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To cite this article: Ionut Dragostin, Oana-Maria Dragostin, Elena Lăcrămioara Lisă, Simona Claudia Stefan, Alexandra Simona Zamfir, Camelia Diaconu & Carmen Lăcrămioara Zamfir (2020): Drugs frequently involved in inducing hypersensitivity reactions, Drug and Chemical Toxicology

To link to this article: <https://doi.org/10.1080/01480545.2020.1746331>



Published online: 05 Apr 2020.



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REVIEW



Drugs frequently involved in inducing hypersensitivity reactions

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ABSTRACT

Adverse drug reactions represent a major public health problem, both from an economic point of view and, mainly, from the point of view of the induced pathology (iatrogenic diseases), being difficult to differentiate from other pathological conditions or even from the treated disease. Thus, these aspects prevent the use of the first-choice drugs needed for a particular treatment, in different therapeutic classes: beta-lactam antibiotics; sulfonamides; macrolide antibiotics; quinolones; non-steroidal anti-inflammatories; corticosteroids; Angiotensin converting enzyme (ACE) inhibitors; general anesthetics; biological drugs; antiepileptic drugs etc. On the other hand, adverse drug reactions represent a major problem for both clinical practice and preclinical research, in order to develop new drugs. Hypersensitivity reactions mainly refer to the adverse effects that can be harmful, disturbing, and sometimes fatal, that appear under the conditions of a normal immune system, including allergies and autoimmune reactions, both triggered by an immunological-allergic mechanism. The main purpose of this paper is to review the main classes of drugs involved in inducing hypersensitivity reactions.

ARTICLE HISTORY

Received 5 February 2020

Revised 13 March 2020

Accepted 17 March 2020

KEYWORDS

intolerance; desensitization; hypersensitivity; allergy; anaphylaxis; autoimmune reactions; allergizing medication

Each body has an immune system consisting of different natural defense mechanisms against aggression by external and internal factors, the immunity being specific and nonspecific. The physiological mechanisms of nonspecific (innate) immunity are not dependent on the recognition of the specific aggression factor, but rather, the same defensive barrier (the skin, mucosal epithelia, enzymes from secretions, phagocytes, the complement, interferons) provides protection against all pathogens. The mechanisms of specific immunity (acquired or adaptable) involve the proliferation of lymphocytes, their differentiation and maturation, the secretion of soluble factors and antigen-specific antibodies, as well as the memorization of the aggressor, i.e., the primary immune response at first exposure, and at the next, the secondary immune response, which is much wider and faster, the resistance of the body being much higher than that of the aggressor (Hăulică 2007).

Taking as a criterion the production mechanisms listed above, several types of ADR (Adverse Drug Reactions) are known: *side effects* (produced by a pharmacodynamic mechanism), *toxic effects* (produced by an organic toxic mechanism), *carcinogenic and mutagenic effects* (both types being produced by a genetic toxic mechanism), *congenital intolerance* (genetic disease), *acquired intolerance* (allergy, produced by an immunological-allergic mechanism), *immunosuppressive effects* (produced by pharmacodynamic, toxic, immunological-allergic mechanisms), *tolerance* (by physiological

adaptation–desensitization of receptors–“down” regulation, *psychological dependence* (euphoria addiction) and *physical dependence* (compensatory physiological adaptation), *drug addiction* that combines tolerance and dependence (by means of “down” regulation, euphoria dependence and physiological compensatory adaptation), *effects that appear when interrupting administration* (“rebound” effect produced by means of an “up” self-regulation, i.e., the sensitization of the receptors from the auto synapse; *abstinence syndrome* produced by an “up” hetero-regulation, sensitizing the receptors from the coupled synapse or *functional adrenal insufficiency*, through a negative “feed-back” mechanism), to which one may add the *effects produced on reproduction and on the fetus* (through secondary toxic and pharmacodynamic mechanisms) (Cristea 2006).

Another classification of adverse reactions can also be made, based on predictability, as follows:

- **Type A**, more frequent and usually predictable through the known pathological mechanisms of the drugs. Predictable type A reactions account for about 80% of all adverse drug reactions, including: overdose, adverse effects, side effects and the type of drug interaction.
- **Type B**, dealing with unpredictable reactions. Unpredictable reactions are most often dosage-dependent and occur only in sensitive patients. Nevertheless, some of these reactions may be predictable, in certain

contexts, as they have demonstrated a close connection with genetic predisposition. Type B adverse reactions are divided into: intolerance to drugs that appears at low doses, sometimes sub-therapeutic (without abnormalities of metabolism, excretion and bioavailability); abnormal effects due to metabolism, excretion or bioavailability disorders; drug allergy (immunologically-mediated adverse reactions) and anaphylactoid reactions (Khan and Solensky 2010).

The skin is often involved in inducing type B reactions, and severe skin reactions (SCARs), such as the Stevens-Johnson Syndrome (SJS), the toxic epidermal necrolysis (TEN), or drug-induced hypersensitivity syndrome (DIHS) (Table 1, Wei *et al.* 2012), which is recently known as DRESS (drug reaction with eosinophilial and systemic symptoms) (Mockenhaupt 2017), are considered to be reactions whose pathophysiology is not completely understood, which can be life-threatening and for which the epidemiological and risk factor assessments are a major necessity. DIHS/DRESS are characterized by highly variable skin eruptions, multi-organ involvement, lymphocyte activation and eosinophilia. In addition, visible skin lesions and increased specific laboratory values can occur (Mockenhaupt 2017), while visceral organ involvement typically manifests as hepatitis but may include nephritis, interstitial pneumonitis or myocarditis (Bouvresse *et al.* 2012). In addition, acute generalized exanthematous pustulosis (AGEP) is known as a reaction accompanied by fever and leukocytosis, while the characteristic pustules appear within a few hours and regress within a few days. In these cases the complications are rare and occur only in patients with a poor overall condition (Sidoroff *et al.* 2001). Patients who experience such reactions need prompt intervention and drug re-exposure must be avoided.

