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.

TRANEXAMIC ACID-INDUCED TOXIC EPIDERMAL NECROLYSIS

A 67-year-old male with a history of cirrhosis due to alcohol abuse, esophageal varices, and multifactorial renal insufficiency was admitted to the hospital with significant rectal bleeding secondary to colopathy due to portal hypertension with thrombocytopenia, elevated creatinine, and anemia. The hemorrhoidal hemorrhagic point was treated with banding and suture, and the patient received a platelet transfusion and red blood cells. The patient was also initiated on tranexamic acid 1,000 mg every 8 hours. Two weeks later, the patient was transferred to a second hospital to be evaluated for possible liver transplantation. His tranexamic acid dosage was reduced to 1,000 mg every 12 hours based on his decreased renal function.

The patient was noted to have a purplish, erythematous macular rash over his trunk, which he stated had started 10 days after tranexamic acid was initiated. With the exception of tranexamic acid, no new medications were added to the patient's chronic medications, which included spironolactone, furosemide, omeprazole, lactulose, and bisoprolol. The patient had no history of tranexamic acid exposure and no drug allergy history. In 1 week's time, the erythematous lesions extended over the patient's face, trunk, and extremities and became confluent. The patient also exhibited blisters and epidermal necrosis as well as multiple mucosal surfaces including the mouth and genitalia. The patient's lips were covered with erosions and hemorrhagic crust with erosions in the oral mucosa.

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According to the National Cancer Institute Common Toxicity Criteria, the skin toxicity was grade IV (grade I, slightly toxic; grade V, most toxic). Results of a skin biopsy were comparable with toxic epidermal necrolysis (TEN). Treatment with tranexamic acid was stopped, and the patient received fluid replacement therapy, oral prednisone (0.4 mg/kg/day), and N-acetylcysteine 2 g every 6 hours based on the empiric diagnosis of TEN. Oral prednisone was administered for 10 days with gradual tapering for 2 weeks. The patient's skin and mucous lesions dried and epithelial tissue was restored. After 2 weeks, the patient developed severe hypotension with progressive deterioration of renal function and a respiratory infection. The patient eventually died secondary to acute renal failure and multiorgan failure.

The adverse reaction was probably caused by tranexamic acid as evidenced by the application of the Naranjo probability scale by the authors. Tranexamic acid is useful in a wide range of hemorrhagic conditions. Tranexamic acid exerts its antifibrinolytic effect by reversibly blocking lysine binding sites on plasminogen and thus preventing fibrin degradation. Although tranexamic acid is usually well tolerated and is considered a relatively safe drug at the doses generally utilized, its increased use has led to reports of anaphylactic shock, urticaria, and angioedema. The authors want to raise the awareness of clinicians of the potential for TEN due to tranexamic acid administration.

Irazabal MP, Martin LM, Gil LA, Gastearna MAI. Tranexamic acid-induced toxic epidermal necrolysis. *Ann Pharmacother*. 2013;47:e16.

HYPOGLYCEMIA CAUSED BY TRAMADOL

The authors investigated whether tramadol (*Ultram*) or codeine could be associated with the occurrence of hypoglycemia, and they compared this to the incidence of hypoglycemia induced by dextropropoxyphene (DXP). To date, only DXP has been clearly associated with the occurrence of hypoglycemia; there are no published case reports of codeine-induced hypoglycemia. There have been several reports of tramadol-induced hypoglycemia in the medical literature. The authors completed an analysis of reports of spontaneous hypoglycemia caused by tramadol, DXP, and codeine that were submitted to the French Pharmacovigilance Database (FPD) from 31 regional pharmacovigilance centers from January 1997 to November 2010.

The authors report that the FPD included 72 cases of hypoglycemia due to DXP, 43 cases of hypoglycemia due to tramadol, and only 1 case with codeine. They analyzed each of the case reports to determine the

underlying conditions or circumstances that could have led to the hypoglycemia. The patients who experienced hypoglycemia were generally elderly (70 ± 20 years of age). Hypoglycemia occurred after a median of 4 to 5 days after the initiation of DXP or tramadol treatment, with most cases observed within 10 days of treatment. The mean (SD) lowest serum glucose concentration was 38 (16) mg/dL in the TXP patients and 45 (18) mg/dL in the tramadol patients. Underlying diabetes was the most frequent risk factor in patients with hypoglycemia; renal insufficiency was also noted. Six patients in the DXP group and 2 patients from the tramadol group experienced recurring hypoglycemia after re-exposure to the same drug.

