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ISMP Adverse Drug Reactions

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Vemurafenib-Associated Pancreatitis

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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.

RASH ASSOCIATED WITH DABIGATRAN

A 59-year-old male was admitted to the hospital and diagnosed with new-onset atrial flutter 10 weeks following a successful bilateral lung transplant. The patient was discharged in normal sinus rhythm, but during cardiac rehabilitation the patient's atrial flutter returned. The patient was then started on dabigatran etexilate (*Pradaxa*) 150 mg twice daily for anticoagulation with an elective cardioversion to follow. For unknown reasons, the patient never initiated dabigatran therapy. The patient was hospitalized shortly thereafter with symptomatic heart failure; during the course of this hospital stay, dabigatran etexilate 150 mg twice daily was started. Five days later, the patient noticed a diffuse, nonpruritic rash on his trunk and lower extremities. The patient then self-discontinued dabigatran and refused the use of any products to relieve the rash.

Six days after discovery of the rash, the patient was readmitted with atrial flutter. On admission, the physician noted a maculopapular rash isolated only to the patient's trunk. Because the rash had improved without therapeutic intervention, no additional therapy for the rash was needed. The rash ultimately resolved 2 days after his recent hospitalization and 7 days after drug discontinuation.

The patient was receiving a number of chronic medications, but the only new medication initiated (other than dabigatran) was furosemide, which was initiated 2 weeks prior to discovery of the rash. The rash resolved, even though the patient continued to

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receive furosemide. The authors state that current product labeling for dabigatran indicates a frequency of 0.1% for rash, pruritus, and urticaria, with additional clinical trial data revealing the occurrence of cutaneous reactions but none with a frequency of greater than 0.03%.

The authors warn that although the incidence of rash is rare with dabigatran, practitioners and patients should be aware of the potential for rash as an adverse effect of dabigatran therapy.

To K, Reynolds C, Spinler SA. Rash associated with dabigatran etexilate. *Pharmacotherapy.* 2013;33(3):e23-e27.

SKIN NECROSIS INDUCED BY GENERIC ENOXAPARIN

Heparin-induced skin necrosis (HISN) is a rare complication of heparin or low-molecular-weight heparin (LMWH) therapy. Cases of HISN are generally associated with antibodies to the heparin:platelet factor 4 complex and/or heparin-induced thrombocytopenia (HIT). The authors cited a recent review that described 25 cases of skin necrosis associated with LMWH therapy through May 2009.[1] The authors report on 4 cases of HISN, all occurring at their institution since the formulary switch from enoxaparin (*Lovenox*) to generic enoxaparin manufactured by Sandoz.

The first case is a 67-year-old female who had been receiving *Lovenox* for over 3 weeks for treatment of a deep vein thrombosis (DVT). Within 24 hours of transitioning to generic enoxaparin, the patient developed HISN at the injection site with scarring persisting for 6 months. Her heparin-dependent antibody (HDA) test was negative. The second case is a 49-year-old male who developed HISN after the first 3 doses of generic enoxaparin. The patient had been exposed to unfractionated heparin in the past and his HDA assay was strongly positive, however the patient did not develop thrombocytopenia or thrombosis.

The third case is a 57-year-old female who was receiving postoperative prophylaxis with generic enoxaparin. On day 13 of prophylaxis, the patient developed 2 local skin necrosis reactions. The HDA assay was positive as was the serotonin release assay, however the patient did not develop thrombocytopenia or thrombosis. The fourth case is a 30-year-old woman who received generic enoxaparin for treatment of a proximal DVT. On day 3 of treatment, she developed inflamed injection site reactions that progressed to subsequent necrosis over several days; this led to hyperpigmented skin changes that persisted beyond 6 months. Her HDA assay was negative.

None of the patients developed thrombocytopenia, new thrombosis, or clinical HIT and only 2 of the 4 cases exhibited a positive HDA assay. In 2 cases, the skin necrosis developed outside the usual time frame of HIT of 5 to 15 days of exposure. The authors note that this fact suggests a novel mechanism of pathology. They include a brief discussion of the facts surrounding the approval of generic enoxaparin by the US Food and Drug Administration (FDA). The generic product was approved after only in vitro analysis, and immunogenicity studies were conducted in healthy volunteers with limited human clinical trial experience.

Gucalp A, Parameswaran R, Lacouture M, et al. Skin necrosis induced by generic enoxaparin. *Am J Hematol.* 2013;88(4):339.