Short history

Some researchers describe the allergy as an “epidemic disease” of the 21st century, with an increasing incidence rate in the last 20 years. However, there are cases of “allergy” described in early medical literature, in various civilizations such as Ancient Egypt (3150 BC), China or in the Greek-Roman tradition, the terms “idiosyncrasy”, “eczema” or “asthma” dating back to those times. *Octavianus Augustus Caesar* (b. 63 BC), the first Roman emperor, is best known in antiquity for his allergy, manifesting the entire triad of an atopic disease (eczema, allergic rhinitis and asthma). In the fourth century BC, *Hippocrates* draws attention to the fact that some foods, although healthy and nutritious for most people, can cause illness, and in the second century BC, *Galen* comes to complement these theories and reports some abnormal reactions caused by certain plants (Ring 2014).

About 100 years ago, Clemens von Pirquet, a young researcher of those times, discovered and reported that the function of the immune system should not be interpreted in the sense of immunization against disease, but in terms of changing the body’s reactivity. Thus, after this discovery, he

introduced the concept of “allergy”, which was initially very difficult to explain by the scientific community at that time, as it diminished the protective role of the immune response (Igea 2013).

In order to define the concept of “allergy”, Clemens von Pirquet conducted a study on a group of children who had systemic complications 8–12 days after the first dose of anti-serum, which was later called “disease serum”. The “antitoxic serum” was introduced into therapeutics in 1891, and systemic complications were interpreted as the result of “nonimmune” causes. The researcher von Pirquet concluded that the “serum sickness” led to some hypersensitivity reactions caused by antibodies. In 1906, von Pirquet published this theory in an article simply entitled “Allergy” (Von Pirquet 1906).

Following this discovery, in 1923, Coca and Cooke were the ones who introduced the term “atopy” to designate certain hypersensitivity phenomena in humans. In addition, these researchers have also made some clarifications on the fact that atopy is nonetheless an allergic manifestation closely related to the hereditary factor and therefore refers to certain particular cases (Coca and Cooke 1923).

Nowadays, the European Academy of Allergology and Clinical Immunology released, in 2001, a report that defines hypersensitivity as a whole of the signs and symptoms resulting from exposure to a particular stimulus. Also, it is important that the exposure is done in doses, which are well-tolerated by healthy people. These hypersensitivity reactions have been divided into non-allergic hypersensitivity, when the immunological production mechanism cannot be proven, and allergic hypersensitivity, when there is a certain type of production mechanism (Johansson *et al.* 2001).

The mechanism of allergy (when hypersensitivity is based on an immunological reaction)

Allergy is characterized as an exaggerated, particular and specific immunological response of an organism to some substances, for example: pollen, dust, food, medicines, insect bites, which in the same amount pose no danger to normal individuals, and is based on the antigen-antibody reaction (Janeway *et al.* 2001).

Since most drug substances have molecular weights that are too low to stimulate the immune system, it is assumed that they or their metabolites must covalently bind to a macromolecule such as proteins to form a multivalent conjugate that is processed and presented to T lymphocytes. This mechanism is not valid for high molecular weight substances, which have a multitude of epitopes, for example proteins or peptides that are used as monoclonal antibodies, or cytokines used as growth factors. The drug reacts with a self-protein or peptide, with the formation of a conjugate or adduct, which is perceived as an antigen, loaded into the major histocompatibility complex (MHC) and transported to the cell surface, where it can interact with T lymphocytes. This process requires an active antigen-carrying cell. Once generated, the MHC-drug-peptide complex is stable, and ligand removal implies the existence of another exchange peptide.

Table 1. Medication associated with severe cutaneous adverse reactions (SCARs).

Skin reactions	Drugs involved
Fixed drug eruptions	Angiotensin-converting enzyme inhibitors (ACEI); calcium channel blockers; non-steroidal anti-inflammatory drugs (NSAIDs); Allopurinol; antiepileptic drugs; antimicrobial chemotherapy drugs; benzodiazepines; proton pump inhibitors.
Drug-induced hypersensitivity syndrome (DIHS)/Drug Reaction with Eosinophilic and Systemic Symptoms (DRESS)	Allopurinol; antiepileptic drugs (carbamazepine, phenytoin, and lamotrigine); beta lactam antibiotics; NSAIDs; sulfonamides.
Stevens Johnson syndrome (SJS) and the toxic epidermal necrolysis (TEN)	Allopurinol; antibiotics; antiepileptic drugs; tuberculostatic drugs; NSAIDs; phenothiazine derivatives.
Acute Generalized Exanthematous Pustulosis (AGEP)	Macrolide antibiotics; aminopenicillins; quinolones; anti-malaria drugs; diltiazem; Nystatin, terbinafine.