The mechanism by which tramadol causes hypoglycemia is still unknown, but there are at least 2 possible explanations. One theory is that a serotonergic-mediated mechanism is substantiated in an animal model showing that serotonin can increase insulin concentrations in mice. Hypoglycemia associated with selective serotonin reuptake inhibitor treatment has been reported, but the clinical evidence is limited to a small number of case reports. The second theory is that hypoglycemia may result from the activation of opioid μ -receptors by tramadol. Again, in an animal model, a dose-dependent lowering of plasma glucose concentrations shortly after tramadol administration was observed. The hypoglycemic effect of tramadol was blocked by pretreatment with an opioid μ -receptor antagonist such as naloxone.

The authors conclude that despite the limitations of their study due to probable underreporting and the lack of knowledge of the characteristics of the whole treated population, tramadol can be associated with hypoglycemia. Hypoglycemia was usually observed within the first 10 days of treatment, particularly in elderly patients and patients with renal insufficiency. Approximately half of the patients experiencing hypoglycemia experienced mild to severe symptoms. The incidence of hypoglycemia is similar to what was previously described with DXP. Clinicians should be aware of this potential adverse effect and patients should be warned, because this adverse effect is not mentioned in the summary of product characteristics.

Bourne C, Gouraud A, Daveluy A, et al. Tramadol and hypoglycaemia: Comparison with other step two analgesic drugs. *Br J Clin Pharmacol*. 2013;75(4):1063-1067.

NEUTROPENIA ASSOCIATED WITH PROLONGED DAPTOMYCIN USE

A 53-year-old woman with B-cell non-Hodgkin's lymphoma developed a methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia complicated by

MRSA septic arthritis during her chemotherapy. The patient did not have a significant clinical response after 11 weeks of vancomycin treatment, and she continued to have significant pain and erythremia. The patient achieved remission of her B-cell non-Hodgkin's lymphoma and completed her chemotherapy. She was then treated with daptomycin 6 mg/kg/day as an alternative to vancomycin therapy.

The patient's leukocyte count at the initiation of daptomycin was 5.6×10^3 cells/ μ L with an absolute neutrophil count (ANC) of 4.1×10^3 cells/ μ L. After 4 weeks of daptomycin treatment, the leukocyte count was 4.2×10^3 cells/ μ L with an ANC of 2.9×10^3 cells/ μ L; after 10 weeks of treatment, the leukocyte count had fallen to 1.6×10^3 cells/ μ L with an ANC of 0.8×10^3 cells/ μ L, and the patient's erythrocyte count and platelet count remained stable.

The patient's medication regimen during daptomycin therapy was metoprolol, nortriptyline, bupropion, lamotrigine, clonazepam, and pantoprazole. The patient had received this medication regimen prior to daptomycin administration and did not receive any additional prescription medications, over-the-counter medications, or herbal or natural products. The patient did not have evidence of a concomitant infection as a cause of her neutropenia nor did she show a relapse of her B-cell non-Hodgkin's lymphoma.

The patient's daptomycin was discontinued after 10 weeks of therapy, and the neutropenia resolved 1 week afterward. The patient's leukocyte count had increased to 5.0×10^3 cells/ μ L with an ANC of 3.4×10^3 cells/ μ L. Assessment of this adverse drug reaction with the Naranjo scale indicated a possible association with daptomycin and the patient's neutropenia.

The authors wanted to alert clinicians that the prolonged administration of daptomycin can cause neutropenia that is reversible upon daptomycin discontinuation. Although the authors did not offer a potential mechanism for the daptomycin-induced neutropenia, they warn that periodic hematologic monitoring should be performed in patients receiving daptomycin.

Knoll BM, Spieler PJ, Kubiak DW, et al. Neutropenia associated with prolonged daptomycin use. *CID*. 2013;56(1 May):1353-1354.

THROMBOTIC THROMBOCYTOPENIC PURPURA ASSOCIATED WITH INTRAVENOUS OPANA ER

The Centers for Disease Control and Prevention (CDC) reported on the intravenous use of the oral product *Opana ER* (oxymorphone HCl extended release). The CDC investigation began when a nephrologist reported 3 cases of unexplained thrombotic thrombocytopenic

purpura (TTP) to the Tennessee Department of Health (TDH). TTP is a rare but serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia. The 3 reported cases were all patients who were intravenous drug users who resided in Tennessee. The TDH conducted a statewide investigation to identify other cases of TTP-like illness that might be associated with injection drug use.

