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# Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals, January 2009

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**Pharmacy & Therapeutics**

# Update

**Drug Information for Health Care Professionals**

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## Medication Rashes: An Overview

*By: Laura Ridgeway, PharmD**

Medication rashes are among the most common adverse effects caused by medications, affecting 2 to 3% of hospitalized patients.[1] Outside of the hospital, approximately 1% of outpatients are affected by adverse cutaneous reactions. These reactions can range from mild to severe and may or may not be mediated by the immune system. Rashes can generally be categorized into 3 groups: 1) rashes that are caused by an allergic reaction to a medication; 2) rashes that are due to a side effect of a medication; or 3) rashes due to hypersensitivity to sunlight that is caused by a medication.[2]

The rashes are usually mild and self-limiting. However, some rashes, such as toxic epidermal necrosis (TEN), which has a mortality rate of up to 30% can be severe and life-threatening.[3] Certain patient populations are more likely to develop adverse cutaneous rashes and skin eruption, including women, elderly patients, HIV or AIDS patients and pediatric patients (boys >9 years old, girls >3 years old).[4] Several medications are likely to cause cutaneous reactions and are listed in Table 1.[5]

Most drug eruptions are due to immunologically mediated reactions that can be divided into 4 classes.

- *Type I reactions* are IgE-dependent reactions and can result in urticaria, angioedema, and anaphylaxis.

- *Type II reactions* are cytotoxic and result in hemolysis and purpura.

**Table 1: Products Known To Cause Drug Rashes**

| Drug | Rate (%) |
|---|---|
| Amoxicillin | 5.1 |
| Ampicillin | 4.5 |
| Co-trimoxazole | 3.7 |
| Semi-synthetic penicillins | 2.9 |
| Red blood cells | 2.0 |
| Penicillin G | 1.6 |
| Cephalosporins | 1.5 |
| Gentamicin | 1.0 |

* At the time of article preparation, Dr. Ridgeway was a candidate at the College of Pharmacy

- *Type III reactions* are related to immune complexes, which can cause serum sickness and urticaria.

- *Type IV reactions* are delayed-type reactions that can result in contact dermatitis and exanthematous reactions.[9] The majority of drug eruptions are due to type this type of reaction.

Non-immunologically mediated reactions occur due to the direct release of mast cell mediators and do not involve the production of antibodies. An example includes red man syndrome, which occurs when the administration of vancomycin is too rapid.

There are several types of rashes and each type can be caused by different classes of medications. Although most medication-induced reactions occur within the first week after initiation, some medications are more likely to cause delayed reactions.[6] It can also be difficult to determine the causative agent when the patient is on several medications and a delayed reaction occurs. Table 2 lists the different type of cutaneous reactions that can occur and the medications associated with these syndromes.[6]

**Table 2: Different rash classifications and the medications most likely to cause them**

| Type of Rash | Medications |
|---|---|
| Exanthematous drug eruptions (ie, morbiliform/maculopapular rash) | Allopurinol, amoxicillin, captopril, carbamazepine, enalapril, lithium, phenytoin, sulfonamides, and thiazides |
| Acne | Corticosteroids, iodides, lithium and phenytoin |
| Drug hypersensitivity syndrome | Carbamazepine, phenytoin, lamotrigine, sulfonamides, allopurinol, dapsone, and nitrofurantoin |
| Urticaria (hives) | Angiotensin converting enzyme (ACE) inhibitors, anticonvulsants, cephalosporins, opiates, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, penicillin, and sulfonamide |
| Angioedema | ACE inhibitors, acetaminophen, amoxicillin, ampicillin, hydrochlorothiazide, naproxen, penicillin, and sulfamethoxazole-trimethoprim |
| Fixed drug eruptions | Acetaminophen, allopurinol, chloral hydrate, metronidazole, penicillin, sulfamethoxazole-trimethoprim, and tetracyclines |
| Stevens-Johnson syndrome and TEN | Allopurinol, amoxicillin, ampicillin, carbamazepine, corticosteroids, phenytoin, sulfa drugs, and valproic acid |
| Photosensitivity reactions | NSAIDs, quinolones, tetracyclines, and amiodarone |

