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PATHOPHYSIOLOGY OF ALLERGIC DRUG REACTIONS

Robert Likić[1] & Daniela Bevanda Glibo[2]

[1]*Department of Internal Medicine, Clinical Hospital Center Zagreb, Zagreb, Croatia*
[2]*Department of Internal Medicine, University Hospital Mostar, Mostar, Bosnia and Herzegovina*

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SUMMARY

Adverse drug reactions (ADR) may be broadly divided into types A and B. Type A comprise the majority of reactions, can affect any individual, and are predictable from the known pharmacologic properties of a drug. Type B are less common, occur in susceptible patients and cannot be predicted. Allergic/immunologic drug reactions are a group of type B ADRs. Based on the time of onset allergic drug reactions can be divided into immediate and delayed and based on their underlaying immunologic mechanism, they can be further subdivided into 4 groups: immediate and mediated by IgE (1), delayed and caused by antibody facilitated cell destruction (2), delayed and caused by drug immune complex deposition and complement activation (3) and delayed and T cell mediated (4). Physicians should always insist on obtaining a thorough patient's history regarding drug allergy as well as on ascertaining details regarding the medication used, its route of administration, dosage and the treatment duration in order to properly assess risk of drug allergies and suggest further work-up in that regard.

Key words: *drug - medication - allergy - pathophysiology*

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INTRODUCTION

Allergic drug reaction is an adverse drug reaction (ADR) arising from the body's immunologic response to a medication. Broadly speaking, all adverse drug reactions can be further subdivided into two categories, type A and type B (Table 1).

TYPE A AND TYPE B DRUG REACTIONS

Type A reactions comprise between 85% and 90% of all ADRs and given sufficient exposure duration and dose, they can be predicted based on the known pharmacologic properties of the drug. Some examples of type A ADRs would be: gastritis with long term use of nonsteroidal antiinflammatory drugs (NSAID) or nephrotoxicity associated with aminoglycoside administration.

Type B reactions are far less common and comprise up to 15% of ADRs. They typically cannot be predicted and are mediated by immunologic or other types of mechanisms. They can be further subdivided into 3 groups: 1. immunologic drug reactions (drug allergy), which result from specific immunologic response to medication and account for between 6 to 10% of total ADRs (Lazarou et al. 1998); 2. idiosyncratic drug reactions, which arise from genetic differences in the patient, such as with azathioprine toxicity developing in patients with thiopurine methyltransferaze (TPMT) deficiency (Lennard 2014, Dern et al. 1981, Lennard et al. 1989); and 3. exaggerated drug toxicity/intolerance which manifests in some patients as pharmacologically caused toxicity of a particular drug appearing at a much lower or sometimes even subtherapeutic dose, such as in patients who develop tinnitus after a single Aspirin dose (Muszkat 2007).

Based on the underlying immunologic mechanism, immunologic ADRs can be divided into 4 groups according to the Gell and Coombs system: Type 1 – immediate in onset and mediated by IgE and mast and basophil cell degranulation; Type 2 – delayed in start and caused by IgG mediated cell destructions; Type 3 – delayed in onset and caused by IgG and drug immune complex deposition as well as complement activation and Type 4. – delayed in onset and T cell mediated.

Furthermore, World Allergy Organization (WAO) has recommended dividing immunologic ADRs into immediate which have onset within one hour of exposure and which are IgE mediated and encompass Gell and Coombs Type 1 reactions and delayed reactions with onset after one hour of exposure, which may be caused by several different immunologic mechanisms and are not IgE related. Gell and Coombs reactions types II, III and IV are all considered delayed reactions, see Table 2 (Pichler 2007, Johansson et al. 2004).