Nevertheless, there are substances that cannot be covalently bound to proteins and some drug reactions occur without antigen processing. This has led to the idea of pharmacological interaction or the p-i hypothesis, for which some inert chemicals are able to non-covalently bind to antigen-bearing structures, such as T cell or MHC receptors, and to produce direct stimulation of the immune response, as is the case with sulfamethoxazole. Most drug substances have been designed so that they can covalently bind to the protein residues of the receptors and enzymes, a fact known as the pharmacophore concept. This concept is based on steric and electronic characteristics, which allow optimal interaction with specific biological targets/triggers or block some biological functions (Pichler 2004).

Hypersensitivity's risk factors

Risk factors associated with the development of such reactions include: age (young and middle-aged people), gender (more common in women than men), some viral infections (the human immunodeficiency virus), genetic polymorphism in the human leukocyte antigen, produced by the major histocompatibility complex (MHC), but also drug-related factors: frequency of exposure, route of administration, their molecular weight. Some other factors also have an important role: the genetic polymorphism involved in drug metabolism, as well as the route of drug administration, the topical or the intramuscular/intravenous route being more likely to trigger allergic reactions as compared to the oral route. On the other hand, in terms of the influence that the molecular weight has in triggering allergies, substances with high molecular weight, such as insulin, serums or haptens, bind more easily to plasma/tissue proteins, inducing an immune response. In this regard, a good example is penicillin whose therapeutic use is associated with a high risk of hypersensitivity (Adkinson 1984).

As explained above, allergenic drugs usually behave as haptens (incomplete antigens), becoming antigenic in the body only after binding to proteins, thus leading to the formation of specific antibodies and having as consequence an allergic reaction, at a subsequent contact.

Commonly involved in allergic reactions, as haptens, penicillins (ampicillin being on the first place), cephalosporins, sulfonamides, barbiturates, pyrazoline derivatives (e.g., naminophenazone), procaine, dextrans, iodine derivatives are described. In addition to these aspects, haptens may cause cross-hypersensitivity or co-sensitization, with a high risk for

many allergenic drugs, such as paracetamol and other aniline derivatives, which may induce a co-sensitization to procaine, hypoglycemic sulphonylurea, antibacterial sulfonamides.

Further on, there will be presented different classes of drugs that cause hypersensitivity reactions:

Beta-lactam antibiotics

Penicillins. Penicillins are the most reactive drugs, with a very high allergenic potential, affecting about 10% of the patients treated with these substances. The most common reactions in this regard are: anaphylaxis, hives, angioedema or skin erythema. The rash, scarlatiniform erythema, purpuric rashes, the Stevens-Johnson syndrome, the serum sickness may occur less often. Out of all these, the most serious allergic reaction, with a frequency of up to 10% of cases, is the anaphylactic shock, for which the evolution is lethal. As an alternative, after performing the prophylactic tests, penicillins can be replaced with carbapenems (Imipenem, Meropenem) or monobactams (Aztreonam, Sulbactam), and if the penicillin treatment is crucial, desensitization is performed. Theoretically, in the case of carbapenems and monobactams, due to the fact that they are also part of the beta-lactam antibiotic category, the allergic reactions are crossed with those of penicillins, but the incidence in these cases is reduced to less than 1% (Cristea 2006, Torres and Blanca 2010).

The term desensitization is defined as a procedure that modifies a patient's immune response to a particular drug, allowing it to be administered temporarily and in safe conditions (Stark *et al.* 1987).

Cephalosporins. In the case of β -lactam antibiotics, adverse reactions at the central nervous system (CNS) level, including neurological and psychiatric disorders, are often overlooked. In this class of antibiotics, cephalosporins appear to be an important cause, with many such cases being quoted in the domain-specific literature regarding adverse reactions at the level of the CNS, leading to encephalopathy and non-convulsive epileptic state (Lacroix *et al.* 2019). In addition, cephalosporins most often cause: fever, maculopapular rashes, with less visible hives and, very rarely, bronchospasm and anaphylaxis. Penicillin-positive skin tests are associated with a low to medium risk of cross-hypersensitivity to the first generation of cephalosporins, whereas with the second and third generations, cross-hypersensitivity is very limited (Campagna *et al.* 2012).

Sulfonamides. Sulfonamides are often responsible for the delayed onset of maculopapular rashes along with the Stevens-Johnson syndrome and toxic epidermal necrolysis, with human immunodeficiency virus subjects being more prone to the development of the above-mentioned conditions, probably due to prolonged exposure and chronic immune stimulation. In addition, hypersensitivity can also be manifested by: fever, angioneurotic edema, allergic vasculitis, photosensitization. Since the combination trimethoprim + sulfamethoxazole (TMP-SMX) is the most widely used, tolerance in this case is common. Moreover, due to the fact that thiazide diuretics with a sulfonamide (indapamide) structure, along with some nonsteroidal anti-inflammatory and anticonvulsant agents, do not present antigenic determinants that induce an immune response in patients with TMP-SMX allergy, they can usually be administered safely. An exception to this rule is sulfasalazine, which is degraded intestinally to sulfapyridine, which has an aromatic immunogenic determinant such as sulfamethoxazole (Strom *et al.* 2003).

