CHAPTER 46

CUTANEOUS DRUG REACTIONS: HOW TO IDENTIFY AND TREAT THEM

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Complications of pharmacotherapy are the most common type of adverse events encountered in the hospitalized patient. Drug-induced cutaneous eruptions are the most common types of adverse drug reactions. Other commonly reported adverse drug reactions include nausea, drowsiness, diarrhea, vomiting, and rash. Cutaneous drug reactions occur in 2% to 3% of all hospitalized patients. It is estimated that inpatients receive an average of nine different drugs per hospitalization, and the average outpatient drug usage is estimated to be two drugs taken on a regular basis. In the United States, more than 1.5 billion drugs are prescribed per year, accounting for more than sixty-thousand drug products. Over 15 million adults take aspirin on a routine basis; more than 10 million adults take at least one class of anti-hypertensive agent; and more than 5 million adults take diazepam and/or antacids.

Skin eruptions and generalized pruritus can be challenging to both the patient and physician. However an understanding of the epidemiology and pathogenesis of cutaneous drug reactions can help one identify the causative agent(s). This manuscript will review the pathogenesis, clinical morphology, diagnosis, and treatment of cutaneous drug reactions.

PATHOGENESIS OF CUTANEOUS DRUG REACTIONS

Drug reactions result from either immunologic or nonimmunologic mechanisms. Immunologic reactions activate host immune pathways and are the true drug allergies. Nonimmunologic mechanisms do not require activation of the host immune response, and are more common than allergic reactions.

Immunologic Reactions

Allergic drug reactions fall into one of four classifications, Type I, II, II or IV, originally described by Gell and Coombs (Table 1). Type I allergies (Allergy of anaphylaxis or immediate) are defined as IgE-dependent drug reactions which manifest primarily in the skin, gastrointestinal, respiratory, and cardiovascular systems (Fig. 1). Common symptoms include: pruritus, urticaria, nausea/vomiting, bronchoconstriction, laryngeal edema, and rarely anaphylaxis and hypotension leading to death. Immediate reactions occur within minutes of exposure to the offending agent, and accelerated reactions occur hours or days after drug

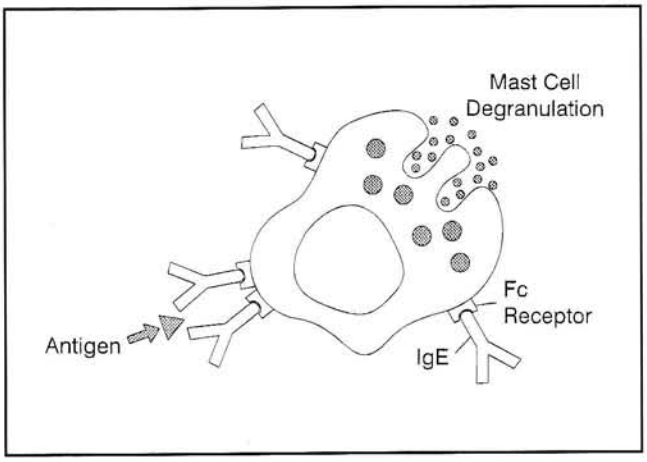

Figure 1. Type I hypersensitivity reaction.

Table 1

CLASSIFICATIONS OF HYPERSENSITIVITY REACTIONS

Type	Description	Example
I	Anaphylactoid	IgE-Mediated Urticaria
II	Cytotoxic	Immune Hemolytic Anemia
III	Immune Complex	Leukocytoclastic Vasculitis
IV	Delayed Hypersensitivity	Allergic Contact Dermatitis

administration. Accelerated reactions are usually urticarial and may include laryngeal edema. Penicillin is the prototype for this type of allergic reaction. The mechanism involves sensitization of a drug-specific IgE antibody bound to mast cells. Mast cells undergo degranulation releasing histamine, heparin, enzymes, prostaglandins, thromboxanes, adenosine, and proteoglycans. These substances then act upon the target organ(s) such as the epidermis.

