

Drug-Induced Urticarias

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Abstract

Drugs may cause urticaria by different mechanisms. The most well-known mechanism is the allergic reaction mediated by immunoglobulin (Ig)E antibodies, which induce acute generalized urticaria. Allergic reactions to β -lactams are the most common cause of adverse drug reaction mediated by IgE antibodies. However, IgE antibodies are not always necessary to activate the release of mediators from mast cells and induce acute urticarias. Some drugs, such as opiates or codeine, act directly on mast cells, and others, such as aspirin and nonsteroidal anti-inflammatories, induce an exacerbation of chronic urticaria by a pharmacological mechanism involving the arachidonic acid metabolism. Additionally, angioedema is a well-known complication of angiotensin-converting enzyme inhibitors by its action on bradykinin, which is a potent vasodilator agent. Topical drugs, such as antibiotics, disinfectants, or anesthetics, may cause urticaria, which sometimes progresses to generalized urticaria and, more rarely, to anaphylactoid reactions.

Index Entries

Urticaria; angioedema; aspirin; nonsteroidal anti-inflammatory drugs; angiotensin-converting enzyme inhibitors.

Introduction

Urticaria is a common skin disease that affects 15 to 25% of people at some point in their lives. It describes circumscribed, edematous, erythematous, pruritic wheals that are widely scattered on the body, and it is often associated with angioedema, which is a non-itchy, pale swelling of subcutaneous or submucosal tissue

(1). Urticaria is classified as either acute or chronic. Acute urticaria is defined as urticaria that has been present for less than 6 wk. Chronic urticaria (CU) is defined as urticaria that has been continuously or intermittently present for at least 6 wk (2). These two types of urticaria respond to different etiological and physiopathological mechanisms, which can be related to drugs. Contact urticaria is a third type of urticaria

Table 1
Drugs That Cause Urticaria

Antibiotics: penicillins, cephalosporins, aminoglycosides, tetracyclines, sulphonamides	Sorbitol complexes
Antifungal agents: fluconazole, ketoconazole	Enzymes: trypsin, streptokinase, chymopapain
Angiotensin-converting enzyme inhibitors	Steroids
Radiographic contrast media	Polypeptide hormones: insulin, corticotrophin, vasopressin
Nonsteroidal anti-inflammatory agents (including salicylate agents)	Hydantoins
Narcotic analgesics	Hydralazine
Anesthetic agents (local and general)	Quinidine
Muscle myorelaxants (curare)	Anticancer drugs
Dextrans	Vaccines
Mannitol	Vitamins
	Protamin

that can be caused by drugs through topical application. Although acute urticaria and contact urticaria may be induced by either immunological or nonimmunological mechanisms, in CU, the aggravation of the skin manifestations may only be related to a nonallergic mechanism that usually involves a pharmacological pathway.

Acute Urticaria and Drugs

Acute urticaria is defined as transient, circumscribed areas of raised erythema and edema of the superficial dermis. It occurs on any part of the skin and fades without a trace within a few hours. Hives lasting less than 6 wk are also called acute urticaria. Acute urticaria is the most frequent type of urticaria and the most common causes are food, drugs, or infections. Insect bites and internal diseases may also be responsible (3). Acute urticaria may be induced by immunological allergy (IgE- or immune-complex-dependent reactions) or by nonimmunological mechanisms.

After exanthematous eruption, urticaria/angioedema is the second most common type of skin reaction caused by drugs. Table 1 lists the most common drugs that cause acute urticaria/angioedema.

Drugs that induce urticarial lesions by nonimmunological manifestations do not need previous sensitization because they act

directly on the mediator release of mast cells. These drugs are opiates, codeine, amphetamine, polymixin B, atropine, muscle relaxants, hydralazine, pentamidine, quinine, and radiocontrast media. Frequently, the urticarial reaction occurs within a few hours or days after the drug administration and disappears within several days following discontinuation of the drug.

Conversely, drug reactions that are immunologically mediated require a period of sensitization. Usually, the initial therapeutic course with the drug is generally uneventful. Nevertheless, an immunological reaction may occur during the first exposure but always after several treatment days (18–21 d). Generally, allergic urticaria is the cutaneous manifestation of a type I reaction that is mediated by IgE antibodies. After the latent period of uneventful therapy with the drug, an IgE-mediated reaction may occur. Thereafter, urticaria may develop within minutes (maximum: 1 h) after the first dose. This immediate hypersensitivity can also produce more severe manifestations, such as angioedema and anaphylaxis, which may be fatal. The allergic reaction mediated by IgE antibodies usually subsides a few hours after discontinuation of the drug (<24 h).

