimicks FAGA and can be called “pseudo male pattern androgenetic alopecia.” The authors state that more study on this topic is necessary, but a clear relationship with aromatase inhibitor use cannot be excluded.

Rossi A, Iorio A, Scali E. et al. Aromatase inhibitors induce “male pattern baldness” in women? *Ann Oncol.* 2013;24:1710-1713.

ACUTE LIVER FAILURE DUE TO ETODOLAC

A 73-year-old female with a history of arthritis was admitted to the hospital with a 2-week history of worsening jaundice, malaise, and nonspecific abdominal pain. Etodolac (*Lodine*) 600 mg twice daily, her only medication, had been initiated 6 months prior to her admission and had been stopped 1 week prior to admission on the advice of her local medical doctor. The patient had no additional risk factors for liver disease, transfusion history, contact history, or travel history. The patient denied the use of any additional medications, herbal remedies, or over-the-counter medications. Multiple records of the patient’s

liver function tests prior to admission revealed no abnormality.

The patient presented with severe jaundice and the following abnormal laboratory findings: bilirubin 525 $\mu\text{mol/L}$ (reference range, $<21 \mu\text{mol/L}$), alanine aminotransferase (ALT) 1,400 IU/L (reference range, 5-38 IU/L), alkaline phosphatase (ALP) 274 IU/L (reference range, 25-140 IU/L), and prothrombin time 16.7 seconds (reference range, 9.8-12.6 seconds). Early in her admission, the patient developed grade II encephalopathy. Acute (IgM) serologies for hepatitis A, B, E, cytomegalovirus, Epstein-Barr virus, and toxoplasma were negative. Hepatitis C and E RNA polymerase chain reactions (PCR) were also negative. Percutaneous liver biopsy revealed findings compatible with drug-induced liver injury.

The patient had a spontaneous clinical recovery. Her liver function returned entirely to normal within 3 months of drug cessation and has remained stable for 2 years since the incident. The authors theorize that the mechanism of etodolac-induced hepatotoxicity remains unclear. Etodolac is a weak inhibitor of the cytochrome P450 system, targeting CYP2C9. Extensive hepatocellular damage resulting in acute liver failure is not theoretically likely on the basis of this interaction. In this case, liver injury developed as a delayed event, 180 days after initiation of etodolac therapy. The timing of the presentation and the absence of rash or eosinophilia mean that a hypersensitivity reaction is unlikely.

The authors conclude that the presentation of acute liver failure is a rare but potentially life-threatening complication of etodolac. The presentation may be delayed, in this case developing 6 months after the onset of treatment. The authors propose regular monitoring of liver function in all patients receiving etodolac, starting within 1 month after initiation of the drug and continuing at extending intervals over a year, to facilitate early identification of adverse hepatic effects.

Sampaziotis F, Brais RJ, Griffiths WJH. A case of acute liver failure due to etodolac. *Br J Clin Pharmacol.* 2013;75(4):1156-1157. ■