ISMP Adverse Drug Reactions:

Influenza Vaccine–Induced Stevens-Johnson Syndrome

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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) 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.

Influenza Vaccine–Induced Stevens-Johnson Syndrome

A 75-year-old male in Japan reported erythematous papules 2 days after receiving his 2015 influenza injection. He reported he has received seasonal influenza vaccine every year since 2014. After receiving his 2016 influenza injection, he noticed erythema on his trunk and extremities 1 day after administration. Two days later, he developed lesions of the eye and oral mucosa. A medication history revealed that the patient does not receive any other medications, and an allergy history revealed the patient is not allergic to eggs. The patient had a low-grade fever of 37.7°C (99.9°F), and a skin biopsy of the lesions on his trunk revealed dyskeratotic keratinocytes in the epidermis and lymphocytic infiltration in the epidermis and dermis. Eosinophils also infiltrated the dermis. On physical exam, the patient had a positive Nikolsky sign. Nikolsky sign is present when slight rubbing of the skin results in exfoliation of the outermost layer. A typical example would be to place the eraser of a pencil on the roof of a lesion and spin the pencil in a rolling motion between the thumb and forefinger. If the lesion is opened (ie, skin sloughed off), then the Nikolsky sign is present/positive. Nikolsky sign is almost always present in Stevens-Johnson Syndrome/toxic epidermal necrolysis.

Detailed laboratory analysis ruled out herpes simplex virus, Epstein-Barr virus, and mycoplasma as possible infectious causes of the patient's condition. Stevens-Johnson syndrome was suspected due to the patient's influenza vaccination as he was not exposed to any other medications. He was

prescribed prednisone 30 mg daily, and the eruption resolved completely after 1 month of treatment.

The authors could not obtain the patient's consent for skin patch testing to confirm the allergy using influenza vaccine. However, he was able to perform patch testing using the additives in the vaccine, which included formalin and thimerosal. Results of the patch testing with these agents were negative. Therefore, the authors hypothesized that the patient developed Stevens-Johnson Syndrome due to the influenza vaccine itself. Since the patient first developed the skin eruption after the 2015 seasonal influenza vaccine injection, a common antigen in the 2014 and 2015 seasonal influenza vaccine could have been the causative agent. The authors speculated that a causative agent might have been A/California/7/2009(X-179A) (H1N1)pdm09, which was a common antigen in seasonal influenza vaccine from 2014 to 2016.

In closing, the authors state, "Clinicians should bear in mind that not only the vaccine but also additives can cause vaccine-related drug eruption. Because influenza vaccine–induced cutaneous adverse events are relatively rare, further investigation is necessary to clarify their pathogenesis."¹

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Vilazodone-Induced Nightmares

A 37-year-old female with a history of major depressive disorder was diagnosed with a recurrence. The patient had been treated with fluoxetine and escitalopram separately with success for 2 prior episodes of major depression. However, the patient reported she was apprehensive to utilize fluoxetine or escitalopram because she experienced abdominal pain, gastritis, and acidity while receiving these medications. She requested to be initiated on a different antidepressant, and vilazodone (Viibryd) was started at a dose of 20 mg daily. The patient reported that after taking the first 3 daily doses, she developed frightening and terrorizing nightmares on 2 consecutive nights. The patient decided to stop taking vilazodone for 2 days, and the nightmares did not recur. She restarted the vilazodone after her self-imposed 2-day drug holiday, and the nightmares appeared again. The patient then decided to stop vilazodone and see her physician. The patient's vilazodone was discontinued, and duloxetine therapy was started and the patient is currently better and recovering.

Vilazodone is a potent selective serotonin reuptake inhibitor and serotonin 1A receptor partial agonist. The author states, "The neurobiological basis for the nightmares associated with vilazodone is unknown and whether neurobiological changes of depression play a role is an area that is nascent and needs further research."² The author hypothesized that the action of vilazodone on 5-hydroxytryptophan-2 receptors may contribute to this phenomenon such as that that has occurred in selective serotonin reuptake inhibitors.