***Exanthematous Drug Eruptions***

Exanthematous drug eruptions, or morbiliform rashes, are the most common cutaneous skin reaction and represent approximately 95% of all drug eruptions. They are often indistinguishable from viral exanthems.[10] Eruptions are generally widespread with fine pink to red lesions that start on the head and neck and can spread quickly.[7] Distribution is typically symmetrical and itching is the most common symptom. The onset is usually within 1 to 2 weeks of initiation and resolves within a week after discontinuation. Medications may be continued with this type of rash when no alternative therapies are available.[4]

***Acne***

Drug-induced acne eruptions typically mimic acne vulgaris. It usually begins with an inflammatory pustule, and comedones are rare.[4] This rash typically has a follicular pattern located primarily on the upper body. The eruptions heal without scarring and can appear in atypical areas like the legs and arms. Treatment generally includes discontinuation of the drug, if possible.

***Drug Hypersensitivity Syndrome***

Drug hypersensitivity syndrome is potentially life-threatening. It is often is associated with rash, fever, and internal organ involvement. A reaction typically occurs 2 to 6 weeks after the drug is initiated and is not related to dose. It occurs most frequently with the first exposure to the drug. Rash

occurs in approximately 87% of patients and can result in Steven-Johnsons syndrome.[7] Treatment involves rapid withdrawal of the causative agent and systemic steroids are often needed.

### *Urticaria*

Urticaria, also known as hives, is a common transient skin eruption. It is characterized by raised, red eruptions that are pruritic. Hives may occur at any age, with up to 20% of the population having at least 1 episode during their lifetime.[10] Chronic urticaria is a condition in which hives last more than 6 weeks and is more common in middle-aged women. Drug-induced urticaria is responsible for almost 5% of cutaneous reactions.[4] Reactions can be immediate or delayed and commonly occur during the first week of treatment. The primary treatment for urticaria is an antihistamine and discontinuation of the offending agent.

### *Angioedema*

Angioedema involves subcutaneous and dermal tissues and is characterized by a hive-like swelling caused by increased vascular permeability. It may occur with or without urticaria and itching is usually absent. Angioedema commonly occurs on the lips, face, and eyes. It may be disfiguring or potentially life threatening if airway obstruction occurs.[6] Gastrointestinal symptoms may occur as well. Antihistamines ($H_1$) are the gold-standard treatment for angioedema.[4] In severe cases, systemic corticosteroids may be needed for therapy but immediate effects should not be expected.

### *Fixed Drug Eruptions*

Fixed drug eruptions are relatively common and represent a distinctive dermatologic reaction. Eruptions typically occur on the mouth, face and genitals. They are demarcated, round, hyperpigmented plaques that reoccur in the same place if re-exposed to the medication. For unknown reasons, women are more affected by fixed drug eruptions than men.[7] Treatment involves discontinuing the medication; topical steroids may be needed.

### *Stevens-Johnson Syndrome and TEN*

Stevens-Johnson syndrome and TEN are severe cutaneous reactions that can result in significant morbidity and mortality. It consists of purpuric lesions with mucosal involvement. Constitutional symptoms such as high fever, nausea, and vomiting are generally present. Epidermal skin detachment is less than 10% of the body surface. TEN is a continuation of Stevens-Johnson syndrome and is characterized by more than 30% of epidermal detachment. Mortality rates are 5% for Stevens-Johnson syndrome and up to 30% for TEN. Penicillins and sulfonamide-related medications are most commonly involved in these disorders.[8] Stevens-Johnson syndrome and TEN can result in severe fluid loss, infections, and increased energy requirements. Rapid discontinuation of the offending drug is required and supportive therapy is recommended. The use of corticosteroids has been controversial and is no longer recommended.[7]

