Getting Under the Skin of Adverse Drug Reactions

Carolyn Hempel, PharmD; Craig Martin, PharmD, BCPS

Abstract: Cutaneous drug reactions are among the most commonly reported adverse drug reactions. Drugs prescribed by orthopedic surgeons, such as antibiotics, opiates, and nonsteroidal anti-inflammatory drugs, are common offenders. Cutaneous drug reactions can range from those that are common, mild nuisances to those that are rare, severe, and life-threatening. Medications should be considered part of a differential diagnosis for any dermatologic condition. It is important to recognize the different clinical features and common drugs that are related to each type of reaction. This review characterizes the different forms of cutaneous drug reactions and the clinical features, proposed mechanisms, and drugs frequently associated with each.

Cutaneous drug reactions are among the most commonly reported adverse drug reactions, with their occurrence in hospitalized patients estimated at 1% to 3%. Cutaneous drug reactions are common reactions caused by many of the drugs that orthopedic surgeons prescribe. Cutaneous drug reactions can range from those that are common, mild nuisances to those that are rare, severe, and life-threatening (e.g., angioedema, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis). It is likely that almost any medication can induce a skin reaction, but drug classes such as antibiotics, antiepileptics, and nonsteroidal anti-inflammatory drugs (NSAIDs) are among those most frequently cited. Antibiotics and NSAIDs are commonly prescribed by orthopedic surgeons. Antiepileptics and antidepressants are not prescribed by orthopedic surgeons as frequently but can be prescribed as treatment for pain or as part of a patient’s medication history. Antimicrobial agents have consistently been found to have the highest reported frequency, with trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolones, and penicillins the most common offenders. It is estimated that the number of cutaneous drug reactions caused by antibiotics is more common in the pediatric population than in the adult population.

Medication-related causes should be considered as part of a differential diagnosis for any dermatologic condition that appears within 2 weeks of treatment initiation. This article characterizes the common forms of cutaneous drug reactions and the clinical features, proposed mechanisms, and medications frequently associated with each. Habit provides information regarding common drugs associated with cutaneous reactions. The Drug Eruption Reference Manual by Jerome Litt, which can be found online (www.drugeruptiondata.com), contains additional information regarding the frequency and types of eruptions associated with a particular medication.

MECHANISM

Cutaneous drug reactions can be divided into 2 classes based on mechanism: immune mediated (approximately 25% of reactions) and nonimmune mediated (approximately 75% of reactions). Immunologic mechanisms include the 4 types of hypersensitivity reactions. The mechanism of a type 1 (immediate) immunologic reaction is mediated by drug-specific immunoglobulin E that binds to mast cells and then leads to release of histo-
mine and leukotrienes. This is an immediate-type reaction that is not dose dependent and requires that a patient is sensitized before the reaction. Common causative agents include penicillins, first-generation cephalosporins, and aspirin. Clinical manifestations of this type of reaction include urticaria, asthma, and anaphylactic shock.

Type II or cytotoxic reactions are mediated through immunoglobulin G and immunoglobulin M antibodies. This involves the binding of an antibody to cells with subsequent binding of complement and cell rupture. Common drugs that cause this type of reaction are penicillins and sulfonamides. Blood dyscrasias such as hemolytic anemia and thrombocytopenia are common clinical patterns.

Type III, or immune complex–mediated reactions, involve circulating immune complexes that deposit in vascular beds or on tissue surfaces and damage tissues. Common clinical patterns include serum sickness, vasculitis, and urticaria, and immunoglobulins are common offenders of this type of reaction.

Type IV reactions are mediated by T-cells causing delayed hypersensitivity reactions. Sensitized lymphocytes react with the drug, liberating cytokines and triggering a cutaneous inflammatory response. This type of reaction can then be divided into 4 subtypes. Morbilliform exanthematous reactions, fixed-drug eruptions, Stevens-Johnson syndrome, and toxic epidermal necrolysis are clinical patterns of this type of reaction, and sulfamethoxazole and anticonvulsants are common causative agents.10-13

Nonimmun-mediated reactions may occur due to genetic enzyme deficiencies, drug accumulation caused by drug interactions or overdose, or reactions caused by the combination of medications and an outside variable, such as ultraviolet radiation.14 Understanding the various types of mechanisms for cutaneous drug reactions is important when identifying the likelihood for cross reactivity, expected time course, and treatment.