Type II allergies (Cytotoxic or antibody-mediated) most commonly affect internal organs rather than the integument (Fig. 2). Drug reactions following this pathway may damage kidneys, heart, lungs, liver, muscle, and peripheral nerves. The mechanism involves the drug binding to circulating antibodies that interact with, and damage or destroy cells. Examples of drugs involved in this type of reaction are quinine and its derivatives.

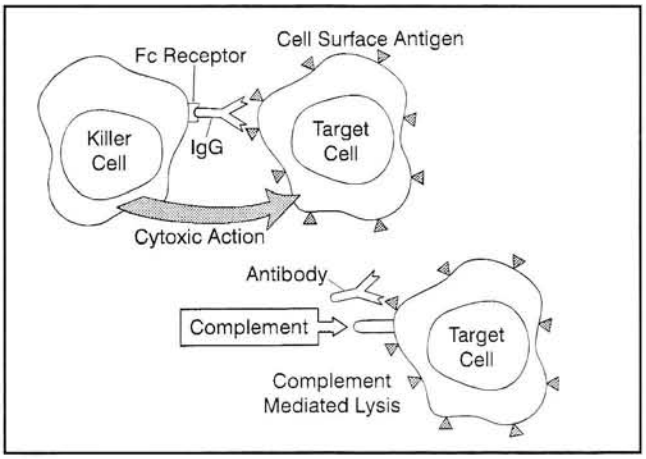

Figure 2. Type II hypersensitivity reaction.

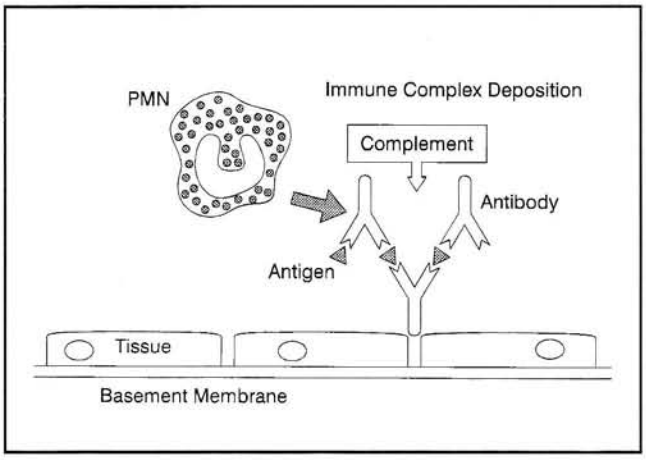

Figure 3. Type III hypersensitivity reaction.

Type III allergies (Immune complex mediated) are based on the acute inflammation resulting from complexes formed by the offending drug, antibody, and complement (Fig. 3). These large immune complex aggregates are deposited in blood vessels and tissues. The prototype for this pathway is serum sickness which is characterized by arthralgias, nephritis, neuritis, edema, and an urticarial, papular, or pruritic eruption. Drugs that produce serum sickness include penicillins, sulfonamides, thiouracils, phenytoin, aminosalicylic acid, and serum.

Type IV allergies (Delayed hypersensitivity) arise more than 24 hours after the encounter of the drug (Fig. 4). The main interaction is between the drug and lymphocyte, causing release of various lymphokines. Macrophages are activated, causing inflammation and tissue damage. Drug reactions usually result in maculopapular or eczematous eruptions. However, other clinical pictures, such as photosensitivity reactions and fixed drug eruptions, also present in this category.

Nonimmunologic Reactions

Nonimmunologic cutaneous reactions are more common than true drug allergies as previously described. Pathogenesis of nonimmunologic reactions include: activation of effector pathways, overdosage, cumulative toxicity, side effects, ecologic disturbance, drug interactions, metabolic changes, and exacerbation of preexisting dermatoses.