### *Photosensitivity Reactions*

Photosensitivity eruptions are due to the combined effects of sunlight and a chemical such as a medication. Phototoxic eruptions are the most common cause of drug-induced photoeruptions. The eruption is usually manifested by an exaggerated sunburn with blisters. Reactions can be immediate or delayed. Treatment involves avoidance of the medication or avoiding sunlight exposure. It is also recommended to limit skin exposure to the sun by wearing long-sleeved clothing and hats. Sunscreen should also be used to help protect against photosensitivity reactions. Broad-spectrum sunscreens that have a sun protection factor (SPF) of at least 30 are recommended. Sunscreens should also be para-aminobenzoic acid (PABA) free, as this can exacerbate photosensitivity reactions.[11]

Cutaneous drug reactions are a major cause of adverse drug reactions. Patients that are on multiple medications are at a higher risk for developing a medication rash. If an adverse event occurs, the agent should be identified and discontinued if possible. Treatment of medication eruptions depends on the specific reaction that occurs. Patients that have experienced a hypersensitivity or severe reaction in the past need to have their therapy closely monitored to help ensure these reactions do not reoccur. The aim is to prevent the recurrence and not to compromise future treatments by contraindicating otherwise useful medications. The situation should be thoroughly assessed to determine the actual causality.

*References available upon request*

# Did You Know...

**FDA Statement on Antiepileptic Drugs and Suicidality**

Food and Drug Administration (FDA) issued a statement on December 16, 2008, as a follow-up to their January 2008 warning, on the increased risk of suicide associated with 11 antiepileptic medications. A warning will be added to the labeling of the following medications:

- Carbamazepine (Tergretol®,Carbatrol®, Tegretol-XR®)
- Felbamate (Felbatol®)
- Gabapentin (Neurontin®)
- Lamotrigine (Lamictal®, Lamictal CD®)
- Levetiracetam (Keppra®, Keppra XR®)
- Oxcarbazepine (Trileptal®)
- Pregabalin (Lyrica®)
- Tiagabine (Gabitril®)
- Topiramate (Topamax®)
- Valproate (Depacon®)
- Zonisamide (Zonegran®)

Manufacturers must also develop a medication guide that can be provided to patients prescribed these medications. Healthcare professionals should be aware of the potential for this risk and monitor patients for changes in behavior that might indicate depression or suicidal thoughts. More information is available at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic.

**Update of Safety Review on Ezetimibe/Simvastatin (Vytorin®)**

FDA released an update on its analysis of data from the ENHANCE trial[1] (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) on January 9, 2009. Preliminary results from this investigation found that the combination of ezetimibe and simvastatin did not significantly reduce carotid (neck) artery thickness more than simvastatin alone, even though the ezetimibe/simvastatin reduced low-density lipoprotein (LDL) to a significantly greater degree. FDA communication indicates that this information does not change the agency's stance that lowering LDL cholesterol reduces the risk of cardiovascular disease. Patients should remain on their prescribed medications and speak with their physicians if they have questions about ezetimibe, simvastatin, or the ENHANCE trial. An ongoing clinical trial, expected to be completed in 2012, will help better determine whether the combination of ezetimibe and simvastatin reduces the risk of cardiovascular events compared with simvastatin alone. More information is available at: http://www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin200901.htm.

[1] Kastelein JJP, Akdim F, Stroes ESG, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358(14):1431-43.

**FDA Statement on Topical Anesthetics**

On January 16, 2009, FDA issued a public health advisory stating that skin numbing products, or topical anesthetics (such as lidocaine), often used to relieve pain caused by mammography or other medical tests and conditions, can cause serious life-threatening complications. These risks include irregular heartbeat, seizures, breathing difficulties, coma, and even death and are seen when the preparation is applied to a large area of skin or a covering is placed over the application area of the product. More information is available at: http://www.fda.gov/medwatch/safety/2009/safety09.htm#Anesthetics.