Allergic reactions to β -lactams are the most well-known causes of adverse drug reaction mediated by IgE antibodies. These acute reac-

tions may be induced by all β -lactams currently available, ranging from benzylpenicillins to other, more recently introduced β -lactams, such as aztreonam. The incidence of such reactions is about 1 in 5000 exposures, less than 10% of which are fatal.

Allergic urticaria may also be induced by a type III reaction that is mediated by immune complexes that activate the complement cascade, with resultant formation of anaphylatoxins, which trigger release of mediators from mast cells and basophils, thus resulting in urticaria. Serum sickness reactions occur when IgG or IgM antibodies combine drug antigen in antigen excess. In this immune-complex-dependent drug reaction, urticaria often is associated with systemic symptoms, such as fever, arthritis, nephritis, neuritis, and papular rash. The allergic reaction appears from between 6 d and 3 wk after initial exposure to the drug and disappears no longer than several weeks after drug discontinuation. Table 2 lists the most frequent drugs responsible for serum sickness.

Some drugs, such as aspirin, may induce immunological and nonimmunological reactions. The frequency of urticaria/angioedema to aspirin in an outpatient population is about 1%. Facial (periorbital) angioedema constitutes the most common form of clinical presentation, and one-third of patients show a mixed clinical pattern of cutaneous (urticaria and/or angioedema) (4). Usually, urticaria/angioedema caused by aspirin should be considered a pharmacological side effect rather than an allergy, even if the clinical manifestations are the same. Intolerance to aspirin occurs within minutes to hours after drug administration and generally subsides 24 to 48 h after discontinuation. Occasionally, angioedema may be very severe, with a swelling of the lips and tongue that may impair swallowing and ventilation. Edema of the larynx or the epiglottis may also induce an upper airway obstruction.

Aspirin is a cyclo-oxygenase (COX) inhibitor. The COX inhibitor is an enzyme that metabolizes arachidonic acid. There are two different arachi-

Table 2
Drugs That Cause Serum Sickness

Allopurinol
Arsenicals and mercurial derivatives
Aspirin
Barbiturates
Captopril
Penicillins and cephalosporins
Furazolidone
Gold salts
Globulin preparations
Griseofulvin
Halothane
Hydralazine
Iodides
Methyldopa
Para-aminosalicylic acid
Penicillamine
Phenytoin
Piperazine
Procainamide
Quinidine
Streptokinase
Sulfonamides
Thiouracils

donic acid COX inhibitors: COX1 and COX2. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX-1 and, therefore, lead to a shunting of arachidonic acid metabolism toward the 5-lipoxygenase pathway. This activation results in an increased synthesis and release of cysteinyl leukotrienes, which induce vasodilatation and edema and, therefore, urticaria. Although COX-2 inhibitors, known as coxibs, seem to be well tolerated by the majority of classic NSAID-sensitive patients, cutaneous reactions to highly selective inhibitors of COX-2 have also been reported (5–9).

Some other drugs are known to be responsible for acute or recurrent localized orbital edemas, including calcium channel blockers, rifampicin, atracurium (muscle relaxant), methylprednisolone, psychotropic drugs, and mannitol. Mechanisms are different for each drug but are usually induced by decreased lymphatic flow or arteriolar vasodilatation (10).

CU and Drugs

CU is actually considered a nonallergic skin disease that is induced by a nonspecific activation of mastocytes. Conversely to acute urticaria, CU is defined by urticarial manifestations involving during a period of at least 6 wk. Therefore, mechanisms that induce urticarial manifestations cannot be mediated by IgE antibodies. In other words, drugs cannot be responsible of allergic CU (11). Nevertheless, some drugs can induce an exacerbation of chronic urticarial lesions and, more specifically, angioedema. Aspirin, NSAIDs, codeine, and morphinic agents are the most common drugs that accelerate the course of CU by a direct action on mast cell release. About 30 to 75% of patients suffering from CU may develop angioedema after administration of acetylsalicylic acid or NSAIDs. It is generally believed that patients who experience acute urticaria after taking aspirin or other NSAIDs are monosensitive, and they should be able to take other anti-inflammatory drugs without difficulty. On the other hand, subjects with intolerance to multiple NSAIDs are more frequently patients with CU. In some cases, intolerance to NSAIDs might precede the onset of CU by years (12).

