ISMP Adverse Drug Reactions

Life-Threatening Hypocalcemia With Denosumab

Anaphylaxis in Two Children Receiving Etanercept

Fondaparinux Hepatotoxicity in a 6-Year-Old Child

Bullous Pemphigoid Induced by Dipeptidyl Peptidase-4 Inhibitors

Severe Neuroleptic Malignant Syndrome With Deep Coma Associated With Aripiprazole

Quetiapine-Induced Tardive Oculogyric Crisis

*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.

LIFE-THREATENING HYPOCALCEMIA WITH DENOSUMAB

A 61-year-old Caucasian female presented with involuntary shaking of the extremities resulting in a fall. The patient also had watery diarrhea 3 days prior. The patient had been diagnosed with stage IV infiltrating ductal carcinoma of the left breast 1.5 years earlier, which progressed to bone metastases 2 months prior to admission. She was to begin receiving a monthly denosumab (*Prolia*, *Xgeva*) regimen and had received her first dose of denosumab 120 mg 1 month

prior to admission. The patient also had a history of diabetic nephropathy with stage 3 chronic kidney disease (CKD). The patient's laboratory data prior to her first dose of denosumab were a blood urea nitrogen (BUN) of 28 mg/dL (reference range, 7-20 mg/dL), creatinine 1.6 mg/dL (reference range [female], 0.6-1.2 mg/dL), ionized calcium 4.9 mg/dL (reference range, 4.4-5.4 mg/dL), phosphorus 4.5 mg/dL (reference range, 2.4-4.1 mg/dL), and parathyroid hormone (PTH) 520 pg/mL (reference range, 10-55 pg/mL). Her current medications included amlodipine, aspirin,

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

levothyroxine, metoprolol, calcium carbonate, calcitriol, anastrozole, glipizide, and atorvastatin.

The patient's pertinent admission labs were ionized calcium 2.3 mg/dL, creatinine 3.3 mg/dL, phosphorus 5.4 mg/dL, and PTH 778 pg/mL and an EKG demonstrating a prolonged QT interval of 520 ms. She was treated for prerenal acute kidney injury with aggressive fluid replacement and intravenous calcium carbonate. With treatment, her creatinine decreased to 1.7 mg/dL and her ionized calcium increased to 4.3 mg/dL after 4 days of hospitalization.

Denosumab is a human monoclonal antibody that inhibits the receptor activator of nuclear factor kappa ligand (RANKL). Hypocalcemia is a known adverse effect of denosumab, however it is mild and transient and generally occurs in patients with severe CKD or end-stage renal disease. In clinical trials, hypocalcemia was not observed in patients receiving denosumab for osteoporosis, but it did occur in patients receiving denosumab for bone metastases. The incidence of hypocalcemia observed with denosumab ranges from 5.5% to 13%.

The authors hypothesize that patients with CKD are at higher risk for developing hypocalcemia, because patients with CKD are more dependent on PTH-mediated bone turnover and inhibition of osteoclastic activity that results in a "hungry bone-like syndrome." The authors state that the product monograph does not warn of a dosage adjustment in patients with moderate renal dysfunction. Because their patient had moderate CKD and experienced potentially life-threatening hypocalcemia, it would be prudent to be aware of this serious adverse effect.

Ungprasert P, Cheungpasitporn W, Srivali N, et al. Life-threatening hypocalcemia associated with denosumab in a patient with moderate renal insufficiency. *Am J Emerg Med.* 2013;31:756e1-756e2.

ANAPHYLAXIS IN TWO CHILDREN RECEIVING ETANERCEPT

A 10-year-old Caucasian boy with juvenile idiopathic arthritis (JIA) had received weekly methotrexate (MTX) 17.5 mg subcutaneous (SQ) injections for 4 years before adding etanercept (*Enbrel*) 25 mg SQ weekly. Immediately following administration of the fifth dose of etanercept, the patient experienced itching and mild periorbital swelling. The next day, the patient experienced rash, nausea, and difficulty breathing. The patient responded to 2 doses of epinephrine, prednisolone, diphenhydramine, and ranitidine. Etanercept was discontinued, and adalimumab

(*Humira*) 40 mg SQ every other week was initiated. The patient has received this regimen for the past 2.5 years with no reported adverse events.

In the second case, a 15-year-old Caucasian girl with JIA was started on etanercept 20 mg SQ twice weekly. Within minutes after receiving her third injection of etanercept, she developed a generalized urticarial rash and dyspnea that responded to antihistamines and prednisone. Her etanercept was discontinued, and adalimumab 20 mg SQ every other week was initiated. The patient has received this regimen for the last 1.5 years without incident.