By the end of October 2012, a total of 15 cases of TTP had been reported with no fatalities. A case control study was conducted and the investigators determined that the cases were associated with dissolving and injecting tablets of *Opana ER* (Endo Pharmaceuticals), a recently reformulated extended-release form of oxymorphone that is only intended for oral administration. Known risk factors for TTP include infection, the Shiga toxin-producing *Escherichia coli* (STEC), and the use of drugs including platelet aggregation inhibitors, quinine, and cocaine.

Fourteen of the 15 patients reported injecting reformulated *Opana ER*. Seven of the 15 were treated for sepsis in addition to TTP-like illness. Twelve patients reported chronic hepatitis C or had positive test results for anti-HCV antibody. Of the 15 patients, 13 were women. All were White; none were pregnant. The 15 patients ranged in age from 22 to 49 years. Clinical characteristics were similar among the patients with and without infection. Patients reported symptoms typical of TTP-like illness, including nausea, abdominal pain, fatigue, and fever. Twelve of the patients were treated with plasmapheresis. The median admission platelet counts for patients without and with infection were 20,000/ μ L and 26,000/ μ L, respectively.

The new formulation of *Opana ER* contains inactive ingredients not found in the original formulation, including polyethylene oxide (PEO) and polyethylene glycol. It is unclear what component or components of reformulated *Opana ER* might trigger TTP-like illness when injected and whether different methods of preparing the drug for injection can increase or decrease the risk from injection.

The CDC recommends that health care providers who prescribe *Opana ER* and pharmacists who dispense it should inform patients of the risks from the drug when used other than as prescribed. Health care providers should ask patients with TTP-like illness of unknown etiology about any intravenous drug abuse. Suspected cases should be reported to public health officials.

Thrombotic thrombocytopenic purpura (TTP)-like illness associated with intravenous *Opana ER* abuse-Tennessee, 2012. *JAMA*. 2013;309(13):1338-1340.

Thrombotic thrombocytopenic purpura (TTP)-like illness associated with intravenous Opana ER abuse-Tennessee, 2012. *MMWR*. 2013;62(1):1-4.

BELL'S PALSY DUE TO VEMURAFENIB

A 63-year-old male had a large destructive lesion in the right calcaneus (heel) that was confirmed as metastatic melanoma. The patient had no previous melanoma history, and a primary melanoma could not be identified at the time of diagnosis. The patient's right foot was amputated for pain control, and palliative radiotherapy was administered to the axillary and femoral metastases. After 2 cycles of dacarbazine chemotherapy, there was progressive disease with a new left-sided rib metastasis. The patient was then initiated on a trial of vemurafenib (*Zelboraf*), which is a potent BRAF inhibitor.

After 8 weeks of therapy with vemurafenib, the patient developed an acute complete right-sided facial palsy, followed 10 days later by facial palsy on the left side of his face. A detailed clinical examination by a neurologist revealed no other neurologic deficits, and an MRI of the brain was unremarkable except for an enhancement of the right seventh cranial nerve in the facial canal. The patient's symptoms were indicative of idiopathic bilateral peripheral facial nerve palsy (Bell's palsy).

Vemurafenib was withheld from the patient; oral prednisone 50 mg daily was initiated and was tapered over a month. During this time, the neurologic deficits resolved completely. A CT scan performed after the resolution of the patient's symptoms revealed a complete remission of the metastatic melanoma without

any evidence of active disease. At this time, vemurafenib was recommended due to its success against the patient's metastatic myeloma. Vemurafenib prolongs overall survival in patients with BRAF V600 mutant melanoma.

The patient received his second course of vemurafenib for 3 months and experienced a sudden loss of vision as a result of an occlusion of the central retinal vein in his right eye. Treatment with vemurafenib was discontinued at this time. The patient had a follow-up CT scan 2 months later that confirmed a complete remission with complete resolution of the lymph node, mediastinal bone, and cardiac metastases. The patient has sustained an ongoing remission for 24 months without any additional systemic therapy.

The authors report that to date they have observed the development of facial palsies in 3 more patients receiving vemurafenib. The clinical assessment and investigations in the authors' patients did not identify known causes associated with facial palsy (ie, varicella zoster virus, reactivation of Lyme disease). This strongly implies that it was directly or indirectly a result of vemurafenib therapy.

The authors warn that clinicians should recognize peripheral facial palsy as an infrequent adverse effect of vemurafenib therapy. Facial palsy occurred 2 to 9 months after the initiation of vemurafenib, and treatment with oral glucocorticoids led to complete resolution of neurologic deficits in 2 of the patients.

Klein O, Ribas A, Chmielowski B, et al. Facial palsy as a side effect of vemurafenib treatment in patients with metastatic melanoma. *J Clin Oncol*. 2013;31(12):e215-e217. ■