Macrolide antibiotics. Macrolide antibiotics have a strong activity on most gram-positive bacteria and some gram-negative bacteria, being widely used in the treatment of infectious diseases, both in humans and animals, since their discovery and introduction into therapeutics. Unfortunately, the widespread use of macrolide antibiotics has inevitably caused their existence even in food, which has attracted the attention of medical authorities in recent years. The existence of macrolide antibiotics, even in a low concentration in food, can cause prolonged and continuous exposure, triggering major adverse effects, such as allergic reaction, intoxication and antibiotic resistance (Liu 2019). In the case of the use of erythromycin, roxithromycin, clarithromycin, azithromycin, the immediate clinical manifestations, reported in both children and adults, are hives, angioedema, rhinoconjunctivitis, and the non-immediate ones include maculopapular rashes, contact dermatitis or non-necrolysis epidermal toxicity (Milković-Kraus *et al.* 2007, Mori *et al.* 2010).

Quinolones. Quinolones are broad-spectrum antibiotics that have been used intensively, causing severe adverse reactions and both immediate and delayed hypersensitivity reactions in approximately 2–3% of treated patients, as mentioned in the domain-specific literature. The phenomenon of cross-reactivity between different quinolones has also been frequent. Hives, angioedema and anaphylactic shock were the most common type I immediate reactions, associated with fluoroquinolones (moxifloxacin, ciprofloxacin and levofloxacin), occurring predominantly among patients with atopy. Other immune-mediated hypersensitivity reactions were rare: hemolytic-uremic syndrome, hemolytic anemia, thrombocytopenia, leukopenia or pancytopenia, acute hepatitis and acute cholestatic jaundice, the Stevens-Johnson syndrome, toxic epidermal necrolysis, acute pancreatitis, acute lymphadenopathy, angioimmune lymphadenopathy, photosensitization. An additional mechanism of quinolones is induced toxicity. Quinolones are suspected of simultaneously provoking

hypersensitivity reactions both as haptens and through drug interactions (p-i) (Neuman *et al.* 2015).

Aminoglycoside. As far as aminoglycoside toxicity is concerned, this includes reversible nephrotoxicity, irreversible ototoxicity in the cochlea and the vestibular organs and, more rarely, neuromuscular blockages and hypersensitivity reactions. Streptomycin and gentamicin are mainly vestibulotoxic, causing dizziness, ataxia and/or nystagmus, while amikacin, neomycin, dihydrostreptomycin and kanamycin are mainly cochleotoxic, causing permanent hearing loss (Farouk *et al.* 2015). The topical use of aminoglycosides (neomycin, gentamicin or tobramycin) causes the appearance of contact dermatitis, the most common clinical manifestation associated with these antibiotics. Particular attention should be paid to patients undergoing such systemic treatment, when the drug may act as an internal allergen (Hmouda *et al.* 2005).

Non-steroidal anti-inflammatories. Non-steroidal anti-inflammatories are some of the most prescribed drugs, used worldwide for their anti-inflammatory, analgesic, antipyretic effect in the treatment of rheumatoid arthritis, osteoarthritis, acute pain, fever and to prevent platelet aggregation.

NSAIDs represent the most heterogeneous pharmacotherapeutic class, characterized by variable indications, different modes of administration and high self-administration rate. These are primarily aimed at treating inflammatory diseases, alleviating acute pain or fever at various stages—acute or chronic (Sandilands and Bateman 2015). Thus, the use is variable regarding the route of administration (oral, parenteral, rectal, topical etc), the duration of administration (single or long-term dose), variable dosage, depending on the indications (high or low doses). This variability in administration often leads to self-medication, in addition to the prescribed medication.

Currently, approximately 8% of all prescriptions contain anti-inflammatory medication, while primary care physicians prescribe 90% of all NSAID prescriptions (Castellsague *et al.* 2012). Several studies have shown that adverse drug effects have a major contribution to hospital admissions. Since the beginning of their introduction into therapeutics, these drugs have been associated with adverse effects at the level of the digestive tract, including erosions of the gastric mucosa, ulcers, bleeding and perforation (Friptuleac *et al.* 2015). Endogenous prostaglandin depletion plays a major role in the production of gastric mucosal lesions. Conventional NSAIDs act by inhibiting cyclooxygenases, COX-1 and COX-2, and adverse gastrointestinal effects are caused by COX-1 inhibition, whereas NSAIDs that produce selective COX-2 inhibition exhibit better gastric tolerance (Cristea 2017).

Medication such as ibuprofen, diclofenac or naproxen may be involved in allergic reactions that involve the immune system, but most often produce reactions similar to intolerance, resulting from abnormalities in prostaglandin and leukotriene synthesis. Symptoms include respiratory disease exacerbation, such as: asthma or nasal polyposis, hives, angioedema, anaphylaxis. Almost all these are caused by cyclooxygenase 1

(COX-1) inhibitors, while selective COX-2 inhibitors (coxibs) rarely produce such reactions, and can be safely administered to hypersensitive patients (Weberschock *et al.* 2007).

Three years after the introduction of aspirin (1899) into therapy, it was incriminated for producing anaphylactic reactions. Thus, in 1902, the first case of angioedema and hives was reported in Poland shortly after aspirin intake. Later, the link between asthma attacks and inhibition of cyclooxygenase by aspirin and other nonsteroidal anti-inflammatory drugs was described in 1970 (Szczeklik and Sanak 2006).

In general, of all the adverse drug reactions, 21–25% are hypersensitivity reactions to NSAIDs, and 0.5–1.9% of them are related to aspirin administration. As aspirin is commonly used as an antiplatelet drug agent in cardiovascular pathology, a study conducted in Portugal investigated the possibility of desensitization to aspirin, using progressive doses up to the effective therapeutic dose, in order to increase tolerance. The results of the study confirm that aspirin desensitization had beneficial effects on the health of each patient included in the study (Duarte *et al.* 2016).