The activation of effector pathways can be accomplished in one of three ways. First, by directly releasing mast cell mediators, which present as urticaria and/or angioedema. Examples

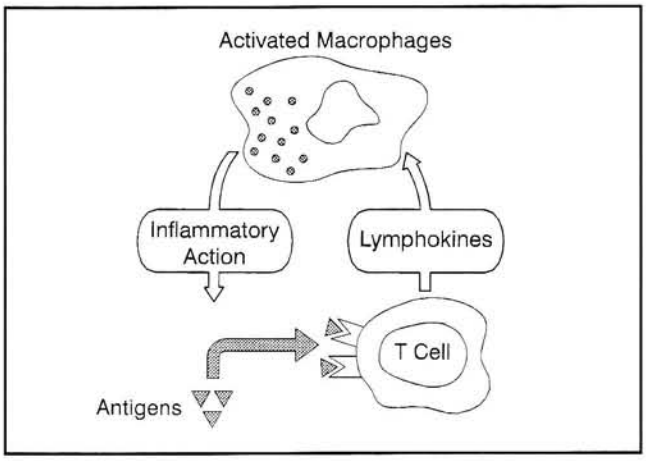

Figure 4. Type IV hypersensitivity reaction.

of drugs causing this reaction include opiates, polymyxin B, curare, and radiocontrast media. A second means of activation of effector pathways includes activation of complement without antibody involvement. This is a major source of urticaria produced by radiocontrast media. Finally, a third mechanism involves the alteration of pathways of arachidonic acid metabolism. This explains anaphylactoid responses to aspirin and nonsteroidal anti-inflammatory agents.

The clinical response to drug overdose is usually predictable for most drugs, usually consisting of an exaggeration of the pharmacological effect of the medication. Overdosage can occur when there is interference with the normal absorption, metabolism and/or excretion of the agent.

Cumulative toxicity results from the abnormal accumulation of the drug or metabolite in the skin. Clinically, one observes a change in color of the skin. The agent may be deposited in the phagocyte cells of the skin or in the mucus membranes. Examples include prolonged administration of heavy metals, such as, silver, bismuth, mercury, and gold.

Side effects occur as part of the normal pharmacologic action of the drug. All drugs have side effects which are actions of the drug that are not the primary therapeutic objective, such as alopecia following chemotherapy. Ecologic disturbance can cause a cutaneous eruption. When an agent such as a broad-spectrum antibiotic alters the normal flora of the skin and/or mucus membranes, anogenital candidiasis and thrush can occur.

There are three mechanisms by which drug interactions can cause cutaneous eruptions. First, drugs that have high protein binding affinity may compete for the same binding sites. A classic example is the reaction involving coumadin and salicylates resulting in cutaneous hemorrhagic eruptions. A second means of drug interaction involves the inhibition or stimulation of certain metabolic enzymes required for degradation of either agent. The third interaction involves interference with the excretion of another agent. An example includes the reduction of renal clearance of penicillin with the co-administration of probenecid.

Metabolic changes caused by drug administration can cause skin eruptions. For example, phenytoin causes an interference with folate absorption or metabolism, which may result in aphthous stomatitis. Also, drugs which alter lipid metabolism may cause xanthomas.

It is well known that certain drugs can exacerbate preexisting dermatoses. Such examples include: beta-blockers and psoriasis, lithium and acne or psoriasis, cimetidine and cutaneous lupus, and vasodilators exacerbating rosacea.

CLASSIFICATION BY CUTANEOUS MORPHOLOGY

The most common cutaneous eruption is the morbilliform pattern, also known as maculopapular or exanthematous eruptions. Antibiotics are the most commonly implicated drugs, but there are many potential causes. These eruptions are usually symmetric consisting of pruritic pink macules and papules which eventually become confluent. The eruptions usually begin on the trunk or areas of pressure. The mucus membranes may be involved, along with the palms and soles, and a mild fever is a common finding. The reaction usually appears within a week after the initiation of therapy; however, with some drugs, especially penicillin, the reaction may occur more than two weeks after therapy has begun. The eruption usually lasts one to two weeks, and may be associated with moderate to severe pruritis.

Urticaria, a skin reaction characterized by pruritis, red-wheals and localized cutaneous edema, develops and resolves quickly. When deep dermal and subcutaneous tissues are involved, the reaction is known as angioedema. Angioedema may involve mucus membranes, and may be a part of a life-threatening anaphylactic reaction. Antibiotics, especially penicillin and sulfa are the most common causative agents. Urticaria is the second most commonly seen cutaneous reaction.

