Pharmacovigilance life cycle

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Pharmacovigilance reinforces safe use of medicines

Most people need pharmacotherapy at some point in their lives. We all are different, and no two persons respond to medicines the same way. What cures one as desired may cause difficult adverse reactions in another one and require a change in the dose, a switch of the medicinal product, or termination of the medication. Pharmacovigilance is needed for correct and safe use of medicines and to obtain as comprehensive information as possible on their use. Pharmacovigilance is one of the key operations of pharmaceutical companies.

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects and all other problems related to medicines. The goal is to ensure appropriate and safe use of medicines. Safety means that the benefits from the medicine to the user are greater than their potential harmful effects.

Development of a new medicine requires perseverance, time and money: development work and market access of a medicine takes 10 to 15 years. Pharmacovigilance is needed all the way: in clinical studies and after granting of the marketing authorisation while the medicine is on the market. As holders of marketing authorisations, pharmaceutical companies are responsible for their products and therefore monitor drug safety actively throughout the life cycle of of the medicines. Companies are obliged to strive for as complete data on their medicines as possible by collecting data on adverse reactions and user experiences.

The objective of pharmacovigilance is to protect public health. This requires detailed planning, continuous evaluation of drug safety and, if needed, implementation of appropriate measures. Such measures may include, for example, addition of warnings or use restrictions in the summary of product characteristics and/or package leaflet, intensified monitoring, further training to health care professionals, etc.

Definition

An adverse reaction is a noxious and unintended response to a medicinal product administered to humans at usual dosages (in case of investigational medicines, before the granting of the marketing authorisation, reactions to all doses administered are relevant) for prophylaxis, diagnostics or treatment of a disease or for modification of body functions. The causal relationship (causality) between the medicinal product and the adverse reaction is assessed to be possible, at the very least.

Why is pharmacovigilance important?

The development of a new medicine starts in a laboratory. After adequate data has been obtained on the properties of the medicinal product, also its safety and efficacy in humans need to be demonstrated. The number of patients enrolled in such clinical studies is always limited, and very rare adverse reactions may not come up in study subjects. Also, patients participating in such studies have been selected rather carefully, and their comorbidities or overall medications are not the same as those in the general public.

The granting of a marketing authorisation means that the risk/benefit balance of the medicinal product in the patient population studied has been assessed to be positive. Completely new adverse reactions may emerge post-authorisation along with the growing number of users of the medicinal product and thereof affect the safety profile of the medicinal product. At the time of the granting of the marketing authorisation, there is either no data at all or only limited data on the effects of the medicinal product on e.g. pregnant or breast-feeding women, children, and elderly patients. This is because clinical studies cannot be conducted on certain patient groups for ethical reasons, or because the possibilities for conducting such studies are very limited.

New adverse reactions are sometimes detected decades after the medicinal product has been placed on the market, and the frequency categories of adverse reactions may change along with increasing data.

All medicines cause adverse reactions. However, not nearly all users experience them, or the reactions are transient or so mild that the medication can be continued. Medicinal products intended for minor diseases or symptoms must not cause life-threatening adverse reactions. Such adverse reactions may however be acceptable for e.g. effective cancer medicines used for the treatment of serious, even fatal diseases. Even in such a case the life-threatening adverse reaction must be very rare, at the very least, and the patient must be carefully monitored to prevent it.

Interactions with other medicinal products, or for example with natural products or food, are one reason for occurrence of adverse reactions. A lot of effort is put into improving management of treatment and supporting patients in controlling adverse reactions so that they can continue using medicinal products which prevent the progress of a disease or reduce premature mortality (e.g. cancer patients). Not even serious adverse reactions always require discontinuation of the medication or a switch to another medicinal product as treatment breaks or dose reductions may allow continuing the medication.

Safety in carrying out pharmacotherapies is important: medicinal products must be used as instructed, situations resulting in interactions should be avoided, and possible adverse reactions should be detected at an early stage so that they can be alleviated and the development of more serious adverse reactions can be prevented. The main goals of pharmacovigilance are to ensure that the risk/benefit balance of the medicinal product remains positive, to reduce the incidence of adverse reactions and the number of fatalities due to adverse reactions, and to lower hospital care costs.