A study conducted in Turkey investigated the relationship between NSAIDs (noted NHS) and chronic hives, rhinitis/rhinosinusitis and bronchial asthma, in order to identify the phenotypes of NHS expression and associated factors in asthma production in patients with NHS as well as the reaction mechanism of NHS. The results showed that chronic hives, rhinitis and asthma commonly accompany NHS, the study also identifying the factors associated with asthma in NHS patients. A certain NSAID may induce different types of reactions in different organ systems, in the same individual or in others. Some patients may develop hypersensitivity to a drug from the NSAID group, and then develop asthma and/or rhinitis and chronic hives (Karakaya *et al.* 2013).

Corticosteroids. Corticosteroids are strong anti-inflammatory and immunomodulatory drugs (steroidal anti-inflammatory drugs), which paradoxically can act as allergens, producing immediate (relatively rare, but potentially severe) and delayed hypersensitivity reactions (Bielory *et al.* 2013). Corticosteroids are widely used in medical practice as therapeutic agents, especially in dermatology, as topical medication, which is why allergic contact dermatitis (type IV delayed reaction, occurring within a few days after exposure) is the most commonly encountered phenotype, through *budesonide* in Spain (Peters *et al.* 2008) and *tixocortol* in the USA. In addition, corticosteroids are also frequently involved in type I allergies (immediate hypersensitivity reaction) and cross hypersensitivity (hydrocortisone and methylprednisolone). In 1950, among corticosteroids, the first case of hypersensitivity was reported, proving that, although they have a high efficiency due to their anti-inflammatory and immunomodulatory properties, under certain conditions, they can behave as allergens.

T cell characteristics were studied and the analysis of skin biopsy samples revealed an inflammatory infiltrate composed of T lymphocytes, CD3 subtype, and a predominant profile of type 2 helper cytokines. Since the chemical structure of corticosteroids is close, co-sensitization reactions (cross

hypersensitivity) frequently occur, which makes it difficult to study sensitization to these drugs. The therapeutic treatment of patients with corticosteroid allergy is particularly complicated (Berbegal *et al.* 2016).

Angiotensin converting enzyme (ACE). Angiotensin converting enzyme (ACE) inhibitors can produce angioedema, however, this type of allergy is rarely encountered, affecting 0.1–2.2% of patients undergoing such treatment. Angioedema may occur immediately after initiation of therapy or after months, even years of administration, being accelerated and accentuated by hereditary angioedema, by age, smoking and cough induced by nonsteroidal anti-inflammatory drugs and ACE inhibitors or concomitant treatment with statins and sirolimus (rapamycin). Because the angioedema is kinin-induced, it does not respond to the usual administration of epinephrine, antihistamines and steroids. In contrast, the new bradykinin B2 receptor antagonist, Icatibant (Firazyr®), a 10-amino acid synthetic peptidomimetic, not yet authorized for this indication, has been shown to be effective in some studies (Gallitelli and Alzetta 2012, Salvaris and Laing 2018). Although these drugs are generally well-tolerated, studies have shown that the use of ACE inhibitors such as enalapril, captopril or lisinopril in antihypertensive therapy may be associated with liver injury (Vinothkumar *et al.* 2019).

General anesthetics. The toxic effects of general anesthetics on the brain have been a serious concern for anesthetists and other clinicians for a long time. Jevtovic-Todorovic *et al.* (2003) have reported the anesthetic combination of midazolam, nitrous oxide and isoflurane as being responsible for inducing persistent apoptotic neurodegeneration, accompanied by memory deficiency. Also, the most commonly used anesthetics (including sevoflurane, isoflurane, desflurane and propofol) are also responsible for the induction of abnormal neuroapoptosis in the brains of laboratory animals, which may trigger significant cognitive dysfunctions (Hirotsu *et al.* 2019). In addition, these can induce anaphylaxis, alongside neuromuscular blockers and intravenous anesthetics such as propofol, thiopentone or etomidate.

Despite all the benefits in the management of acute and chronic pain, the application of local anesthetics results in significant fluctuations in the plasma concentrations and, as a result, can cause severe adverse reactions in patients (Wang *et al.* 2019). In the case of inhalational anesthetics, no reaction was reported (Mertes *et al.* 2012).

Biological drugs. Biological drugs such as monoclonal antibodies (such as Infliximab) may stimulate the immune response because they contain variable regions of murine origin. The humanized monoclonal antibody, Alemtuzumab, can induce immune responses in nearly 23% of patients with multiple sclerosis, and 100% human antibodies, such as Adalimumab, are immunogenic in approximately 2–4% of cases with Crohn's disease and perhaps even more in subjects with rheumatoid arthritis. Also, recombinant drugs, such as Abatacept and Etenercept, elicit immune responses in

3–18% of patients. Most anti-drug antibodies are immunoglobulin G isotopes, but some of the reactions have been associated with Immunoglobulins E, as is the case with Infliximab, Tocilizumab, Cetuximab, Natalizumab, Rituximab, or Trastuzumab (Liu 2011). In general, biological agents are well-tolerated, with mild adverse reactions, but the caused immunosuppression may promote the occurrence of neoplasms, with an increased incidence of non-melanoma skin cancer (Duiă 2014).

