Exanthematous drug eruptions, also called morbilliform or maculopapular drug rashes, are the most common drug-induced eruptions, occurring in 1 to 5% of first-time users of most drugs. Exanthematous drug eruptions are usually self-limited mild reactions, but severe cutaneous reactions can occur. This issue of CLIPS briefly summarizes an article that reviews different types of eruptions, causative drugs, distinguishing characteristics of drug-induced and viral exanthems, and management. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Types of drug-induced eruptions
- Exanthematous drug eruptions
  - Idiosyncratic, T-cell-mediated, delayed (type IV) hypersensitivity reactions that present as a symmetric, widespread rash composed of pink or red macules and papules often with low-grade fever (<101.4 °F) and pruritis.
  - Causative agents include penicillins, cephalosporins, sulfonamide antibiotics, quinolones, allopurinol, and aromatic amine antiseizure medications (carbamazepine, phenytoin, and lamotrigine).
  - Severe but rare forms of T-cell-mediated reactions are Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS).
- Urticaria
  - IgE-mediated, immediate (type I) hypersensitivity reactions that present as lesions with central blanching and red rims lasting less than 24 hours; may be accompanied by anaphylaxis and angioedema
  - Causative agents are nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin converting enzyme inhibitors (ACEIs).
- Photosensitivity eruptions
  - Ultraviolet or visible-light activation of a drug that presents as a sunburn-like reaction with possible blistering in exposed areas.
  - Causative agents include thiazide diuretics, doxycycline, amiodarone, quinolones, voriconazole, and vemurafenib.
- Fixed drug eruptions
  - Small (usually <8 cm in diameter), red, round plaques that may sting and result in long-lasting hyperpigmentation. Eruptions recur at the same sites (lips, genitalia, and acral skin) upon reexposure to the causative drug.
  - Causative agents include penicillins, NSAIDs, and acetaminophen.

Characteristics that differentiate drug-induced exanthems from viral exanthems
- Both drug-induced and viral exanthems (e.g., measles, rubella, fifth disease) are characterized by a rapid onset of widespread, symmetric eruptions composed of pink to red papules that may coalesce and may be accompanied by fever, malaise, sore throat, and conjunctivitis.
- Characteristics of drug-induced exanthems
  - Onset is typically 4 to 21 days after a patient initiates therapy with a causative medication. Peak reaction is reached within 2 days following discontinuation of the causative agent. Exanthems fade within a week after drug elimination.
  - Some drugs cause skin eruptions that differ from typical exanthematous drug eruptions. Tyrosine kinase inhibitors may cause papulopustular eruptions, while telaprevir, interferon α, and ribavirin can cause eczematous eruptions.

CONTINUED NEXT PAGE
Characteristics that differentiate drug-induced exanthems from viral exanthems (continued)

- Characteristics of viral exanthems
  - The rash accompanying measles often begins on the head and neck and spreads rapidly, beginning a few days after the onset of fever, cough, coryza, and conjunctivitis. White spots appear on the buccal mucosa.
  - Rubella has measles-like symptoms but milder in intensity with fever, adenopathy, and arthralgias.
  - Roseola infantum is characterized by a pink, short-lived rash accompanied by high fever for 3-5 days in young children. In adults, cervical adenopathy is present, as well as fever that may persist for months.
  - Erythema infectiosum (fifth disease) causes a “slapped cheek” appearance with fever 2-4 days before generalized rash, which begins on proximal extremities in young children. Adults have arthralgia and fever.
  - In patients with infectious mononucleosis, rash may occur within 3 days following aminopenicillin administration.
  - Acute graft-versus-host disease occurs 2-4 weeks after transplantation and is difficult to distinguish from exanthematous drug eruption.
  - Acute HIV seroconversion occurs 1-6 weeks after infection and is characterized by fever, myalgias, arthralgias, and lymphadenopathy. A symmetric rash involving the face, palms, and soles may occur.

Severe reactions

- Signs of a severe cutaneous reaction include temperature >101.4 °F, blisters, lymphadenopathy, mucous membrane involvement, rash involving >50% of body surface, and facial edema and erythema.
- Drug-induced rashes must be evaluated to determine if progression to a severe cutaneous reaction (SJS, TEN, AGEP, DRESS, serum sickness-like reactions, cutaneous leukocytoclastic vasculitis) is likely.
  - Serum sickness-like reactions may include exanthematosus and urticarial eruptions, lymphadenopathy, and arthralgia; causative agents include minocycline, cephalexin, cephalosporins, and biologic agents.
  - Cutaneous leukocytoclastic vasculitis, characterized by erythematous and purpuric papules on the lower extremities, may be caused by drugs such as propylthiouracil.
  - SJS-TEN is characterized by severe, acute blistering with full-thickness loss of epidermis and mucous membrane involvement. Causative agents include aromatic amine antiepileptics, nevirapine, sulfonamides, allopurinol, sulfasalazine, and sertraline.
  - Signs of DRESS include widespread rash and eosinophilia without mucosal involvement. The most common causative agents are aromatic amine antiepileptics.
  - AGEP is marked by rapid onset of nonfollicular pustules on red, swollen skin with facial edema and leukocytosis. Causative agents include aminopenicillins, hydroxychloroquine, macrolides, quinolones, diltiazem, sulfasalazine, and terbinafine.

Management of drug-induced exanthems

- Identifying the drug-induced reaction and discontinuing the causative drug are the most important steps in management.
- Oral antihistamines (diphenhydramine or hydroxyzine) may relieve symptoms of pruritus. Potent topical glucocorticoids may also provide relief but should not be used on the face or intertriginous areas.
- Systemic glucocorticoids or cyclosporine can be used as early treatment of SJS-TEN to reduce mortality.
- Cross-allergy between cephalosporins with different side chains is infrequent; patients can change to another cephalosporin. Cross-allergy between antimicrobial sulfonamides and non-antimicrobial sulfonamides (diuretics, some NSAIDs, and some anti-diabetic agents) is unlikely. Cross-allergy between aromatic amine antiepileptics is frequent; patients should switch to antiepileptics which are not aromatic amines.
- Regardless of the causative agent, patients who experience drug hypersensitivity are twice as likely as other patients to experience future hypersensitivity reactions to any medication.

Summary

- Pharmacists should recognize drugs typically associated with exanthematous drug eruptions, such as certain types of antibiotics, antiepileptics, NSAIDs, and allopurinol. To identify the causative agent, the timing of drug administration relative to rash onset must be determined.
- Management of mild to moderate drug-induced exanthems includes antihistamines and topical glucocorticoids.
- Patients with signs and symptoms of severe cutaneous reactions should receive immediate medical attention.

Prepared by: Heiyung Lee, Pharm.D. Candidate  Reviewed by: Rachel Thomas, Pharm.D., M.S.