Dabigatran-Induced Pustular Eruptions

A 71-year-old female was initiated on dabigatran (Pradaxa) for stroke prevention secondary to atrial fibrillation. After taking two 150-mg doses of dabigatran, she noticed numerous mildly tender and itchy eruptions on her palms and on the bottom of her feet; however, she did not experience respiratory or oropharyngeal symptoms. Her other current medications included pantoprazole, methimazole, and amiodarone. She had no known drug allergies, but she once had a palmar rash after eating shellfish. She otherwise had never had any problems with her skin and had not family history of psoriasis.

On physical examination, the patient had numerous discrete pustules on the bilateral palmar and plantar surfaces with minimal erythema of the underlying skin. She denied any recent shellfish ingestion that could have caused her dermatologic reaction. A punch biopsy was performed, and although the skin lesions clinically appeared pustular, the results were consistent with an eczematous drug reaction. A full battery of laboratory tests were performed including a complete blood count, iron studies, chemistry panels, liver function, thyroid function, and coagulation studies, and all were within normal limits except for a mild anemia.

The patient declined any topical or systemic treatment for her palmar and plantar symptoms. Her dabigatran was

discontinued and her lesions began to clear at once. The patient was not restarted on dabigatran, and enoxaparin was initiated for anticoagulation without a recurrence of palmar and plantar symptoms. The authors evaluated this adverse reaction with the Naranjo scale, and it scored a 7 which indicates the patients' adverse reaction was probably due to dabigatran.

The authors point out that the most common adverse reaction with dabigatran therapy is dyspepsia; however, there are very rare instances of allergic edema and anaphylaxis. The authors searched the medical literature and found 4 case reports of cutaneous eruption due to dabigatran. The first report occurred in a 20-year-old male who received dabigatran for stroke prevention due to atrial fibrillation. This patient had an eruption on his thigh and forearm after 2 weeks of receiving dabigatran 150 mg twice daily. His condition resolved after dabigatran discontinuation and a topical corticosteroid. The second case occurred in a 78-year-old male who had a diffuse, full-body, pruritic rash after receiving 2 doses of dabigatran 150 mg. This patient's condition resolved after discontinuation of dabigatran and administration of diphenhydramine. The third case occurred in a 59-year-old male who developed a rash after receiving dabigatran 150 mg twice daily for 5 days. The fourth case occurred in a 74-year-old female who developed leukocytoclastic vasculitis 1 week after taking dabigatran 150 mg twice daily.

In closing, the authors state, "It is important to monitor for and report hypersensitivity reactions in patient taking dabigatran. Drug exanthems may cause discomfort or even herald more serious hypersensitivity reactions. Patients experiencing these reactions may discontinue therapy without notifying a physician and consequently place themselves at risk for embolism or stroke."³

Neurotoxic and Cardiotoxic Symptoms After Cannabis Concentrate Exposure

A 17-year-old athletic male was discovered naked in his bed with seizure-like activity. He had no medical history or recent illness. When emergency services arrive, the patient was agitated with a temperature of 102°F and was hypertensive with a systolic blood pressure in the 190's; however, he was not hypoxic. The patient then proceeded to try to escape the ambulance several times and eventually required intubation for safe transport. The patient did not have any signs of trauma, and he exhibited twitches and jerks of his extremities mixed with purposeful movements. The patient had an undetectable serum alcohol concentration, and urine drug screen was positive only for tetrahydrocannabinol metabolite (carboxy-THC).

The patient was sedated with propofol, midazolam, and fentanyl and sent for a brain magnetic resonance imaging (MRI). The brain MRI did not reveal baseline or provoked activity suggestive of epileptogenic foci. The patient continued to be hypertensive, hyperthermic, and tachycardiac despite sedation. The patient had a persistently elevated

troponin I (TnI) as high as 1.04 ng/mL (normal range ≤ 0.04 ng/mL). The patient's echocardiogram and electrocardiograms were persistently normal throughout this time. Blood, cerebrospinal fluid, urine, and sputum cultures were all negative which helped to rule out a possible infectious etiology for the patient's symptoms. The patient's urine was sent for confirmatory tandem liquid chromatography mass-spectroscopy (t-LCMS) analysis. The patient's urine was analyzed for 109 substances and was only found to be positive for carboxy-THC and cotinine.