Most biologic drugs have a high potential of increased hypersensitivity reactions (whether they are interferons, interleukins, or monoclonal antibodies), especially since many of them are relatively recently used in cancer therapy, with insufficient data on this aspect. In a study on the incidence of hypersensitivity reactions to individual biologic drugs, reductions in their episodes were achieved, by premedication with antipyretics and antihistamines, in the group of high-risk patients and, for more severe situations, when treatment with biological drugs had to be continued, corticosteroids were used. Biological drugs can develop mild to particularly severe hypersensitivity reactions, an important role being played by the patient's individual profile, along with other contributory risk factors (Isabwe *et al.* 2017).

On the other hand, the use of biological drugs for the treatment of cancer is increasingly common, even in the context of the disadvantage of hypersensitivity reaction occurrence. These can range from mild/localized to severe/generalized, leading to anaphylaxis (Holmes Gobel 2007). In addition, there are studies showing that reactions with skin manifestations that occur during biologic drug therapy are closely related to women, and of these, psoriasis and shingles are the most commonly encountered (Hernández *et al.* 2013).

Antiepileptic drugs. Antiepileptic drugs, used for the chronic treatment of epilepsy, are also considered to be therapeutic agents that can produce hypersensitivity reactions, many sources incriminating them for producing severe cutaneous adverse reactions. Hypersensitivity caused by the administration of antiepileptic drugs was first reported in 1934 as “the nirvanol sickness”, after the name phenytoin, used as “sedative of the nervous system”. Phenytoin and carbamazepine are the drugs that are most commonly involved in the production of cutaneous reactions, which are sometimes accompanied by fever, leukopenia and eosinophilia. 15% of patients treated with the above-mentioned drugs, develop cutaneous reactions within four weeks of starting the treatment, such as maculopapular or erythematous rashes. According to a study conducted at the Neurological Clinic in Kielce, Poland, 95% of skin hypersensitivity reactions were recorded during treatment with the following anticonvulsants: carbamazepine, phenytoin, lamotrigine or oxcarbazepine, carbamazepine presenting the highest risk. There have been no hypersensitivity reactions associated with skin lesions in the case of gabapentin, topiramate, levetiracetam, vigabatrin and phenobarbital therapy. In conclusion, antiepileptic drugs with an aromatic ring in their structure, had the highest incidence of adverse cutaneous reactions. At the same time, endogenous and environmental risk factors

played a major role, with women of childbearing age being at a more increased risk than men, fact which suggests hormonal involvement in these reactions (Błaszczuk *et al.* 2015).

In addition to the listed adverse reactions, systemic lupus erythematosus induced by drugs, such as: *hydralazine*, *procainamide*, *methyl dopa*, *phenytoin*, *isoniazid*, has many similarities to the naturally occurring disease: arthralgia, myalgia, fever, pleurisy, anemia, rash.

Also, another condition is immunologically mediated insulin resistance that may be due to the production of anti-insulin or even anti-insulin antibodies that usually occur 12 months after the start of treatment (James 1990). In the treatment of diabetes, *sulphonylureas* are usually well-tolerated, the most common side effect being hypoglycemia, more common in those with long duration of action, such as chlorpropamide and glibenclamide. However, all sulfonylureas can cause hypoglycemia, usually due to an overdose. For this reason, in order to prevent hypoglycemia, it is recommended to start treatment with a low dose that can be increased at intervals of 2–4 weeks, until the desired glycemic level is reached. The reported frequency of hypoglycemia in this case, in the elderly, is variable and often ignored, usually taking into account only severe hypoglycemia.

Risk factors for hypoglycemia include age-related renal function, simultaneous use of insulin or insulin sensitizers, in people over 60 years of age, recent hospitalizations, alcohol abuse, caloric restriction, multiple medication, or medication that potentiate sulfonylurea actions (Olokoba *et al.* 2012).

Other rare adverse drug reactions that may occur during treatment with sulphonylureas are nausea, hypersensitivity reactions, at the skin level, such as erythema multiforme, exfoliative dermatitis and, more rarely, photosensitivity. Occasionally, these can cause abnormalities in liver function tests, which can rarely lead to cholestatic jaundice, hepatitis, and liver failure (Sola *et al.* 2015).

In a study conducted on 1310 french patients with diabetes, who were hospitalized for myocardial infarction, hospital mortality rates were significantly lower in patients previously treated with sulphonylureas as compared to other oral antidiabetic drugs, insulin or to the lack of proper medication. Among patients receiving sulfonylureas, mortality was significantly lower in patients receiving glycazamide or glimepiride than glibenclamide, which is not selective for pancreatic sulfonylurea receptors (Zeller *et al.* 2010).

Patients who cannot control their blood sugar levels can rapidly achieve significant improvements through metformin (Glucovance, Glibomet, Bidiab) sulfonylurea combination therapy (Nestler 2008). According to recent recommendations, they may also be associated with glitazones (Avandaryl, Duetact), GPL-1 analogs, DPP-4 inhibitors, or long-acting insulin, when combination with metformin alone fails to reach the target glycemic level (Sola *et al.* 2015).

In the drug development process, the evaluation of the potential for hypersensitivity, as well as for other adverse reactions, has been the subject of different studies that examined whether it is possible to create a predictive model for detecting these reactions. The data obtained suggest that the drugs with the potential of hypersensitivity, induce hyperplasia of the germinal center in the organ, this

histological lesion serving as a predictive biomarker for the appearance of hypersensitivity to the drugs (Akitoski *et al.* 2013).