**CLASSIC DRUG REACTION PATTERNS**

**Exanthematous Reactions**

*Exanthema* is a general term used to describe reactions that burst forth on the skin. Typical characteristics of exanthematous reactions include morbilliform (resembling measles) or maculopapular lesions. Exanthematous reactions account for approximately 95% of cutaneous drug reactions. Exanthematous reactions can occur at any time, but most often occur within 7 to 10 days of drug initiation.8 The eruption typically begins on the trunk and can spread to involve the extremities in a symmetrical fashion. Systemic symptoms such as fever and chills may be involved. Other common characteristics include erythema and burning or itching.

Drugs commonly causing exanthematous eruptions include penicillins, TMP-SMX (up to 60% in human immuno-deficiency virus–infected patients), and antiepileptic medications. The exact mechanism of exanthematous reactions is unknown, but it may be a delayed hypersensitivity mechanism. Ampicillin is a common cause of this type of exanthematous maculopapular reaction with no immunologic mechanism. Concomitant viral syndromes may exacerbate this reaction. For example, patients who receive ampicillin while infected with the Epstein-Barr virus have an 80% chance of experiencing this type of reaction.1,8

Treatment of any exanthematous reaction involves discontinuation of the causative drug. The reaction typically resolves within 1 to 2 weeks; however, it may worsen for a few days before improvement. Continuation of the offending agent may eventually lead to erythroderma or generalized exfoliative dermatitis, which can be severe.11

Practitioners should also be aware of a severe syndrome that typically begins with a morbilliform-type eruption. Drug-induced hypersensitivity syndrome, or drug rash with eosinophilia and systemic symptoms, is an idiosyncratic adverse drug reaction that begins within the first 2 months of initiation of a drug.15 This syndrome is characterized by fever, malaise, and facial edema, along with organ involvement (eg, kidney or liver).16 The mortality rate can be up to 10% if left untreated and the causative agent continued. Antiepileptic drugs and sulfonamides are the most common causes of this type of hypersensitivity reaction. Morbilliform eruptions may also be the initial presentation for other serious reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and serum sickness. Each of these should be considered as a part of the differential diagnosis, which is why it is recommended to discontinue the suspected agent in this type of reaction.

In addition to drug discontinuation, symptomatic relief provided by antihistamines and corticosteroids can be useful.8 Eruption will usually recur with rechallenge, although not always, such as in cases of ampicillin reaction with a person infected with Epstein-Barr virus. However, rechallenge is not recommended due to the potential for a more severe reaction.

Patients and physicians should be aware of the symptoms and severity of the reaction. This will help determine whether another drug from a similar class may be used. For example, if a patient has a severe penicillin allergy, treatment should be to avoid any antibiotic with a beta lactam ring and to use antibiotics such as macrolides, fluoroquinolones, sulfonamides, or vancomycin. Other patients who may not have had a severe reaction to a beta lactam antibiotic may be able to use a cephalosporin, which has a similar structure, yet its cross reactivity is likely less than 10%. Patients and clinicians should be aware of hypersensitivities and knowledgeable of other drugs within
the same class with which they may also react.

**Urticaria**

Drug-induced urticaria, the second most common form of cutaneous drug reaction, refers to hives that manifest as raised pruritic red wheals of various sizes. Drug-induced urticaria is often difficult to distinguish from urticaria arising due to nondrug factors. It may appear after the first exposure of a drug but often requires multiple exposures. On initial sensitization, an immunoglobulin E-mediated reaction occurs between 7 and 14 days; however, in a patient who has previously been sensitized, the reaction can occur within minutes to hours. Penicillins, cephalosporins, sulfonamides, tetracyclines, and antiepileptic agents are often associated with immunoglobulin E-mediated urticaria.

If the reaction is related to serum sickness, immunoglobulin G or immunoglobulin M may be involved, resulting in immune complexes that deposit in small vessels. Urticaria due to an immune complex reaction may occur within 7 to 10 days of initial exposure or within 12 to 36 hours of exposure in a previously sensitized patient. Penicillins and sulfonamides can also cause this type of reaction. Urticaria can also be nonimmune mediated, which may involve complement activation and release of cutaneous mast cell mediators. Opioids, hydralazine, and radiocontrast media are common causes. Nonimmune-mediated reactions may occur any time from 20 minutes to 4 hours after administration.

