# Lecture 02: Clinical pharmacology of ADRs

## 1. Basic information

| | |
|---|---|
| Author: | Netherlands Pharmacovigilance Centre Lareb |
| Version date: | 17 Nov 2017 |
| Content: | This hand-out describes general clinical pharmacological aspects of ADRs and provides background information on the lecture 'Clinical Pharmacology of adverse drug reaction, 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 'Clinical pharmacology of adverse drug reactions', by R. van Eekeren, The Netherlands.

| | |
|---|---|
| **Learning objectives:** | To classify ADRs according to pharmacology, time-relationship and risk factors. |
| **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 Clinical pharmacology of ADRs in a 2-week pharmacovigilance course |
| Audience: | Pharmacy students, 1st year Master phase |

# 2. Lecture: Clinical pharmacology of adverse drug reactions

Outline

1. Introduction
2. Classification system 1: Pharmacological ADRs
3. Classification system 2: type A and type B ADRs
4. Classification system 3: DoTS
5. Risk factors in children
6. Risk factors in elderly

## 2.1 Introduction

In the 16th century, Paracelsus already stated that all substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy. This is an early description of dose-relatedness of adverse drug reactions (ADRs). Dose-relatedness is one of the characteristics of pharmacological effects.

## 2.2 Classification system 1: Pharmacological ADRs

### *Primary and secondary ADRs*

Many ADRs can be traced to a pharmacological property of the drug. ADRs can be related to the known pharmacological mechanism affecting the target organ. These are called primary ADRs, and can be interpreted as an exaggerated therapeutic effect. For example, hypotension causing dizziness by beta-blocking agents indicated for hypertension. Or increased bleeding tendency by anticoagulants.

ADRs also can occur in other organ systems than the target organ for pharmacotherapy, related on other clinical pharmacological properties of the drug. These are called secondary ADRs. For example, Raynaud phenomena by beta-blocking agents due to peripheral vasoconstriction; or gastro-intestinal bleeding by NSAIDs, caused by reduction of mucosal protection due to inhibition of COX-1 enzymes normally producing prostaglandins that stimulate mucus and bicarbonate secretion and vasodilatation, all actions that protect stomach mucosa.

### *Causes for pharmacological ADRs*

The occurrence of pharmacological ADRs can have different causes. Provoking circumstances can be pharmaceutical in origin, that is related to the product of the drug. A change in formulation, for instance after generic substitution, can lead to a change in bioavailability, causing an increase or decrease in therapeutic effect, or causing adverse drug reactions. For drugs with narrow therapeutic windows one should be very alert when drug formulations change.

Changes in pharmacokinetics of a certain drug in a person, can alter the concentration in blood or in (target) organs. Due to ageing, comorbidity or food or drug interactions the absorption, distribution, metabolism and elimination of drugs may alter. Increased drug levels are usually related to increased risk of pharmacological ADRs. For example, impaired renal function decreases elimination of many renal excreted drugs.

Genetic polymorphisms can alter drug metabolism, for instance Cytochrome P450 enzymes involved in phase 1 reactions like oxidation, reduction and hydrolysis of many compounds. Poor metabolizers

for CYP enzymes have higher blood levels of the drugs involved, resulting in an increased risk of ADRs.

Drug-drug interactions can increase the risk of ADRs in various ways.

- Pharmacokinetic drug-drug interactions can induce or inhibit drug metabolism or influence absorption; for example CYT P450 enzyme inhibition.
- Pharmacodynamic drug-drug interactions can lead to addition of similar ADRs; for instance anticholinergic effects of antidepressants and antihistamines.
- Pharmacodynamic drug interactions can affect receptor responses; for example, beta-blocking agents and the increased risk of hypoglycemia and altered perception of symptoms of hypoglycemia using oral blood glucose lowering drugs.
- Pharmacodynamic drug interactions can cause changes in physiological functions, causing changes in effectiveness or excretion of other drugs; for example NSAIDs with the use of lithium, causing a decrease of renal clearance of lithium resulting in lithium toxicity.

