Lecture 01: General Introduction on PV

1. Basic information

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Content:	This hand-out describes general aspects on pharmacovigilance and provides background information on the lecture 'Introduction PV', by Prof. Dr. E.P. van Puijenbroek, 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 1: understanding the importance of PV.

Current subject

Text to lecture on 'Introduction PV', by Prof. Dr. E.P. van Puijenbroek, The Netherlands

Learning objectives:	Definition of pharmacovigilance Definition of seriousness of ADRs History of pharmacovigilance Organisation of drug safety in The Netherlands and Europe
Target audience:	Medical, pharmacy, nursing students; all years
Requirements:	None
Additional methods:	1) write an essay on a drug-induced disaster; 2) interview a patient that experienced a serious ADR

Origin:

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Date:	2017
Aim:	Introductory lecture on PV in a 2-week pharmacovigilance course
Audience:	Pharmacy students, 1st year Master phase

2. Lecture: Introduction on Pharmacovigilance

Outline

1. Introduction of pharmacovigilance
2. Drug safety in practice
3. Need for monitoring safety of drugs
4. Organization of pharmacovigilance

2.1 Introduction

Public concerns

Uncertainty about the safety of commonly used medicines, gives rise to concerns in the public. Future health care professionals need to realize that adverse outcomes of drug use occur and are mostly unpredictable. They need to learn what to tell patients about the knowledge on safety of drugs and how to act in situations when adverse drug reactions occur.

PV definition

The WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug related problem.

The major concern for pharmacovigilance, is the post-marketing surveillance phase of a drug. Although a drug is extensively studied in clinical trials, knowledge on adverse outcomes of drug use in practice is lacking. Experiences of adverse outcomes of drug use in practice help to detect, assess and understand adverse drug effects. This knowledge derived from practice can help to prevent adverse drug effects in future patients. This process is also called signal detection.

ADR definition

An adverse drug reaction is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, therapy or for the modifications of physiological function.

Although most ADRs are noxious, sometimes an unexpected beneficial effect is detected. For example: abnormal growth (hypertrichosis) of eye lashes, induced by prostamides (or synthetic prostaglandin $F_{2\alpha}$ –analogues) like bimatoprost. This class of drugs is used for increased intraocular pressure or glaucoma. For cosmetic purposes, the adverse drug effect of hypertrichosis has been turned into a new indication: eye lash hypotrichosis. A better known adverse drug effect that turned into a new indication is the platelet aggregation inhibition of Aspirin® (acetylsalicylic acid), used as an analgesic causing increased bleeding tendency.

Note the terminology: an ADR is a response (or reaction) of a drug in a person, implying a causal relationship between drug action and a person's physiological reaction that is experienced as harm. Some articles or sources of information mention 'ADE' (adverse drug event) which is an event that is temporarily associated with the use of a drug, but which is not necessarily causally related. [For example: dry cough in someone since he started an antibiotic for a respiratory infection.] The same accounts for 'AE' (adverse event) for which a causal relationship between the event and drug has not been established, and which might rely on coincidence. [For example: in a trial 5% of the treatment group experienced nausea to 4% of the control group.] It is rather confusing that a 'side effect' can

account for ADR, ADE and AE, depending on the context. In fact, only an ADR is a true side effect of a drug.

Seriousness

Seriousness of an ADR is related to its life threatening nature and is defined as any untoward reaction to the medicinal product that 1) results in death, 2) is life-threatening, 3) requires hospitalization or prolongation thereof, 4) causes permanent incapacity or disability, 5) causes birth defects or 6) causes other medically important conditions.

This is not the same as perceived severity of ADRs by patients, which has impact on their health condition, quality of life and might influence drug use.

2.2 Drug safety in practice

Hospitalizations

Adverse drug reactions can cause serious health problems. Studies indicate that ADRs account for approximately 5-6% of all acute hospitalizations. About half of these hospitalizations could have been prevented by better monitoring, timely recognition of the symptoms and by knowledge about certain risk factors for occurrence of ADRs. Therefore healthcare professional (HCP) knowledge about the safe use of drugs in daily practice is important to reduce drug-induced patient harm.

In The Netherlands, in 2008, the HARM (Hospital Admission Related to Medication) study has been performed. Based on this study, steps were taken to make guidelines for prevention of these drug-related hospital admission.
In 2017 a successive research on the Dutch situation has been published, which showed that the rate of drug-related acute admissions in the elderly population (aged > 65 years) has not decreased from 2008 to 2013. Still, common drugs that cause well known ADRs account for approximately 5% of all acute hospitalizations, in the elderly about 10%. Thus, prevention of ADRs and timely recognition of risk-factors for ADRs need to be improved.

2.3 Need for monitoring safety of drugs

History

Because of the thalidomide disaster, causing limb deformities in babies whose mothers took thalidomide during pregnancy, people started to realize that the safety of drugs should be monitored closely.

Phocomelia is a very rare congenital anomaly, which was already known in the 18th century. In the 1950's more children were born with deformed or absent limbs, caused by teratogenic effects of thalidomide (Softenon®, Distaval®). This drug was used against morning sickness or as sedative. In 1961 thalidomide was withdrawn from the market.

Thalidomide is a racemic mixture of molecules, of which S-thalidomide is the bioactive form. Although the exact mechanism in not clear, thalidomide is thought to inhibit angiogenesis (forming of blood vessels) and to generate reactive oxygen species that damage and kill cells. These actions gave a new therapeutic use for thalidomide is multiple myeloma (cancer), leprosy and some other off-label uses.