Anti-tumor necrosis factor alpha (TNF α) drugs are considered highly effective and remarkably safe for children with JIA. Anti-TNF α drugs are divided into 2 types: monoclonal antibodies to TNF α (infliximab and adalimumab), and a fusion protein containing a TNF receptor (etanercept). A small number of adults have experienced an anaphylactic reaction with etanercept monotherapy and some have received etanercept and MTX. It is hypothesized that the combination of etanercept and MTX can provoke an asthma-like anaphylactic reaction.

The authors suggest that these cases highlight the importance of discussing this potential adverse effect with parents and their families. Both children had allergic reactions between the third to fifth dose of etanercept, which suggests that allergic reactions may occur early in therapy. The authors suggest that it should be considered whether to provide self-administered epinephrine (*EpiPen*) to all children treated with etanercept, especially in those patients who have had severe allergic reactions to other medications. Both patients responded well to adalimumab without incident after etanercept was discontinued.

Crayne CB, Gerhold K, Cron RQ. Anaphylaxis to etanercept in two children with juvenile idiopathic arthritis. *J Clin Rheumatol.* 2013;19(3):129-131.

FONDAPARINUX HEPATOTOXICITY IN A 6-YEAR-OLD CHILD

A 6-year-old child with a left-sided axillary venolymphatic malformation diagnosed at 9 days of life had been receiving the low-molecular-weight heparin enoxaparin (*Lovenox*) 100 IU/kg/day. The child was receiving enoxaparin for persistent pain in the left upper limb probably related to a thrombosis due to the veno-lymphatic malformation. Over time, the dose of enoxaparin was gradually increased to 200 IU/kg/day, because of increased pain intensity and enlargement of the veno-lymphatic malformation. Three days after the last increase in dose of enoxaparin,

a clinical examination uncovered a growth of the left axillary tumor and occurrence of a superficial tuberous angioma. Because of the pain recurrence in the face of the increased dosage, enoxaparin was replaced with fondaparinux 2 mg daily.

Thirty hours after the initiation of fondaparinux, the child began to complain of nausea and vomiting. Severe toxic cytolytic hepatitis was evidenced with a 15-fold increase in alanine and aspartate aminotransferases (ALT 509 and AST = 720 IU/L; reference range, 5-40 IU/L) and a 5-fold increase in glutamyl transpeptidase (GGT 161 IU/L; reference range, <35 IU/L), and alkaline phosphatase (ALP 278; reference range, 100-400 IU/L). Tests for hepatitis A, B, and C as well as other possible viral etiologies were negative. Fondaparinux was immediately discontinued, and enoxaparin was reintroduced without incident. Clinical and laboratory signs of liver injury resolved over the next 5 days with a return to baseline levels of AST and ALT.

The authors stated that the mechanism of fondaparinux-related hepatotoxicity is unclear, but it may not be related to the drug metabolites because in physiologic conditions, fondaparinux does not undergo hepatic metabolism and is recovered in the urine unchanged. In their case, the authors surmise that inflammatory mediators may have contributed to sensitize hepatocytes to injurious effects of an unknown compound. Finally the authors state that monitoring of liver function tests might be useful especially in the initial days after fondaparinux initiation, because clinical experience with fondaparinux is limited in children.

Orostequi L, Medejel N, Kone-Paut I, et al. Fondaparinux (Arixtra) hepatotoxicity in a 6-year-old child. *J Hepatol*. 2013;58(1):195-198.

BULLOUS PEMPHIGOID INDUCED BY DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Bullous pemphigoid (BP) is a skin disorder characterized by large blisters; in severe cases, there are multiple blisters called *bullae*. The blisters may break open and form ulcers or open sores. The blisters are usually located on the arms, legs, or middle of the body, with about one-third of persons with bullous pemphigoid developing blisters in the mouth.

In France, a 61-year-old man with type II diabetes and hyperlipidemia presented to his local hospital with a 2-month history of pruritus and a 3-week history of tense bullae. On physical exam, it was noted that the patient had 450 bullous hemorrhagic lesions on his trunk and limbs with no mucosal involvement. The patient stated that the pruritus developed 5 months

after starting vildagliptin and metformin (*Eucreas*) and ezetimibe. Complete immunofluorescence and antibody analyses were completed and the diagnosis of BP was confirmed. Vildagliptin was stopped 2 weeks after the first bullous lesion appeared. Only 1 week after vildagliptin was discontinued and only 4 days after the initiation of topical corticosteroids, the patient had no active lesions.

The authors stated that only 7 cases of vildagliptin-induced BP and 1 case of sitagliptin-induced BP have been reported in the literature. This case is important because of the temporal relationship between the start of vildagliptin and initiation of BP and as the striking improvement after vildagliptin was discontinued without using any systemic treatment.