SEROTONIN SYNDROME WITH CONCOMITANT USE OF TAPENTADOL AND VENLAFAXINE

A 39-year-old male was admitted to the hospital twice within 12 days for symptoms of total body tremors, anxiety, and excessive sedation. The total body tremors were not apparent seizures, and the patient remained conscious throughout these episodes. The patient did have a history of seizures as a child, but he could not recall many details of the experiences.

During the first admission, the patient complained of chills, diarrhea, and a severe headache. He had taken venlafaxine (*Effexor XR*) 75 mg daily for many years; his medication history also revealed zolpidem 10 mg as needed at bedtime, ranitidine 150 mg twice daily, and tapentadol ER (*Nucynta ER*) 100 mg twice daily. The patient had recently been switched from oxycodone/acetaminophen to tapentadol for the management of chronic back pain. During this first admission, tapentadol was discontinued and morphine sustained release 45 mg twice daily was initiated. An EKG, CT of the head, chest x-ray, and Cardiolite stress test were all normal. Urine and blood cultures were also negative. The patient was discharged 2 days after admission and was told to resume his previous home medications.

The second admission occurred 10 days later when the patient presented with the same symptoms of total body tremors, anxiety, and excessive sedation. A drug interaction between tapentadol and venlafaxine was suspected; both drugs were discontinued, and the patient was placed on morphine sustained release 30 mg twice daily for his back pain. The patient improved following discontinuation of both medications and was discharged 2 days later. He was discharged on morphine, which was then transitioned to 1 to 3 tablets per day of oxycodone/acetaminophen 5/325 and cyclobenzaprine 10 mg 3 times daily.

The authors conclude that this is a possible case of serotonin syndrome induced by the additive serotoninergic effects of tapentadol and venlafaxine. Tapentadol is a synthetic, centrally active analgesic, which is structurally

and pharmacologically related to tramadol. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake.[2]

Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs. Serotonergic drugs comprise selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, drugs that affect the serotonergic neurotransmitter system (eg, mirtazapine, trazodone, and tramadol), and drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]). Serotonin syndrome may occur within the recommended doses of these agents. It can include mental-status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) and can be fatal.[2]

The authors note that caution is advised when tapentadol is co-administered with other drugs that may affect serotonergic neurotransmitter systems such as SSRIs, SNRIs, MAOIs, and triptans. If concomitant treatment of tapentadol with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Case report submitted by: Lance E. Rhodes, PharmD, Director of Pharmacy, Garrett County Memorial Hospital, Oakland, Maryland, and David E. Cobb, PharmD Candidate, West Virginia University School of Pharmacy.

ETANERCEPT-INDUCED HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP) is a type of vasculitis that causes bleeding in the capillaries in skin, joints, intestines, and kidneys. The main symptom is a purplish rash, typically on the lower legs and buttocks. HSP often causes abdominal pain and aching joints and, in some patients, kidney manifestations.

A 61-year-old Caucasian male who had a history of ankylosing spondylitis (AS) with long-standing debilitating pain requiring significant opiate use, morning stiffness, and magnetic resonance evidence of active disease was treated with etanercept (*Enbrel*) 50 mg subcutaneously weekly. AS is a chronic inflammatory disease that primarily affects the axial skeleton. Extra-articular manifestations are less common but can typically involve the ascending aorta and aortic valve. AS is a disorder with an unclear etiology, however overexpression of tumor necrosis factor alpha is a feature.

After 5 months of treatment with etanercept, the patient reported improved AS symptoms. Four weeks prior to presentation, the patient noted a nonblanching rash affecting the lower extremities without other systemic symptoms. A serum creatinine (Cr) was 1.1 mg/dL (reference range, 0.6-1.2 mg/dL), but urinalysis was not performed at that time. The patient was treated with prednisone 20 mg daily for leukocytoclastic vasculitis (LCV) secondary to a drug reaction by the dermatology service, and etanercept was discontinued. A skin biopsy confirmed LCV with IgA and C3 predominance.