In type 1 reactions, drug specific IgE can be found as surface receptors on mast cells and basophils in the body. Upon exposure, drug molecules or their metabolites bind to these IgE antibodies leading to activation of the immune cells causing signs and symptoms of allergy including urticarial rash, flushing, pruritus, angioedema of extremities, larynx, face, wheezing, gastrointestinal symptoms, hypotension and/or anaphylaxis. Characteristically, there is no fever or serum C reactive protein elevation in type 1 reactions. The drugs most commonly implicated in type 1 reactions include: beta lactam antibiotics (penicillins, cephalosporins), neuromuscular blocking agents, quinolones, platinum based chemotherapeutics (for example carboplatin and oxaliplatin), foreign proteins, including biologic drugs (cetuximab, rituximab); (Sachs et al. 2006, Manfredi et al. 2004, Schmid et al. 2006).

Table 1A. Classification of adverse drug reactions (Celik et al. 2009)
Type A: Reactions occurring in most normal patients, given sufficient dose and duration of therapy: Common and predictable

Drug reaction	Examples
Overdose	Hepatic failure (acetaminophen) Metabolic acidosis (aspirin)
Side effects	Nausea, headache (with methylxanthines) Oral thrush or vaginal candidiasis (with glucocorticoids) Nephrotoxicity (with aminoglycosides)
Secondary or indirect effects	Diarrhea due to alteration in GI bacteria after antibiotics Phototoxicity (with doxycycline or thiazide diuretics)
Drug interactions	Macrolide antibiotics increasing theophylline, digoxin, or statin blood levels

Table 1B. Classification of adverse drug reactions (Celik et al. 2009)
Type B: Drug hypersensitivity reactions restricted to a small subset of the general population: Rare and mostly unpredictable

Drug reaction	Examples
Intolerance	Tinnitus after a single aspirin tablet
Idiosyncrasy (pharmacogenetics)	G6PD deficiency: Hemolytic anemia after antioxidant drugs (eg, dapsone) TMPT deficiency: Toxicity during azathioprine therapy Pseudoallergic reaction (with NSAIDs)
Immunologic drug reactions (allergy)	Anaphylaxis from beta-lactam antibiotics Photoallergy with quinidine Immune-mediated thrombocytopenia (with heparin) Serum sickness (with antivenom preparations) Vasculitis (with phenytoin) Stevens-Johnson syndrome (with trimethoprim-sulfamethoxazole) Drug-induced hypersensitivity syndrome (with allopurinol in HLA-B*58:01 individuals)

Table 2. Gell and Coombs classification of immunologic drug reactions (Weiss & Adkinson 1998)

Type	Description	Mechanism	Clinical features
I Immediate reaction (within one hour)	IgE-mediated, immediate-type hypersensitivity	Antigen exposure causes IgE-mediated activation of mast cells and basophils, with release of vasoactive substances, such as histamine, prostaglandins, and leukotrienes.	Anaphylaxis Angioedema Bronchospasm Urticaria (hives) Hypotension
II	Antibody-dependent cytotoxicity	An antigen or hapten that is intimately associated with a cell binds to antibody, leading to cell or tissue injury.	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Damage is caused by formation or deposition of antigen-antibody complexes in vessels or tissue. Deposition of immune complexes causes complement activetion and/or recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors.	Serum sickness Arthus reaction
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (ie, types IVa to IVd).	Contact dermatitis Some morbilliform reactions Severe exfoliative dermatoses (eg, SJS/TEN) AGEP DRESS/DiHS Interstitial nephritis Drug-induced hepatitis Other presentations

Type 2 reactions are rare and involve antibody mediated cell destruction, usually when a drug molecule binds to the surface of certain cellular types, thus acting as antigen and causing subsequent binding of antibodies to cell surfaces leading to these cells being targeted by macrophages for clearance. Clinical presentation may include thrombocytopenia (heparin, NSAIDs, vancomycin), neutropenia (propylthiouracil, flecainide), hemolytic anemia (cephalosporins, penicillins, NSAIDs) with patients otherwise being asymptomatic or presenting with fulminant illness.