Fixed drug eruptions appear as oval, erythematous plaques with or without vesicles. These lesions recur at the same site upon subsequent exposure of the offending agent. This drug reaction is an exception to the general rule that drug eruptions are symmetric. These eruptions are initially well-demarcated, dusky red plaques that fade after a week. Areas of residual hyperpigmentation may last for months or years. A fixed drug eruption can occur anywhere on the skin, however the areas of frequent involvement include the palms and soles, lips, and glans penis. The most common cause of a fixed drug reaction is tetracycline.

Lichenoid drug eruptions may appear identical to lichen planus. These lesions can be characterized by the "five P's": purple, polygonal, papules, pruritic, and peripheral. Histopathologically, eosinophils are seen more frequently in drug-induced lichen planus. Gold and antimalaria drugs are most often implicated in lichenoid eruptions. Antihypertensive agents such as beta blockers and ACE inhibitors are also common causes of this drug reaction.

Erythema nodosum is a panniculitis which is characterized by tender, erythematous, dough-like nodules that are usually located on the anterior leg. There are many etiologies of erythema nodosum which include: streptococcal, tuberculosis, and deep fungal infections, sarcoidosis, inflammatory bowel disease, and drug reactions. Oral contraceptives are the most common cause of drug-induced erythema nodosum.

Vasculitis may be due to a number of etiologies including infections, malignancies, cryoglobulinemia, serum sickness, collagen vascular diseases and drug-induced. The hallmark dermatological lesion in vasculitis is "palpable purpura." However, lesions can vary and may present as erythematous macules or papules, urticarial lesions, bullae, and hemorrhagic vesicles. The most common causes of drug-induced vasculitis includes allopurinol, thiazides, penicillin, and phenytoin.

Toxic epidermal necrolysis can be a life-threatening drug reaction characterized by a full-thickness sloughing of the epidermis from the dermis. This syndrome is a medical emergency and patients should be hospitalized and treated like a burn patient. There can be profound volume loss, electrolyte imbalances, and the risk for bacterial infection is great. The onset is usually acute, and in adults drugs are the most common cause. This reaction is most often associated with allopurinol, but has also been seen with nonsteroidal anti-inflammatory agents, sulfonamides, and measles vaccine. Clinically, drug-induced toxic epidermal necrolysis may be confused with staphylococcal scalded skin syndrome.

Erythema multiforme is an acute, self-limiting, inflammatory reaction of the skin characterized by distinctive iris and/or target lesions. When the reaction is severe, involving mucous membranes with accompanying fever and malaise, the proper terminology becomes Stevens-Johnson syndrome. Precipitating factors include infections, such as herpes simplex, neoplasms, and therapeutic agents. The agents most commonly implicated include the long-acting sulfonamides, penicillins, phenytoin, and phenylbutazone. The pathogenesis of erythema multiforme/Stevens-Johnson syndrome is uncertain. However, there is speculation of an immune complex-induced lymphocyte-mediated mechanism.

Photosensitivity reactions involve the sun-exposed areas of the skin. The most common sites include the malar area of the face, lower lip, extensor surfaces of the hands and arms, and the upper portions of the chest and back. The upper lids, behind the ears, and below the chin are often spared. The morphology of the skin eruption is variable. Erythematous plaques with or without scale, eczematous dermatitis, vesicles, bullae, and sunburn-like reactions all occur. Drugs that are known to cause this reaction include tetracycline, thiazide diuretics, and sulfonamides.

Table 2 lists the various patterns of drug reactions. The drugs listed in each category are the most frequently reported causes of each reaction.

DIAGNOSIS

It is important to remember that any agent can cause a cutaneous eruption. When evaluating a cutaneous eruption, one should gather information such as onset of the rash, current medications (prescription and over the counter), allergies, recent illnesses, and prior history of dermatoses.