Mechanisms underlying multiple intolerance to NSAIDs in patients with CU appear to be the same as those implicated in acute urticaria, with evidence that these reactions result from the interference of aspirin-like drugs with arachidonic acid metabolism.

Recurrent angioedema is also a known side effect of angiotensin-converting enzyme (ACE) inhibitors (0.1–0.5% of patients treated by ACE inhibitors) (13,14). The mechanism that induces angioedema is not related to an allergy but is directly related to the ACE that is a potent inhibitor of kinase II (15). Consequently, it facilitates the breakdown of bradykinin and the increase in bradykinin levels. This overproduction of bradykinin results in continued prostaglandin E₂ synthesis, vasodilation, increased

vascular permeability, and increased interstitial fluid. Together with the cough, angioedema is the most common complication of ACE inhibitor therapy (16). Angioedema generally occurs within 2 to 6 mo of administration of the drug, although longer durations of therapy (several years) are not uncommon. Lip and tongue swelling are the most common airway manifestations. About 0.1 to 0.5% of patients treated by ACE inhibitors may develop angioedema, which sometimes requires endotracheal intubation. The periodicity of angioedemas is variable from one per week to one per month or less.

Angiotensin receptor antagonists or angiotensin II receptor blockers (ARBs) are not expected to produce angioedema, because they do not inhibit the catabolism of bradykinin and do not increase bradykinin levels. However, it is now apparent that angioedema is occasionally associated with angiotensin receptor antagonist therapy and may be more likely to occur in patients who have previously experienced angioedema while receiving ACE inhibitors (17–20). Therefore, clinicians should exercise caution when using ARBs in patients with a history of angioedema secondary to ACE inhibitors (21).

One case of recurrent amiodarone-induced angioedema has been also reported (22).

Contact Urticaria and Drugs

Contact dermatitis caused by drugs usually presents as a typical eczema but, less commonly, can present as an urticaria. Drug-contact urticaria is a transient, wheal-and-flare response at the site of cutaneous contact with a topical application of a drug. The lesions occur within minutes to an hour and resolve within a few minutes (<2 h) and leave normal skin. Contact urticaria may be produced by immunological or nonimmunological mechanisms. Similarly to generalized IgE-dependent urticarias induced by systemic drugs, the pathogenesis of immunologically mediated contact urticaria is

caused by an antigen antibody, type 1, IgE-mediated hypersensitivity reaction.

Nonimmunological contact urticarias are not as well studied regarding their pathogenesis because various mediators (substance P, histamine, leukotrienes, prostaglandins, etc.) may initiate the urticarial response. They require that a subject have no prior sensitization, and they are not mediated by antibodies. Generally, the reaction remains localized. Conversely, immunologically mediated urticaria may spread beyond the site of contact and progress to generalized urticaria and, more rarely, to anaphylactoid reactions with the involvement of extracutaneous organs with asthma, rhinitis, and gastrointestinal tract symptoms. Antibiotics (penicillin, cephalosporin, gentamycin, neomycin, bacitracin, streptomycin, chloramphenicol, etc.) used by medical personnel and chemists may provoke contact urticaria through administration to patients or other handling. More frequently, these antibiotics can induce contact urticaria when included in topical preparations, such as cream, ointment, auricular, or eye drops. Neomycin, which is the most widely used topical antibiotic, causes acute localized contact eczema and induces contact urticaria. Bacitracin has been reported to induce severe anaphylaxis. Contact urticaria has also been described with topical anesthetics, such as benzocaine and, more recently, lidocaine contained in Emla cream (23).

Chlorhexidine, which is widely used as an antiseptic and disinfectant, may induce adverse skin reactions, such as contact dermatitis, photosensitive dermatitis, and contact urticaria. Recently, an increasing number of immediate-type allergies (IgE-mediated), such as contact urticaria, occupational asthma, and severe anaphylactic shock, have been reported (24,25).

Therefore, physicians should be aware of the allergic side effects of these topical drugs before administering them in systemic ways.

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