Urticarial reactions may be a sign of more serious syndromes, such as angioedema, serum sickness, and anaphylaxis. Angioedema is described as subcutaneous tissue swelling and is usually a nonpruritic reaction that lasts from a few hours up to 5 days. Angiotensin-converting enzyme inhibitors are commonly associated with angioedema. Serum sickness–like reactions are defined by the presence of fever, urticarial rash, and arthralgias that last up to 1 to 3 weeks after initiation of drug therapy. Cefaclor, a second-generation cephalosporin that is now uncommonly used, can be associated with serum sickness.

Urticaria associated with systemic anaphylaxis, which is manifested by respiratory distress, vascular collapse, or shock, is a medical emergency. Antibiotics are common culprits of these events. Management of urticarial reactions involves discontinuing the causative agent and treatment with oral antihistamines. If systemic involvement exists, such as serum sickness, oral corticosteroids may be necessary.

**Fixed-drug Eruptions**

A fixed-drug eruption is a solitary, erythematous, round or oval lesion that is reddish, purple, or brownish in color and is sometimes accompanied by blisters, bullae, or vesicles. The lesion may be associated with burning or itching prior to developing the hyperpigmented macule or bullae. This type of reaction does not normally have systemic involvement and may appear any time from days to weeks after drug initiation and from minutes to hours after reexposure. The areas that are most frequently affected are hands, feet, tongue, penis, and perianal areas.

The mechanism of fixed-drug eruptions is not well understood; some theories suggest a genetic component or a reaction to drug excipients. Sulfonamides, tetracyclines, metronidazole, and NSAIDs are often implicated in fixed-drug eruptions. Resolution generally occurs within 7 to 10 days after discontinuation. If a patient is rechallenged with the offending agent, the fixed-drug eruption will appear within hours of ingestion at the identical skin site and new lesions will often appear. In this type of reaction, oral challenge to confirm diagnosis is a safe and common practice.

**Erythema Multiforme-like Reactions**

Erythema multiforme-like reactions can be divided into 2 groups: erythema multiforme minor and erythema multiforme major, which can then be divided into Stevens-Johnson syndrome, Stevens-Johnson syndrome/toxic epidermal necrolysis, and toxic epidermal necrolysis. These represent variants of the same disease process and can be differentiated by the pattern and distribution of skin lesions, as well as the extent of skin detachment involved.

Erythema multiforme minor is an inflammatory disease often associated with a preceding acute upper respiratory tract infection, herpes simplex virus infection, or pneumonia caused by *Mycoplasma spp.* Erythema multiforme is associated with systemic symptoms, such as fever and a flu-like syndrome, before the skin rash appears. The prototypical lesion is a dusky erythematous patch resembling a bullseye that first affects the extremities. Most cases of erythema multiforme are associated with causes other than drugs, such as infection, with drugs accounting for approximately 20% of cases.

Stevens-Johnson syndrome and toxic epidermal necrolysis are uncommon but severe reactions characterized by an initial prodrome including fever, malaise, myalgia, and arthralgia, which lasts for 1 to 14 days prior to cutaneous sequelae. The estimated yearly incidences of Stevens-Johnson syndrome and toxic epidermal necrolysis are 1.2 to 6 and 0.4 to 1.2 cases per million population, respectively. Mortality ranges from 5% in Stevens-Johnson syndrome to 40% in toxic epidermal necrolysis.

The mechanism that leads to the development of Stevens-Johnson syndrome or toxic epidermal necrolysis is only partially understood. It appears that certain patients are incapable of detoxifying key reactive intermediate drug metabolites, placing them at higher risk of Stevens-Johnson syndrome and toxic epidermal necrolysis. The major distinguishing factor between the 2 is the body surface area involved. Epidermal skin detachment affecting 1% to 10%
of total body surface area is classified as mild Stevens-Johnson syndrome, 10% to 30% is classified as Stevens-Johnson syndrome/toxic epidermal necrolysis overlap, and more than 30% is classified as toxic epidermal necrolysis.

Treatment of Stevens-Johnson syndrome or toxic epidermal necrolysis involves immediate discontinuation of the offending agent, supportive care, and avoidance of other drugs that have evidence of cross reactivity. Optimal treatment remains undefined and may include immune therapy with immunoglobulin G, high-dose corticosteroids, cyclophosphamide, cyclosporine, or tumor necrosis factor-alpha inhibitors. Systemic corticosteroids remain a mainstay of therapy despite the lack of strong evidence to support their benefit in Stevens-Johnson syndrome.

