Lecture 03: Drug allergy

1. Basic Information

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Content:	This hand-out describes Drug allergy and provides background information on the lecture 'Drug allergy', by R. van Eekeren, The Netherlands. This lecture is part of the **WHO PV core curriculum for university teaching**. The outline of this core curriculum consists of 5 key aspects on pharmacovigilance. This lecture refers to key aspect 2, 3 and 4: preventing, recognizing and managing ADRs.

Current subject

Text to lecture on 'Drug allergy, by R. van Eekeren, The Netherlands

Learning objectives:	Knowing the meaning of terms like allergy, hypersensitivity and intolerance Explain differences in immunological reaction according to the Gell and Coombs classification and give some examples Be able to discuss if a drug should be considered as contra-indicated and what consultation with other health care providers is necessary.
Target audience:	Medical, pharmacy, nursing students; End-Bachelor, Begin-Master
Requirements:	Knowledge on pharmacology, pharmacotherapy
Additional methods:	problem solving cases or real patients during internships, collecting information on specific ADRs and apply classification systems, identify risk factors.

Origin

Author:	R. van Eekeren, PharmD, The Netherlands Pharmacovigilance Centre Lareb
Date:	2017
Aim:	Lecture on Drug Allergy in a 2-week pharmacovigilance course
Audience:	Pharmacy students, 1st year Master phase

2. Lecture: Drug allergy

Outline

1. Various types of hypersensitivity
2. Some diagnostics
3. Recordings and actions
4. Exam question examples

1. Terminology of drug allergy

Adverse drug reactions can be divided into two major groups: type A and type B. Type A reactions can be explained from a pharmacological action and are dose dependent. Type B reactions are called hypersensitivity reactions, which can be either allergic and non-allergic in nature.

In true allergic reactions, the immune system is involved. Pseudo-allergic reactions refer to various mechanisms that mimic symptoms of allergic reactions, without activation of the immune system.

Idiosyncrasy is a certain susceptibility in an individual that increases the risk of a certain hypersensitivity reaction or side effect. The cause for idiosyncrasy is often unknown. Enzyme deficiencies or genetic variability may play a role. Some specific examples are: hemolytic anemia with nitrofurantoin in patients with G6PD-deficiency; increased risk for Steven's Johnson Syndrome with carbamazepine in Han-Chinese people with HLA*50:02 mutation.

Intolerance is a poorly defined term. It may refer to an unexplained sensitivity to a drug. This term should be avoided, since different meanings may cause misinterpretation. This can be an unusual low threshold for type A reactions, or refer to atypical or unknown reactions.

Allergic hypersensitivity

For developing an allergic reaction, a small molecule drug or its reactive metabolite form a covalently bond conjugate with a protein. This conjugate can be recognized by the immune system as a foreign antigen. Gell and Coombs classified allergic hypersensitivity into four categories.

Type I reactions are mediated by IgE (immunoglobulin E) and may cause urticarial, angio-edema and the life-threatening condition anaphylaxis. Antigens cross-link with mast cells via specific IgE antibodies. Binding of the antigen stimulates mast cell degranulation with release of mediators such as histamines and leukotrienes. These mediators can cause local allergic reactions or anaphylaxis. These reactions occur within minutes in previously sensitized persons and are called immediate hypersensitivity.

Example type I (from spontaneous ADR reporting): a female, aged 56, was investigated with fluorescein for retinopathy (iv administration of fluorescein for angiography). Shortly after administration she developed signs of anaphylaxis and died from anaphylactic shock despite treatment with epinephrine, clemastine and dexamethasone. Previous exposure to fluorescein was unknown, but should have been present since previous sensibilisation is necessary for developing an IgE mediated reactions. Administration of beta blocking agents (metoprolol) may have increased the risk of a severe reaction by (partly) inhibiting the effect of epinephrine. The combined use of metoprolol and epinephrine can also result in hypertension and bradycardia.

Anaphylaxis is the most severe form of a type I allergic reaction, mediated by IgE. When besides es skin reactions other organs are involved, the reaction is called anaphylaxis. Due to release of

histamine and other inflammatory mediators, airways react with bronchospasm and laryngeal swelling. Gastro-intestinal symptoms are nausea, vomiting and abdominal pain. Due to massive vasodilatation a patient can collaps, accompanied by cardiac arrhythmia and hypoxia this condition may have a fatal outcome. A first type 1 allergic reaction can be rather mild, but after a next exposure the reaction might more severe.

Type 2 reactions cause cytotoxicity, especially of blood cells resulting blood dyscrasias. Antibody dependent cytotoxicity arises when IgM and/or IgG antibodies target modified autologues proteins that bind to these cells. Tissue damage results from direct action of cytotoxic cells or activation of complement system. Target cells are destroyed or removed. Clinical manifestations include drug-induced haemolytic anaemia, thrombocytopenia and neutropenia. These reactions require a sensibilisation period of at least 5 days to weeks after first exposure and may be asymptomatic at first.

Type 3 allergic reactions are immune-complex mediated and arise when immune complexes are not fully cleared by the reticulo-endothelial system and are deposited in tissue. This occurs predominantly in small blood vessels. Antibody mediated activation of complement system results in an inflammatory response which may be enhanced by the release of reactive oxygen species. Examples of type 3 reactions are serum sickness like reaction, systemic lupus erythematosus.