Table 3. Common examples of pseudoallergic drug reactions (Celik et al. 2009)

Drug	Clinical reaction(s)	Presumed mechanism
Aspirin and other NSAIDs	Exacerbations of rhinitis, asthma (in patients with aspirin-exacerbated respiratory disease) Urticaria/angioedema (NOTE: Urticaria may also result from a type I, IgE-mediated allergic reaction)	Inhibited prostaglandin production and enhanced leukotriene production
Opiates	Pruritus, urticaria	Direct stimulation of mast cells and/or basophils causing release of mediators
Vancomycin	Flushing during infusion	Direct stimulation of mast cells and/or basophils causing release of mediators
Radiocontrast media	Anaphylaxis, shock (NOTE: Some may be type I, IgE-mediated allergic reactions)	Unknown mechanism
Ciprofloxacin	Urticaria (most reactions)	Direct stimulation of mast cells and/or basophils causing release of mediators
Local anesthetics	Syncope	Vasovagal reflex
Protamine	Hypotension, pulmonary hypertension	Unknown mechanism
Choline	Pruritus, urticaria	Unknown mechanism
Isoniazid	Hepatitis	Unknown mechanism

Type 3 reactions are uncommon and usually present as vasculitis, serum sickness or drug fever, all mediated by drug-antibody complexes forming after prolonged, high dose drug administration. Drug antibody complexes precipitate in various tissues thus activating complement with ensuing inflammatory response. Drug induced vasculitis characteristically presents with palpable purpura, fever, petechiae, arthralgias, urticaria, elevated erythrocyte sedimentation rate and low complement levels. Drugs most commonly associated with vasculitis include penicillins, cephalosporins, allopurinol, sulfonamides and phenytoin. Furthermore, serum sickness (fever, purpuric rash, arthralgia and/or glomerulonephritis) can be a complication of antitoxins like botulism, rabies and venoms (Froehlich & Verma 2001, Relyveld et al. 1998, Siegrist 2007).

Type 4 reactions are typically delayed in onset by at least 48 to 72 hours, sometimes by days to weeks after exposure to culprit drug, as they involve activation of T lymphocytes. Patterns of cutaneous involvement associated with type 4 reactions include: contact dermatitis, maculopapular (morbiliform) eruptions, drug fever, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug induced hypersensitivity syndrome. Occasionally with T-cell mediated hypersensitivity, organ involvement occurs in the absence of skin findings, or skin findings are minor and overlooked. Such presentations include isolated, drug-induced hepatitis, isolated interstitial nephritis, and isolated pneumonitis (Clark et al. 2006, Schaerli et al. 2004, Storrs 1991, Pleasants et al. 1994).

PSEUDOALLERGIC DRUG REACTIONS

Pseudoallergic drug reactions are adverse drug reactions that mimic allergic drug reactions, but in which the role of immune system has not been established, see Table 3. Another name for these reactions is "nonimmune hypersensitivity reactions" and they can range in severity from mild to fatal, hence they should be treated in the same manner as immunologic allergic reactions (Johansson et al. 2004). Pseudoallergic reactions are especially difficult to distinguish clinically because they can be similar or identical in presentation to true allergic reactions (Pichler 2018).

CONCLUSIONS

Although the different types of allergic drug reactions have characteristic signs and symptoms, and the timing of onset of symptoms may also be helpful in distinguishing one type of reaction from another, there is significant clinical overlap among them, hence clinicians should always insist on obtaining a thorough history of the patient with drug allergy as well as on ascertaining details regarding the medication used, its route of administration, dosage and the treatment duration in order to properly assess risk of drug hypersensitivity and suggest further work-up in that regard.

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Contribution of individual authors:

Robert Likić: conception and design of the publication, writing the first draft participate in drafting the article.

Daniela Bevanda Glibo: participate in revising it critically for important intellectual content, approval of the final version.

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Correspondence:
Robert Likić, MD
Department of Internal Medicine, Clinical Hospital Center Zagreb
Kišpatićeva 12, 10 000 Zagreb, Croatia
E-mail: robert.likic@mef.hr