## 2.3 Classification system 2: type A and type B

### *Type A*

Type A ADRs refer to pharmacological ADRs. The 'A' is named 'Augmented' for indication primary ADRs, but can also stand for 'phArmacological', indicating both primary and secondary pharmacological ADRs.

The majority of all ADRs are type A ADRs. These are generally dose-dependent and occur rather often. Based on their pharmacological properties, many ADRs are predictable. The frequent type A ADRs are recognized in clinical trials in pre-marketing phase.

Dose-dependency also related to pharmacokinetics: the timing of ADRs can relate to time to reach maximum plasma concentration or to peak plasma concentrations. The recovery from ADRs can also be related to elimination half-life, where 5 times the half-life is thought to be enough for complete clearance of a drug from the body. This is called 'dechallenge', when is a drug is withdrawn an resolving of the reaction occurs within acceptable time and without additional treatment. Of course, when treatment is necessary, you should treat the patient. In that case, the dechallenge isn't a valid plea for an ADR. Rechallenge is a readministration, on purpose, to see if the adverse reaction will recur. When serious ADRs are expected, a rechallenge is unethical and should not be performed.

Dose-dependency can be used for management of the ADR. After withdrawal of the drug, the ADR is reversible. Dose reduction can also be a solution for resolving the ADR, but with continuous therapeutic effect of the drug. This is a matter of trial and error, slowly increasing the dose until good therapeutic effect is reached or until adverse reactions occur.

### *Type B*

Type B ADRs are named 'bizarre', since their unpredictable character and potential serious nature. These ADRs refer to hypersensitivity reactions or idiosyncratic reactions. Idiosyncrasy is a genetic or (yet) unknown feature of an individual, causing increased sensitivity for developing specific ADRs (type B). These can apply to enzyme deficiencies or to abnormal receptor activity.

Type B reactions are rather rare and not always detected in clinical trials in the pre-marketing phase. These reactions are not dose-dependent. Timing of the type B ADR can relate to known

sensibilisation periods for allergic reactions in which the immune system is involved. Withdrawal of the drug is necessary for recovery of the reaction. Additional treatment is often required.

Although, skin reactions are well known drug hypersensitivity reactions, all organs can be affected. These are explained in more detail in the lecture about drug allergy.

Each classification system has limitations. It is not always clear is an ADR fits in type A or type B. Nor is it always clear why some patient develop (type A) ADRs and others do not. If the mechanism of a reaction is not quite clear, this classification system cannot be used.

## 2.4 Classification system 3: DoTS

The DoTS is another approach to classify ADRs, and is developed by Aronson and Ferner. This approach describes properties of an individual ADR, such as dose (Do), timing (T) and susceptibility (S).

- Dose: can be divided into subtherapeutic, therapeutic and supratherapeutic. Reactions that also occur at subtherapeutic doses are called hypersensitivity, which can be allergic and non-allergic in nature. Collateral effects are reactions that occur at therapeutic doses, similar to type A reactions at normal dose. Reactions at supratherapeutic dosages are toxic reactions or exaggerated pharmacological effects in high dosages or toxic drug levels.
- Timing: Some ADRs follow specific time patterns, other are time independent. Time dependent reactions are subdivided in rapid reactions (related to high infusion rates), first dose (allergy or collateral like hypotension with ACE-inhibitors), early (days to weeks; allergy or collateral such as nitrate induced headache; some are persistant, others are self-limiting and disappear while continuing the drug), intermediate (weeks to months), late (after chronic use, cumulative dose), delayed (slow development of the ADR).
  Time-independent reactions can occur at any time during therapy: because of their nature or due to altered patient related aspects (like changes in kinetics) or exogenous effects by drug-interactions.
- Susceptibility: general risk factors for pharmacological ADRs are altered pharmacokinetics, age, renal function, altered metabolism. Risk factors for hypersensitivity reactions are ethnicity, genetic, previous sensitization. For some ADRs specific risk factors are known in literature.