Serum sickness like reaction refers to a reaction that was originally seen in patients who had been administered with horse antiserum for diphtheria (Bela Schick and Clemens Pirquet in 1905). The patients, mostly children developed fever, arthralgias, rash and lymphadenopathy. This reaction was caused by allergy to foreign immunoglobulins. Besides foreign serum, drug can be involved in a serum sickness like reaction. Examples of drugs are various antibiotics (cephalosporins, ciprofloxacin, penicillins and others), bupropion, allopurinol and others. Common symptoms are: fever, skin eruption, arthralgias, gastro-intestinal complaints and lymphadenopathy. Sometimes, internal organs are involved, such as vasculitis, renal failure, neuropathy. Serum sickness like reactions develops in 1-3 weeks after first exposure of a certain drug. The reactions is self-limiting although the offending drug should be withdrawn as soon as possible; anti-inflammatory agents and antihistamines may be useful to treat symptoms.

Type IV allergy is cell-mediated and describes reactions that take more than 12 hours to evolve. Cytotoxic T cells recognize antigenic stimuli presented indirectly via MHC molecules on antigen presenting cells. If the cell has been primed by co-stimulatory signals, it will release cytokines which cause cell destruction and may also elicit an inflammatory response. Since in skin T cells are largely present, these reactions frequently affect the skin and examples include contact dermatitis and tuberculin type hypersensitivity and many rashes and serious skin reactions such as DRESS, Steven's Johnson syndrome / Toxic epidermal necrolysis, AGEP. In severe cases, also internal organs may be involved, such as lungs (pneumonitis) and liver (hepatitis).

The case report of type IV reaction refers to a spontaneously report to a pharmacovigilance center. An elderly was treated for neuropathic pain with carbamazepine. She reported eczema as a skin eruption possibly due to carbamazepine. Latency is unknown in this case, but carbamazepine was switched to oxcarbazepine and the complains worsen. Until after discontinuation of this drug and treatment with topical corticosteroids, the symptoms resolve. Note there is a structural relationship between carbamazepine and oxcarbazepine resulting in cross-hypersensitivity.

Non-allergic hypersensitivity

In contrast to allergic hypersensitivity, in non-allergic hypersensitivity the immune system is not involved. This group includes pseudo-allergy and idiosyncrasy.

In pseudo-allergy, other non-immune mediated mechanisms cause reactions that have similar symptoms of true allergic reactions. Based on symptoms, the difference between true allergy and pseudo-allergy is difficult. Two important features of pseudo-allergy are: they can occur at any time during treatment, also on the very first exposure, and allergy tests (skin prick test, patch test, immunoglobulin tests) will be negative. Mechanisms that are involved in pseudo-allergy include direct mast cell stimulation (opiates, ciprofloxacin, vancomycin) resulting in pruritus, urticaria, flushing; alteration in bradykinin (ACE-inhibitors) or leukotrienes (NSAIDs) resulting in angio-edema or exacerbation of asthma or hay fever; direct complement activation by radio contrast media resulting in anaphylaxis and sometimes shock.

Idiosyncrasy refers to an individual's hypersensitivity that has a specific genetic predisposition or to a reaction without a known mechanism. Thus, only a specific group of patients is susceptible for this kind of reactions, which can be allergic and non-allerg. Some of the susceptibilities are known, but the majority is unknown.

Examples of well-known idiosyncratic reactions:

- Hemolytic anaemia caused by drugs such as nitrofurantoin, sulfasalazine, hydroxychloroquine, glibenclamide and others, in patients with G6PD deficiency; mainly prevalent in people from African, South East Asian and Chinese descent. Glucose-6-phosphate dehydrogenase is an enzyme essential in the formation of GSH (glutathione), a major anti-oxidant in erythrocytes. People with G6PD deficiency lack proper function of this enzyme, resulting in low amounts of GSH. Drugs that form reactive oxygen species damage erythrocytes that are normally protected by GSH.
- Bone marrow suppression by azathioprine in patients with TPMT. Azathioprine is a prodrug which is metabolized to 6-mercaptopurine and further metabolized to 6-tioguanine and 6-methylmercaptopurine. TPMT (thiopurine methyl transferase) is one of the enzymes involved in this metabolism. People with TPMT deficiency are at increased risk of severe myelosuppression by azathioprine and 6-mercaptopurine, which is a toxic property of these substances.

Diagnosis

In all cases of suspected cases of drug allergy, a correct anamnesis of the event is crucial for identifying the culprit cause. This includes a description of detailed clinical manifestation, all drugs and cofactors and patient history with prior exposure to suspect drug. Based on symptoms and timing, a rough discrimination between type I and type IV can be made.

For some true allergic reactions, additional diagnostics are available. Investigations for Type I reactions (IgE mediated allergy) are skin prick test, serology test (blood test with IgE antibodies) and an oral challenge test if necessary. For type IV reactions, patch testing can be performed and an oral challenge test if necessary. For non-allergic reactions these tests will be negative and only an oral challenge test is an option. Oral challenge test should be performed with caution and only in situations when the exact cause for the reaction is necessary to know for further treatment options.

Recordings

To prevent future exposure to a drug, detailed recording of the event, drug and circumstances is important. The aim is to provide an advice for future use. For instance, when a patient had a true

type I allergic reaction to amoxicillin, future use should be avoided. But if a patient had severe gastrointestinal complaints while using amoxicillin, the drug can be used in future without recurrence of the events.

2.5 Literature used in this lecture:

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5. Medscape Emedicine serum sickness via www.emedicine.medscape.com/article/332032 25-9-2018
6. Youngster I, Arcavi L, Schechmaster R, Akayzen Y, Popliski H, Shimonov J, Beig S, Berkovitch M. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. Drug Saf. 2010 Sep 1;33(9):713-26.