Conclusions

In conclusion, there are a large number of substances involved in the production of different types of drug hypersensitivity reactions and even if they are less frequent, such a reaction is a serious adverse effect that sometimes results in death. In addition, although there has been much progress in the management of adverse drug reactions, in general, and hypersensitivity reactions, in particular, eliminating their negative consequences remains a challenge for the economy, but especially for the public health.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

- Adkinson, N.F., Jr. 1984. Risk factors for drug allergy. *The Journal of Allergy and Clinical Immunology*, 74 (4Pt 2), 567–572.
- Akitoski, T., *et al.*, 2013. Oral administration of drugs with hypersensitivity potential induces germinal center hyperplasia in secondary lymphoid organ/tissue in Brown Norway rat, and this histological lesion is a promising candidate as a predictive biomarker for drug hypersensitivity occurrence in humans. *Toxicology and Applied Pharmacology*, 271, 30–40.
- Berbegal, L., DeLeon, F.J., and Silvestre, J.F., 2016. Hypersensitivity reactions to corticosteroids. *Actas Dermo-Sifiliograficas*, 107 (2), 107–115.
- Bielory, L., *et al.*, 2013. An algorithm for the management of allergic conjunctivitis. *Allergy and Asthma Proceedings*, 34 (5), 408–420.
- Błaszczuk, B., Lason, W., and Czuczwar, S.J., 2015. Antiepileptic drugs and adverse skin reactions: An update. *Pharmacological Reports : Pr*, 67 (3), 426–434.
- Bouvresse, S., *et al.*, 2012. Toxic epidermal necrolysis, DRESS, AGEP: Do overlap cases exist? *Orphanet Journal of Rare Diseases*, 7 (1), 72–75.
- Campagna, J.D., *et al.*, 2012. The use of cephalosporins in penicillin-allergic patients: a literature review. *The Journal of Emergency Medicine*, 42 (5), 612–620.
- Castellsague, J., *et al.*, 2012. Individual NSAIDs and upper gastrointestinal complications. *Drug Safety*, 35 (12), 1127–1146.
- Coca, A.F., and Cooke, R.A., 1923. On the classification of the phenomena of hypersensitiveness. *The Journal of Immunology*, 8, 163–182.
- Cristea, A. N., 2006. *Tratat de farmacologie*. București: Editura Medicală.
- Cristea, A. N., 2017. *Tratat de farmacologie*. București: Editura Medicală.
- Duarte, T., *et al.*, 2016. Hypersensitivity to aspirin and urgent percutaneous coronary intervention: a therapeutic challenge. *Revista Portuguesa de Cardiologia (English Edition)*, 35 (11), 619.e1–619.e5.
- Duiă, A.L., *et al.*, 2014. Risk of non melanoma skin cancer in psoriasis patients with biologic therapy (up to date). *Romanian Journal of Hematology and Oncology*, 2(2), 98–102.
- Farouk, F., *et al.*, 2015. Challenges in the determination of aminoglycoside antibiotics, a review. *Analytica Chimica Acta*, 890, 21–43.
- Friptuleac, G., Sabau, D., and Vladislav, V., 2015. Aspecte ale morbidității prin boli ale aparatului digestiv în relație cu unii factori de risc. *Sănătate Publică, Economie Și Management În Medicină*, 3 (60), 41–43.
- Gallitelli, M., and Alzetta, M., 2012. Icatibant: a novel approach to the treatment of angioedema related to the use of angiotensin-converting enzyme inhibitors. *The American Journal of Emergency Medicine*, 30 (8), 1664.e1–2.
- Hăulică, I., 2007. *Fiziologie umană*, Ediția a III -a, Ed. București: Medicală, 217–227.
- Hernández, M.V., *et al.*, 2013. Cutaneous adverse events during treatment of chronic inflammatory rheumatic conditions with tumor necrosis factor antagonists: Study using the spanish registry of adverse events of biological therapies in rheumatic diseases. *Arthritis Care & Research*, 65 (12), 2024–2031.
- Hirotsu, A., *et al.*, 2019. Maternal exposure to volatile anesthetics induces IL-6 in fetal brains and affects neuronal development. *European Journal of Pharmacology*, 863, 172682.
- Hmouda, H., *et al.*, 2005. A rare case of streptomycin-induced toxic epidermal necrolysis in a patient with tuberculosis: a therapeutic dilemma. *Annals of Pharmacotherapy*, 39 (1), 165–168.
- Holmes Gobel, B., 2007. Hypersensitivity reactions to biological drugs. *Seminars in Oncology Nursing*, 23 (3), 191–200.
- Igea, J.M., 2013. The history of the idea of allergy. *Allergy*, 68 (8), 966–973.
- Isabwe, G., *et al.*, 2017. Management of adverse reactions to biologic agents. *Allergy and Asthma Proceedings*, 38 (6), 409–418.
- James, R. P., 1990. *Allergic drug reactions, clinical methods: the history, physical and laboratory examination*, 3rd ed, Boston: Butterworths.
- Janeway, C. A., Jr, Travers, P., and Walport, M., 2001. *Immunobiology: The Immune System in Health and Disease*, New York, Garland Science.
- Jevtic-Todorovic, V., *et al.*, 2003. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *The Journal of Neuroscience: The Oscience*, 23 (3), 876–882.
- Johansson, S.G.O., *et al.*, 2001. A revised nomenclature for allergy. *Allergy*, 56 (9), 813–824.
- Karakaya, G., *et al.*, 2013. Non-steroidal anti-inflammatory drug hypersensitivity in adults and the factors associated with asthma. *Respiratory Medicine*, 107 (7), 967–974.
- Khan, D.A., and Solensky, R., 2010. Drug allergy. *The Journal of Allergy and Clinical Immunology*, 125 (2), S126–S137.
- Lacroix, C., *et al.*, 2019. Serious central nervous system side effects of cephalosporins: a national analysis of serious reports registered in the French Pharmacovigilance Database. *Journal of the Neurological Sciences*, 398, 196–201.
- Liu, A., *et al.*, 2011. Desensitization regimens for drug allergy: state of the art in the 21st century. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*, 41 (12), 1679–1689.
- Liu, Y., *et al.*, 2019. Sensitive analysis of trace macrolide antibiotics in complex food samples by ambient mass spectrometry with molecularly imprinted polymer-coated wooden tips. *Talanta*, 204, 238–247.
- Mertes, P.M., *et al.*, 2012. Hypersensitivity reactions in the anesthesia setting/allergic reactions to anesthetics. *Current Opinion in Allergy and Clinical Immunology*, 12 (4), 361–368.
- Milkočić-Kraus, S., Macan, J., and Kanceljak-Macan, B., 2007. Occupational allergic contact dermatitis from azithromycin in pharmaceutical workers: a case series. *Contact Dermatitis*, 56 (2), 99–102.
- Mockenhaupt, M., 2017. Epidemiology of cutaneous adverse drug reactions. *Allergologie Select*, 1 (1), 96–108.
- Mori, F., *et al.*, 2010. Sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy. *Annals of Allergy, Asthma & Immunology*, 104 (5), 417–419.
- Nestler, J.E., 2008. Metformin for the treatment of the polycystic ovary syndrome. *The New England Journal of Medicine*, 358 (1), 47–54.
- Neuman, M.G., *et al.*, 2015. Quinolones-induced hypersensitivity reactions. *Clinical Biochemistry*, 48 (10–11), 716–739.
- Olokoba, A.B., Obateru, O.A., and Olokoba, L.B., 2012. Type 2 diabetes mellitus: a review of current trends. *Oman Medical Journal*, 27 (4), 269–273.
- Peters, S.P., *et al.*, 2008. Long-term safety and asthma control with budesonide/formoterol versus budesonide pressurized metered-dose inhaler in asthma patients. *Allergy and Asthma Proceedings*, 29 (5), 499–516.
- Pichler, W.J., 2004. Immune mechanism of drug hypersensitivity. *Immunology and Allergy Clinics of North America*, 24 (3), 373–397.

