74 Cutaneous Drug Reactions

Kanade Shinkai, Robert S. Stern, Bruce U. Wintroub

Cutaneous reactions are among the most frequent adverse reactions to drugs. Most are benign, but a few can be life threatening. Prompt recognition of severe reactions, drug withdrawal, and appropriate therapeutic interventions can minimize toxicity. This chapter focuses on adverse cutaneous reactions to systemic medications; it covers their incidence, patterns, and pathogenesis and provides some practical guidelines on treatment, assessment of causality, and future use of drugs.

USE OF PRESCRIPTION DRUGS IN THE UNITED STATES

In the United States, more than 3 billion prescriptions for over 60,000 drug products, which include more than 2000 different active agents, are dispensed annually. Hospital inpatients alone annually receive about 120 million courses of drug therapy, and half of adult Americans receive prescription drugs on a regular outpatient basis. Many patients use over-the-counter medicines that may cause adverse cutaneous reactions.

INCIDENCE OF CUTANEOUS REACTIONS

Several large cohort studies established that acute cutaneous reaction to drugs affected about 3% of hospital inpatients. Reactions usually occur a few days to 4 weeks after initiation of therapy.

Many drugs of common use are associated with a 1–2% rate of rashes during premarketing clinical trials. The risk is often higher when medications are used in general, unselected populations. The rate may reach 3–7% for amoxicillin, sulfamethoxazole, many anticonvulsants, and anti-HIV agents.

In addition to acute eruptions, a variety of skin diseases can be induced or exacerbated by prolonged use of drugs (e.g., pruritus, pigmentation, nail or hair disorders, psoriasis, bullous pemphigoid, photosensitivity, and even cutaneous neoplasms). These drug reactions are not frequent, but neither their incidence nor their impact on public health has been evaluated.

In a series of 48,005 inpatients over a 20-year period, morbilliform rash (91%) and urticaria (6%) were the most frequent skin reactions. Severe reactions are actually too rare to be detected in such cohorts. Although rare, severe cutaneous reactions to drugs have an important impact on health because of significant sequelae, including mortality. Adverse drug rashes are responsible for hospitalization, increase the duration of hospital stay, and are life threatening. Some populations are at increased risk of drug reactions, including patients with collagen vascular diseases, bone marrow graft recipients, and those with acute Epstein-Barr virus infection. The pathophysiology underlying this association is unknown, but may be related to immunocompromise or immune dysregulation. Risk of drug allergy, including severe hypersensitivity reactions, is increased with HIV infection; individuals with advanced HIV disease (e.g., CD4 T lymphocyte count <200 cells/μL) have a forty- to fiftyfold increased risk of adverse reactions to sulfamethoxazole (Chap. 226).

PATHOGENESIS OF DRUG REACTIONS

Adverse cutaneous responses to drugs can arise as a result of immunologic or nonimmunologic mechanisms.

NONIMMUNOLOGIC DRUG REACTIONS

Examples of responses that arise from nonimmunologic mechanisms are pigmentary changes related to dermal accumulation of medications or their metabolites; alteration of hair follicles by antimetabolites and signaling inhibitors; and lipodystrophy associated with metabolic effects of anti-HIV medications. These side effects are mostly toxic, predictable, and sometimes can be avoided in part by simple preventive measures.

IMMUNOLOGIC DRUG REACTIONS

Evidence suggests an immunologic basis for most acute drug eruptions. Drug reactions may result from immediate release of preformed mediators (e.g., urticaria, anaphylaxis), antibody-mediated reactions, immune complex deposition, and antigen-specific responses. Drug-specific T cell clones can be derived from the blood or from skin lesions of patients with a variety of drug allergies, strongly suggesting that these T cells play a role in drug allergy in an antigen-specific manner. Specific clones were obtained with penicillin G, amoxicillin, cephalosporins, sulfamethoxazole, phenobarbital, carbamazepine, and lamotrigine (medications that are frequently a cause of drug eruptions). Both CD4 and CD8 clones have been obtained; however, their specific roles in the manifestations of allergy have not been elucidated. Drug presentation to T cells was major histocompatibility complex (MHC)-restricted and may involve drug-peptide complex recognition by specific T cell receptors (TCRs).

Once a drug has induced an immune response, the final phenotype of the reaction probably depends on the nature of effectors: cytotoxic (CD8+) T cells in blistering and certain hypersensitivity reactions, chemokines for reactions mediated by neutrophils or eosinophils, and collaboration with B cells for production of specific antibodies for urticarial reaction. Immunologic reactions have recently been classified into further subtypes that provide a useful framework for designating adverse drug reactions based on involvement of specific immune pathways (Table 74-1).

Immediate Reactions Immediate reactions depend on the release of mediators of inflammation by tissue mast cells or circulating basophils. These mediators include histamine, leukotrienes, prostaglandins, bradykinins, platelet-activating factor, enzymes, and proteoglycans. Drugs can trigger mediator release either directly ("anaphylactoid" reaction) or through IgE-specific antibodies. These reactions usually manifest in the skin and gastrointestinal, respiratory, and cardiovascular systems (Chap. 376). Primary symptoms and signs include pruritus, urticaria, nausea, vomiting, abdominal cramps, bronchospasm, laryngeal edema, and, occasionally, anaphylactic shock with hypotension and death. They occur within minutes of drug exposure. Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, and radiocontrast media are frequent causes of direct mast cell degranulation or anaphylactoid reactions, which can occur on first exposure. Penicillins and muscle relaxants used in general anesthesia are the most frequent causes of IgE-dependent reactions to drugs, which require prior sensitization. Release of mediators is triggered when polyvalent drug protein conjugates cross-link IgE molecules fixed to sensitized cells. Certain routes of administration favor different clinical patterns (e.g., gastrointestinal effects from oral route, circulatory effects from intravenous route).

Immune Complex–Dependent Reactions Serum sickness is produced by tissue deposition of circulating immune complexes with consumption of complement. It is characterized by fever, arthritis, nephritis, neuritis, edema, and a urticarial, papular, or purpuric rash (Chap. 385). First described following administration of nonhuman sera, it currently occurs in the setting of monoclonal antibodies and other similar medications. In classic serum sickness, symptoms develop 6 days or more after exposure to a drug, the latent period representing the time needed to synthesize antibody. Cutaneous or systemic vasculitis, a relatively rare complication of drugs, may also be a result of immune complex deposition (Chap. 385). Cephalosporin and other medications, including monoclonal antibodies such as infliximab, rituximab, and omalizumab, may be associated with clinically similar "serum sickness–like" reactions. The mechanism of this reaction is unknown but is unrelated to complement activation and immune complex formation.

Delayed Hypersensitivity While not completely understood, delayed hypersensitivity directed by drug-specific T cells is an important mechanism underlying the most common drug eruptions, i.e., morbilliform eruptions, and also rare and severe forms such as drug-induced hypersensitivity syndrome (DIHS) (also known