Twelve hours after the patient was admitted to the hospital, his friends revealed he occasionally used "dabs" but no other illicit substances. "Dabs" are a cannabis concentrate formed by the extraction of desired cannabinoids using a solvent, frequently butane. Once the solvent evaporates, a "dab" of the concentrate is volatilized and inhaled using a delivery device. Street names for "dabs" also include "oil," "wax," and "budder."

The patient's parents reported that the patient had recently taken an over-the-counter urine drug screen test and had tested negative. After his hospital admission, his family then searched his bedroom and discovered an e-cigarette and "dabs"; however, they did not find any other illicit substances. The "dab" sample recovered from the patient's bedroom was analyzed, and it was found to contain tetrahydrocannabinol (THC) at 20.5% while cannabidiol (CBD) was undetectable. The patient was extubated approximately 36 hours after hospital admission, and he confirmed his use of a "dab" on the morning he was found in his bed but denied the use of any other substances. The patient was discharged 5 days later without any lasting neurologic sequelae.

The authors point out that there is a dose-dependent relationship between THC exposure and both tachycardia and hypertension. Several studies have reported THC-induced vasospasm causing myocardial and cerebrovascular events. This effect may be related to alterations in serotonin and catecholamine neurotransmission from the high total dose of THC and to an increased THC:CBD ratio. THC inhibits serotonin reuptake and diminishes stores of adrenal catecholamines, whereas CBD has a dose-dependent affinity for presynaptic 5-HT_{1A} autoreceptors which inhibit neurotransmitter release. The authors suggest, "It is reasonable to conclude that increased THC:CBD ratios favor stimulatory effects over inhibitory ones. Higher THC doses in "dabs"

might exacerbate vasoconstriction, tachycardia, and hypertension magnifying its cardiotoxicity."⁴

Rosuvastatin-Induced Skin Eruption

A 78-year-old-female noticed a small erythematous eruption on her extremities approximately 1 month after initiating rosuvastatin for hypercholesteremia. She then gradually developed a generalized erythematous eruption. The patient did not report any history of drug hypersensitivity or other allergic diseases and reported no flu-like symptoms in recent years. Upon examination, the patient has small erythematous plaques and papules on her extremities and trunk, but there was no involvement with mucus membranes. Skin biopsy revealed lymphocytic and eosinophilic infiltration in the upper dermis, and rosuvastatin-induced drug eruption was suspected. The patient then had a rosuvastatin skin patch test with a 20% rosuvastatin concentration, and a positive reaction was observed 48 hours after the test was administered. Ultimately, the patient was diagnosed with a maculopapular-type drug eruption due to rosuvastatin. She was treated with betamethasone ointment and her rosuvastatin was stopped and her condition improved.

The authors reviewed the literature, and there are 32 cases of dermatologic adverse effects reported with statins; however, this is the first report with rosuvastatin. In reviewing the case reports, there was a larger incidence in male patients (1.5:1) and the mean age of patients was 63.8 years.⁵

References

1. Oda T, Sawada Y, Okada E, et al. Stevens-Johnson syndrome after influenza vaccine injection. *J Investig Allergol Clin Immunol*. 2017;27(4):274-275.
2. DeSousa A. Nightmares associated with vilazodone in a patient with major depressive disorder. *J Clin Psychopharmacol*. 2016;36(6):737.
3. Schleichert R, Goldner R, Dickfeld T. Palmoplantar pustular eruption due to dabigatran. *Cutis*. 2016;97:E10-E11.
4. Rickner SS, Cao D, Kleinschmidt K, Fleming S. A little "dab" will do ya' in: a case report of neuro-and cardiotoxicity following use of cannabis concentrates. *Clin Toxicol*. 2017;55(9):1011-1013.
5. Oda T, Sawada Y, Yamaguchi T, et al. Drug eruption caused by rosuvastatin. *J Investig Allergol Clin Immunol*. 2017;27(2):140-141.