Aouidad I, Fite C, Marinho E, et al. A case report of bullous pemphigoid induced by dipeptidyl peptidase-4 inhibitors. *JAMA Derm*. 2013;149(2):243-244.

SEVERE NEUROLEPTIC MALIGNANT SYNDROME WITH DEEP COMA ASSOCIATED WITH ARIPIPRAZOLE

A 15-year-old who had a 1-year history of altered impulsive, disorganized, and bizarre behavior was initiated on aripiprazole (*Abilify*) 2.5 mg daily as monotherapy and titrated carefully to 20 mg daily over a 4-week period. Three weeks after reaching his 20 mg daily dose, the patient developed mild symptoms of the flu with a temperature of 36.7°C to 38.5°C (98.1°F to 101.3°F). At this time, aripiprazole was not discontinued because the patient did not exhibit symptoms of neuroleptic malignant syndrome (NMS). Four days later, the patient complained of nausea and vomiting; 3 hours later, he became unresponsive and lost consciousness. He had strong muscle spasms and extension of all the limbs with simultaneous deviation of the head and eyes to the left and was biting his tongue. The patient was suspected to have status epilepticus, however his EEG examination showed no epileptic activity. A cerebrospinal fluid sample was also obtained and did not indicate an active central nervous system infection.

While the patient was comatose, he was unresponsive to pain or any other stimuli. The patient then exhibited significant EPS symptoms including muscle rigidity, spasms, lockjaw, oculogyric crisis, hypersalivation, opisthotonus, and an irregular breathing pattern. Aripiprazole was discontinued, and bromocriptine 15 mg daily was initiated and titrated up to 30 mg daily over 3 days; bromocriptine was discontinued on day 7 due to adverse gastrointestinal effects. The patient remained in a coma and intubated for 5 days during which he fulfilled the criteria for

NMS: fever 39°C to 40°C (102.2°F to 104°F), not responding to cooling medication, rigidity, incontinence, tachycardia, labile blood pressure (SBP 130-200 mm Hg), leukocytosis, and an elevated creatinine kinase level of up to 1,700 U/L.

By the fifth day, the patient's consciousness improved followed by a fast recovery. Subsequent EEG showed extensive disturbances that normalized within 1.5 months. The patient also had an MRI result consistent with cytotoxic edema related to posterior reversible encephalopathy syndrome (PRES), which is a condition that has been associated with NMS in prior studies. The patient's MRI normalized within 1 month after recovery.

Three case reports of aripiprazole-induced NMS in adolescents have been published. The dosages of aripiprazole were between 5 and 15 mg daily, and NMS developed within 2 to 3 days after aripiprazole initiation. The authors point out that their case report was different than prior reports in that the patient was antipsychotic-naïve and the NMS did not manifest until 7 weeks after initiation of aripiprazole. The patient had a rapid onset of NMS and life-threatening symptoms leading to a deep coma and PRES changes on MRI. The authors also point out that the use of aripiprazole in children and adolescents should be further studied due to the risk of NMS in this population.

Riala K, Lahti A, Anttila E, et al. Aripiprazole-related severe neuroleptic malignant syndrome with deep coma and organic brain changes in an antipsychotic-naïve adolescent boy. *J Clin Psychopharmacol*. 2013;33(1):126-127.

QUETIAPINE-INDUCED TARDIVE OCULOGYRIC CRISIS

Oculogyric crisis (OGC) is a neurologic adverse effect of dopamine-blocking drugs characterized by spasmodic deviation of the eyes, mostly upwards; however, it is less frequently seen with atypical antipsychotics. OGC is considered a dystonic reaction but has never been reported with quetiapine (*Seroquel*).

An 18-year-old male who was diagnosed with paranoid schizophrenia was initially treated unsuccessfully with risperidone. Risperidone was discontinued, and quetiapine was gradually initiated and titrated up to a dose of 200 mg daily in 2 divided doses. The patient developed acute episodes of deviation of the eyes with the inability to look down or straight. These episodes lasted approximately 15 to 20 minutes and were diagnosed as OGC. The patient experienced no other involuntary movements or associated changes in psychiatric symptoms.

The patient presented to the emergency department during one of the episodes of OGC and was started on trihexyphenidyl 2 mg daily, which resolved the OGC symptoms. He was continued on quetiapine and trihexyphenidyl for 2 years and has had good symptom control and no recurrence of OGC.

The authors advise vigilance for the possibility that OGC may result from the use of relatively "safe" drugs such as quetiapine. If OGC does occur, it may respond to low doses of an anticholinergic agent such as trihexyphenidyl.

Ghosh S, Dhrubajyoti B, Bhattacharya A, et al. Tardive oculogyric crisis associated with quetiapine use. *J Clin Psychopharmacol*. 2013;33(2):266. ■