An Australian doctor, called Mc Bride, sent in a letter to the editor of The Lancet, calling for the teratogenic effects of thalidomide: 'Have any of your readers seen similar abnormalities…'. This was the first report of an adverse drug event (causality had not been established in that time), and is

being seen as the start of pharmacovigilance practice. Therefore, Medication Evaluation Boards and spontaneous reporting centers were instituted in many countries.

Another drug-induced disaster was the use of di-ethylstilbestrol (DES) in pregnant women to prevent miscarriages, causing serious health problems in the offspring. Daughters from mothers that used DES, have an increased risk on cervical cancers and deviations in the shape of the uterus. This drug had been used from 1946-1974. Since the effects on offspring of the users of this drug, people still suffer from these adverse (teratogenic) drug reaction.

Limitations of clinical trials

In the clinical development phase of a drug, a compound is tested on efficacy and safety. But, finally when a drug is approved for marketing, the safety profile of a drug is not complete. Two major limitations of clinical trials can explain this lack of knowledge on safety of a drug.

First, clinical trials are developed to prove efficacy of the treatment. Of course, all adverse events are taken into account, but the size of the trials can be too small to detect uncommon or rare adverse drug reactions. Also, the duration of a trial can be too short to evaluate long-term effects of a drug.

Second, there is a gap between study population and the population in practice that is going to use the drug. In clinical trials drugs are tested on healthy young male volunteers. Children, females and pregnant women are mostly excluded. There are also strict criteria for age, comorbidity and concomitant medications. In real practice, other safety issues or adverse drug reactions can be expected, based on population differences. Due to ageing, pharmacokinetics of drugs in individuals change, for instance: lean body mass decreases, water and fat distribution changes and renal function declines. Comorbidity and other patient conditions can be risk factors for developing adverse drug reactions. Concomitant medications of polypharmacy increase the risk of drug interactions and might cause similar or additional adverse drug reactions. Adverse drug reactions negatively influence patient compliance to pharmacotherapy (people stop taking the drug because of an ADR), but non-compliance also influences the occurrence of ADRs. For instance, people change the dose or the way or timing of administration or take drug-holidays. Thus, the target population for a certain drug is completely different from the population on which the drug has been tested.

2.4 Organization of pharmacovigilance

Although drugs have been extensively studies in pre-marketing trials, post-marketing safety has to be assured. In the post-marketing phase, new information on safety is derived from spontaneous reporting systems (SRS) or from additional studies. This new knowledge is constantly used for monitoring the balance between efficacy and safety of a drug.

There are many parties involved in pharmacovigilance, which may differ between countries.

National

In The Netherlands, the Medicines Evaluation Board (MEB, in Dutch: College ter beoordeling van Geneesmiddelen, CBG), is responsible for all national marketed drugs; their task is to evaluate the risk/benefit balance. Healthcare professionals and patients can report ADRs via a web based reporting form to the national PV center. The PV center is responsible for the monitoring of the safety of drugs and vaccines, by collecting and analyzing ADR reports from practice. Signals of new knowledge on ADR or other safety issues are being discussed with the MEB and disseminated by publications. All reports are shared with the European Medicines Agency (EMA) and with the WHO by sending them to the ADR database of the WHO-Uppsala Monitoring Centre (UMC). Reporting of serious ADRs in mandatory for physicians and pharmacists in The Netherlands.

Marketing authorization holders (MAH) keep responsible for their marketed drugs and have to update the safety of their products periodically in Periodic Safety Update Reports (PSUR). For newly marketed drugs, MAHs write Risk Management Plans (RMP) to point out which risks can be expected and to manage them.

The Inspectorate of Health (In Dutch: Inspectie voor de Gezondheidszorg IGZ) is the supervisory body on the health system and the parties involved in pharmacovigilance.

International

In Europe, for centrally registered drugs, EMA is a MEB in which MEB's and PV centres of all countries are represented. The Pharmacovigilance Risk Assessment Committee (PRAC) discusses current safety issues of drugs and vaccines on a European level.

The UMC-WHO database of ADRs, also called VigiAcces®, collects all reported ADRs from countries that are members of WHO. This worldwide database is used for signal detection of new knowledge on ADRs.

Where to find information on ADRs and drug safety

Official product information can be found in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL), provided by the MEB (national or EMA) or FDA.
On national levels, healthcare professionals use other sources adjusted to their professional group, for instance the Farmacotherapeutisch Kompas for physicians in The Netherlands.
ADR databases often show all reported ADRs and related publications on their website. This is informative but not conclusive on possible adverse drug reactions. Due to underreporting and selection bias in voluntary reporting, no frequencies can be calculated, nor is causality established in every single report.

www.cbg-meb.nl/geneesmiddeleninformatiebank

www.ema.europa.eu/ema/

https://www.accessdata.fda.gov/scripts/cder/daf/

https://www.farmacotherapeutischkompas.nl/

www.lareb.nl

http://www.vigiaccess.org/

2.5 Literature used in this lecture:

1. Leendertse A, Egberts A, Stoker L, Bemt vdP, HARM Study group. Frequency of and risk factors for preventable medication related hospital admissions in The Netherlands. Arch Intern Med 168[17], 1890-1896. 2008.
2. Kaeding M, Schmalter J, Klika C. Pharmacovigilance in the European Union. Practical implementation across member states. Springer; 2017.
3. WHO. The importance of pharmacovigilance. 2002.
4. 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