The author uses the acronym TOM (Timing, Other Explanation, Morphology) to outline the steps in evaluating a suspected drug reaction. Timing: Most drug eruptions present during the first two weeks of administration. Reactions that occur after two weeks are less likely drug-induced. Other Explanation: Remember that drug eruptions can mimic nearly all the morphological expressions in dermatology. Drug eruption is always first on the list of differential diagnoses in light of a sudden, symmetrical, skin eruption. Always consider other etiologies such as: infectious (viral exanthem, bacterial induced vasculitis), exacerbation of existing or preexisting dermatoses (psoriasis), and coincidental/unrelated dermatitis. Morphology: As described previously, there are numerous cutaneous morphological patterns in which drug eruptions may present. Extensive study and research has not only proven which agents are

Table 2

FREQUENTLY REPORTED DRUG REACTIONS

Acneiform
- Corticosteriods
- Oral Contraceptives
- Phenytoin
- Iodides
- Lithium

Alopecia
- Anticoagulants
- Antimetabolites (5-FU, 6-Mercaptopurine, Methotrexate)
- Trimethadione
- Vincristine

Erythema Multiforme
- Barbiturates
- Chlorpropamide
- Griseofulvin
- Phenytoin
- Penicillin
- Phenothiazines
- Sulfonamides
- Thiazides

Erythema Nodosum
- Bromides
- Codeine
- Iodides
- Oral Contraceptives
- Salicylates
- Sulfonamides
- Penicillin

Fixed Drug Eruptions
- Barbiturates
- Meprobamate
- Oral Contraceptives
- Phenacetin
- Phenolphthalein
- Phenylbutazone
- Salicylates
- Sulfonamides
- Tetracyclines

Lichenoid
- Salicylates
- Chlordiazepoxide
- Chloroquine
- Gold
- Quinacrine
- Quinidine
- Thiazides

Lupus Erythematosus
- Chlorpropamide
- Griseofulvin
- Hydralazine
- Isoniazid
- Penicillin
- Phenothiazines
- Phenylbutazone
- Phenytoin
- Procainamide
- Sulfonamides
- Thiouracils

Photosensitivity
- Griseofulvin
- Nalidixic acid
- Phenothiazines
- Piroxicam
- Psoralens
- Quinidine
- Sulfonamides
- Sulfonylureas
- Tetracyclines
- Thiazides

Toxic Epidermal Necrolysis
- Allopurinol
- Barbiturates
- Phenytoin
- Phenylbutazone
- Penicillin
- Sulfonamides
- Tetracylines
- Thiazides

Vasculitis
- Allopurinol
- Gold
- Phenytoin
- Phenothiazines
- Propylthiouracil
- Sulfonamides
- Thiazides

Vesiculobullous
- Barbiturates
- Bromides
- Iodides
- Penicillin
- Penicillamine

more likely to cause a drug eruption, but also, their corresponding morphological pattern. With this information, one can assess the likelihood of a particular agent causing a particular cutaneous eruption.

Other factors that are involved with the diagnosis of a drug eruption include dechallenge and rechallenge. The *sine qua non* of the diagnosis is resolution following dechallenge and recurrence on rechallenge (provocation).

TREATMENT

Once the diagnosis of drug eruption has been made, the offending agent should be discontinued, if possible. One must weigh the risks and benefits of continuation or cessation of an agent. With respect to patients taking multiple medications, all drugs not absolutely necessary should be discontinued, with special attention directed toward the agents that have statistically shown to be common offenders. Further treatment other than supportive care is rarely needed. Topical and oral corticosteriods as well as antihistamines may be beneficial for quick relief of inflammation, edema, and pruritis.

The treatment of life-threatening drug reactions such as anaphylaxis requires parenteral administration of epinephrine and cardiopulmonary support. Toxic epidermal necrolysis requires hospitalization, preferably in a burn unit if available.

Cutaneous eruptions are common complications of pharmacotherapy. Making the diagnosis of cutaneous drug reactions and identifying the causative agent can be challenging. Previous experience with medications has provided invaluable quantitative and qualitative information. Knowledge of the most common agents associated with cutaneous eruptions and their predictable patterns can aid the physician in identifying the offending drug.

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