Despite the relative paucity of positive data, corticosteroids do not appear to be harmful to patients with Stevens-Johnson syndrome. However, this may not be the case in toxic epidermal necrolysis. Although most case series have shown they provide neither benefit nor harm, other investigators purport to have demonstrated an increased morbidity or mortality when steroids are used to treat toxic epidermal necrolysis due to an increased risk of infection.18 These authors recommend other treatment options.19

Photosensitivity

Acute photosensitivity ranges from common polymorphous light eruptions to rare photo allergies.20 Photosensitivity refers to reactions that occur when a photosensitizing agent in or on the skin reacts with ultraviolet light, often in doses smaller than those associated with sunburn. Up to 8% of cutaneous drug reactions are photosensitivity eruptions. Typically, a photosensitivity reaction occurs within hours to days of exposure to sunlight and may last up to 1 week or more.

Reactions resemble moderate to severe sunburns, with erythema, blistering, weeping, and desquamation. Phototoxic and photoallergic reactions occur in sun-exposed areas of the skin; however, widespread eruptions can occur, which may suggest a systemic photosensitizing agent. Reactions are dose related and are most commonly seen in patients who have been exposed to high doses of both the drug and ultraviolet rays.

One’s susceptibility to this type of syndrome is variable and likely based on drug absorption and metabolism, as well as the amount of melanin in the skin. Fluoroquinolones, tricyclic antidepressants, and NSAIDs are classes of drugs that have been reported to be frequent photosensitizers, with fluoroquinolones being the most potent. Other antibiotics, such as TMP-SMX and tetracyclines, have also been implicated. Management of photosensitivity reactions includes limiting exposure to the sunlight, using potent sunscreen, and wearing protective clothing.20

**THE BOTTOM LINE**

- It is important that skin reactions are identified and adverse drug reactions are documented in the patient record so their recurrence can be avoided.
- Knowledge of the different mechanisms and common drugs associated with the different clinical features of cutaneous drug reactions will help identify the likelihood for cross reactivity, the expected time course, and treatment.
- Practitioners should be aware of the severe syndromes that may be associated with the common clinical manifestations of cutaneous drug reactions.
- Understanding the structure and classes of medications while also recognizing the severity and type of reaction a patient had will determine future treatment options and classes of medications that are used.

**REFERENCES**

9. Litt JZ. D.E.R.M. Drug Erup-
10. Roychowdhury S, Svensson
CK. Mechanisms of drug-in-
duced delayed-type hypersens-
sitivity reactions in the skin.
11. Lee A. Adverse Drug Reac-
tions. 2nd ed. London, UK:
12. Ardern-Jones MR, Friedmann
PS. Skin manifestations of drug
2011; 71:672-683.
13. Wolff K. Fitzpatrick’s Color
Atlas and Synopsis of Clini-
cal Dermatology. 6th ed. New
Companies; 2009.
14. Svensson CK, Cowen EW, Gas-
pari AA. Cutaneous drug reac-
tions. Pharmacol Rev. 2001;
53:357-379.
15. Bachot N, Roujeau JC. Differ-
tential diagnosis of severe cuta-
nous drug eruptions. American
Journal of Clinical Dermatol-
16. Knowles SR, Shear NH. Rec-
ognition and management of
severe cutaneous drug reac-
tions. Dermatol Clin. 2007; 25:
245-253.
17. French LE. Toxic epidermal
necrolysis and Stevens Johnson
syndrome: our current under-
standing. Allergol Int. 2006;
55:9-16.
18. Worswick S, Cotliar J. Ste-
vens-Johnson syndrome and
toxic epidermal necrolysis: a
review of treatment options.
DermatolTher. 2011; 24:207-
218.
19. Engelhardt SL, Schurr MJ, Hel-
gerson RB. Toxic epidermal
necrolysis: an analysis of refer-
ral patterns and steroid usage.
J Burn Care Rehabil. 1997;
18:520-524.

---

**CALL FOR CME REVIEW ARTICLES**

ORTHOPEDICS is seeking CME Review articles for upcoming publications. Please contact the Managing Editor, Cindy K. Bush, ELS, at ckbush@slackinc.com or visit www.Healio.com/ORTHO for more information on the submission process.