## 2.5 Risk factors for ADRs in children

Children are not just small adults. Due to growth and development, pharmacokinetics alters during the young age. For many medicines, efficacy and safety are not specifically established for young children. That is why many drugs are used off-label in this group. Next to altered pharmacokinetics, some ADRs occur more frequently in children compared to adults.

### *Absorption*

In children, gastrointestinal absorption of drugs may fluctuate due to variable gastric emptying time, reduced gastric acid secretion, variable intestinal motility and reduced microbial flora. The bioavailability of a drug might be higher than expected in young children, which increases the risk for ADRs. Children also are more susceptible for systemic effects after dermal administration of drugs. They have are relatively large body surface area with an increased permeability for compounds, especially newborns and neonates. Furthermore, the skin of children is thinner and easily damaged thus increasing absorption of substances applied to the skin.

### *Distribution*

The distribution of a drug depends on is lipophilicity or hydrophilicity and the percentages of fat tissue and body fluids of the body composition. In the very young, the body fluid compartment is relatively large, but fat tissue increases to the toddler age and decreases slowly until puberty.

The blood brain barrier (BBB) is still developing in children. The tight junctions between cells have openings through which small molecules can cross the BBB. This is why drugs can have ADRs in the central nervous system in the young. For example, the frequency of extrapyramidal symptoms with domperidone and metoclopramide is higher in children compared to adults.

### *Metabolism*

Hepatic metabolism is developing during childhood. This affects the metabolism of drugs as well, affecting the half-life of a drug.

### *Excretion*

In neonates, the renal blood flow and glomerular filtration rate are decreased. After a few months these increase to the adult level.

### *Pharmacodynamic reactions*

Some drugs may cause paradoxal or central stimulating effects in children. These include antihistamines, benzodiazepines and ketotifen.

## 2.6 Riskfactors for ADRs in elderly

Due to physiological changes in aging, in elderly people the risk for ADRs increase. Most important is that changes in ageing vary among individuals and are hard to predict. Polypharmacy because of multiple diseases accounts for the greatest risk for ADR development. ADRs are a major cause of non-adherence of drug use. Due to cognitive impairment and practical problems drug use might also be affected.

In the elderly, body composition changes (reduction of lean body mass and increase of adipose tissue), which alters distribution pharmacokinetics. Also, homeostasis reduces and tissues and organs become more vulnerable. Considering pharmacokinetics, absorption of drugs can be affected due to reduced esophageal and intestinal motility, longer gastric transit time and increased pH of the stomach. Elimination by liver metabolism may reduce due to decline of metabolism capacity and due to decreased blood flow through the portal vein thus reducing firs-pass metabolism. Renal function declines in approximately two-third of elderly people, reducing clearance of drugs.

One major risk in the elderly populations is falling causing bone fractures and bleeding. Balance problems are common in the elderly due to inadequate responses to vestibular system, baroreceptors, vision and muscle responses. All drugs that affect blood pressure, dizziness, movement and muscle strength contribute to the risk of falling.

Exam questions:

Question 1: answer D (anaphylactic shock is a type B reaction, stomach bleeding is a serious type A reaction)

Question 2: answer Dizziness due to orthostatic hypotension using an ACE-inhibitor is a primary type A reaction (directly related to intended pharmacological property). The DoTS: C (Do: occurs at

therapeutic dose, T: often seen with first dose, S: risks of developing this ADR is affected by age, renal function)

## 2.5 Literature used in this lecture:

1. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med. 2004 May 18;140(10):795-801. PMID: 15148066
2. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ. 2003 Nov 22;327(7425):1222-5. Review. Free PMC Article.
3. TRC: Teaching Resource Centre Pharmacology. Internet source. Available via: https://coo.lumc.nl/trc/default.aspx?direct=true