Four weeks later while still receiving prednisone 10 mg daily and colchicine without etanercept treatment, the patient presented to the hospital with worsening fatigue, new-onset peripheral synovitis, and petechiae involving both lower extremities up to his proximal thighs, lower abdomen, back, and hands. On exam, the patient was afebrile with normal vital signs. Extensive petechiae with coalescence and lower-extremity edema were present on dependent areas up to the lower abdomen and back. Lab data revealed a serum Cr 3.3 mg/dL that was elevated from 1.1 mg/dL 4 weeks prior. Complete blood count and liver function tests were within normal limits. Erythrocyte sedimentation rate was 69 mm/h (reference range, male < 17 mm/h) and C-reactive protein was 3.9 mg/dL (reference range, <10 mg/dL). Urinalysis showed proteinuria and microscopic red blood cells (31-60 per high-powered field). Serum IgA was 430 mg/dL (normal, 80-350 mg/dL), antinuclear antibody (ANA) 1:80, and antihistone antibody 6.3 U (normal ≤1 U).

A clinical diagnosis of HSP induced by etanercept was suspected, and the patient was treated with intravenous pulse methylprednisone 1 g/day for 3 days followed by prednisone 1 mg/kg daily. A renal biopsy performed on day 3 revealed diffuse mesangial proliferative glomerulonephritis with segmental membranoproliferative features. Treatment was continued with high-dose corticosteroids with tapering of prednisone 10 mg every 2 weeks to prednisone 0.5 mg/kg followed by a slower taper. After 7 months, the patient showed resolution of small joint synovitis and skin rash with normalization of his serum Cr to 1.2 mg/dL. He continued to have residual lower extremity edema. There has not been a recurrence of HSP since discontinuation of etanercept.

This case adds to the growing literature of TNF inhibitor (TNFi)–induced vasculitis and describes an uncommon case of TNFi-induced HSP in an AS patient. Although the development of HSP subsequent to TNFi

use in patients with rheumatic diseases other than SA has been reported, there is a paucity of information in SA patients. The authors call for more study to identify the risk factors for the development of HSP in patients with AS. Renal function and urinalysis should be assessed in patients being treated with TNFi who develop new synovitis or skin rash. Rechallenging patients with the same TNFi should be avoided since HSP may recur.

Rolle AS, Zimmerman B, Poon SH. Etanercept-induced Henoch-Schönlein purpura in a patient with ankylosing spondylitis. *J Clin Rheum*. 2013;19(2):90-93.

VEMURAFENIB-ASSOCIATED PANCREATITIS

Vemurafenib (*Zelboraf*) is a BRAF kinase inhibitor indicated in metastatic melanoma patients with BRAF V600E mutation. Vemurafenib has not been associated with pancreatitis to date.

A 49-year-old male with unresectable, stage IV melanoma was treated with first-line and investigational agents, but treatment was discontinued due to disease progression. The patient had a 4-month washout period since his last chemotherapy regimen, and it was determined that he was BRAF V600E mutation-positive. Treatment with vemurafenib was started at a dose of 960 mg orally twice daily. Two weeks after initiation, the patient presented to the emergency room with epigastric pain, elevated blood pressure, and a serum lipase of 1,544 units/L (reference range, <160 units/L). Common probable causes of pancreatitis were ruled out (gallstones, alcohol use, and infection), and the pancreatitis was attributed to vemurafenib therapy. The patient was also receiving lisinopril, metoprolol, opiates, prochlorperazine, senna, and docusate. Opiates and lisinopril can cause pancreatitis, but the patient's symptoms dissipated upon discontinuation of vemurafenib. Therefore due to temporal considerations, these drugs were excluded as possible causes.

Based on the severity of the patient's condition and the survival advantage provided by vemurafenib, a rechallenge was attempted. Vemurafenib was initiated at a lower dose of 480 mg twice daily, however the patient developed pancreatitis after 2 doses. Vemurafenib was discontinued, and the patient had a complete resolution of symptoms. The authors point out that in light of the temporal relationship and rechallenge with vemurafenib, the Naranjo Scale yielded a score of 9 indicating a definite probability that the patient's pancreatitis was caused by vemurafenib.

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(Continued from page 541)

labels that look alike when the same company manufactures both products.

FDA has asked manufacturers to use tall-man lettering on container labels and carton packaging (risperidone, ropinirole) to help distinguish between the 2 products. FDA has also asked the manufacturers to change individual labels and carton packaging to provide better visual differentiation between the generic products. When prescribing either drug nonelectronically, the drug name should be printed and the purpose of the drug should be included in the prescription. In pharmacies, the products should not be stored near each other, and tall-man letters should be used for storage, labeling, and computer listings.

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