- Ring, J., 2014. History of Allergy in Antiquity. *Chemical Immunology and Allergy*, Bergmann K-C, Ring J (eds). Basel: Karger, vol 100, p. 2–14.
- Salvaris, P.J., and Laing, J., 2018. Orolingual angioedema treated with Icatibant post-thrombolysis for ischaemic stroke. *Journal of Clinical Neuroscience*, 49, 38–39.
- Sandilands, E. A., and Bateman, D. N., 2015. *Non-steroidal anti-inflammatory drugs*. Amsterdam: Elsevier, 185–186.
- Sidoroff, A., et al., 2001. Acute generalized exanthematous pustulosis (AGEP) – a clinical reaction pattern. *Journal of Cutaneous Pathology*, 28 (3), 113–119.
- Sola, D., et al., 2015. Sulfonyleureas and their use in clinical practice. *Archives of Medical Science: AMS*, 11 (4), 840–848.
- Stark, B.J., et al., 1987. Acute and chronic desensitization of penicillin-allergic patients using oral penicillin. *The Journal of Allergy and Clinical Immunology*, 79 (3), 523–532.
- Strom, B.L., et al., 2003. Absence of crossreactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *New England Journal of Medicine*, 349 (17), 1628–1635.
- Szczeklik, A., and Sanak, M., 2006. The broken balance in aspirin hypersensitivity. *European Journal of Pharmacology*, 533 (1-3), 145–155.
- Torres, M.J., and Blanca, M., 2010. The complex clinical picture of β -lactam hypersensitivity: penicilins, cephalosporins, monobactams, carbapenems and clavams. *Medical Clinics of North America*, 94 (4), 805–820.
- Vinothkumar, G., et al., 2019. Effect of *Coccinia indica* leaf extract on angiotensin converting enzyme (ACE) inhibitor induced hepatotoxicity in wistar albino rats. *Clinical Nutrition Experimental*, 24, 24–33.
- Von Pirquet, C., 1906. Allergie. *Munch Med Wochenschr*, 30, 1457–1458.
- Wang, B., et al., 2019. Recent advances in polymer-based drug delivery systems for local anesthetics. *Acta Biomaterialia*, 96, 55–67.
- Weberschock, T.B., et al., 2007. Tolerance to Coxibs in Patients with Intolerance to Non-steroidal Anti-inflammatory Drugs (NSAIDs): a systematic structured review of literature. *Archives of Dermatological Research*, 299 (4), 169–175.
- Wei, C.-Y., et al., 2012. A recent update of pharmacogenomics in drug-induced severe skin reactions. *Drug Metabolism and Pharmacokinetics*, 27 (1), 132–141.
- Zeller, M., et al., 2010. Impact of type of preadmission sulfonyleureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. *The Journal of Clinical Endocrinology and Metabolism*, 95 (11), 4993–5002.