Multitude of pharmacovigilance stakeholders

Within the European Union (EU), the European Medicines Agency (EMA) has a central role in drug safety monitoring. Its main tasks are coordination of the European pharmacovigilance activities, production of information on the safe and effective use of medicinal products, and the management and maintenance of the European adverse reaction database. The Agency collects and analyses data from all sources available, including case reports on individual patients, epidemiological studies and clinical studies. The Agency assesses together with the national drug safety authorities of the EU member states risk management plans and safety update reports submitted by marketing authorisation holders, risk/benefit relationships, likelihood and severity of risks and risk factors, as well as the need for further investigations or restrictions in risk management. In Europe, drug safety is supervised and implemented by the European Commission and the European Medicines Agency as well as the drug regulatory authorities of the EU member states – in Finland, by the Finnish Medicines Agency FIMEA. In the United States, the drug regulatory authority is the Food and Drug Administration (FDA). Also the World Health Organization (WHO) has a significant role in drug safety. WHO has promoted patient safety by collecting and analysing adverse reaction data for 50 years to date. The data collected on adverse reactions in Finland ends up in the databases of WHO and EMA as well.

Also pharmaceutical companies have several statutory obligations related to drug safety monitoring. The marketing authorisation holders are obliged to monitor the safety of medicinal products on the market and to take any neces sary steps if changes in the risk/benefit relationship are detected. Information on such changes must be submitted to the supervisory authorities within the designated time limits, and the authorities must be immediately notified of an emerging safety concern related to the risk/ benefit relationship of a medicinal product. If needed, the authorities may request further investigations. Various official procedures are in place for updating the product information of medicinal products and for implementation of other safety measures. The urgency of these measures varies. Close cooperation between marketing authorisation holders and Fimea is critical in the monitoring of adverse reactions and implementation of risk management measures.

Health care professionals and users of medicinal products participate in pharmacovigilance activities by reporting adverse reactions and user experiences on medicinal products. Also utilization of pharmacovigilance-related data and tools, such as training materials and patient alert cards, constitutes one part of the pharmacovigilance activities.

Adverse Reaction Register

In Finland, data on adverse reactions caused by drugs and vaccines is recorded in the Adverse Reaction Register of Fimea; all data on suspected adverse reactions and user experiences reported by the Finnish health care professionals and users of medicines is saved in this register.

The primary purpose of the reporting system is to detect previously unrecognized rare adverse reactions not yet listed in the package leaflets or summaries of product characteristics of me dicinal products. To attain this goal, all adverse reactions - including those already known - and especially those caused by new medicines, serious adverse reactions, and suspected adverse reactions related to medicines under additional monitoring should be reported to the Adverse Reaction Register.

After the granting of the marketing authorisation, the use of the medicinal product increases rapidly and expands to new patient populations, which is why the black inverted triangle signifying intensified monitoring has been a requirement for all new active substances since 2013. The authorities may place a medicinal product under additional monitoring also later, if needed.

The Adverse Reaction Register can be utilized for signal detection. A signal means that a specific adverse reaction is reported on a specific medicinal product repeatedly. This does not yet substantiate whether the medicinal product has actually caused the adverse reaction or not. After reaching near certainty on the connection between the specific adverse reaction and the specific medicinal product, the causal relationship must be assessed and the need and nature of possible further measures evaluated. Further measures aim to reduce risks related to the use of the medicinal product. For example, the use of the medicinal product may be restricted to a certain patient population only. Warnings added to the summary of product characteristics direct to a safer use of the medicine. The number of reports to the Register cannot be used to deduce the frequency of individual adverse reactions, or to compare the safety of different active substances.

Establishment of a comprehensive pharmacovigilance register and collection of reliable data are key components in pharmacovigilance.

Reporting of adverse reactions

An adverse reaction is a noxious and unintended effect caused by a medicinal product.

It is important to report suspected adverse reactions and user experiences on medicinal products. The report can be made by anyone who becomes aware of the adverse reaction, including the user of the medicinal product. A mere suspicion on an adverse drug reaction is enough to make a report. The reports should be submitted either to Fimea or the marketing authorisation holder of the medicinal product. The electronic reporting form for adverse effects can be found on the Fimea website in Finnish (http://www.fimea.fi/laaketurvallisuus_ja_tieto/laakkeiden_turvallisuus/haittavaikutuksista_ilmoittaminen/). Unless further clarifications are needed, Fimea does not separately confirm the reception of adverse reaction reports or comment on them in any way.

It is good to remember that in Finland health care professionals and users of medicinal products are urged to report certain types of adverse reactions in particular and especially suspected adverse effects related to new medicinal products or those under intensified monitoring. Besides this, the law obliges marketing authorisation holders to collect data even on all well-established medicinal products and their adverse reactions, as well as comprehensive data on user experiences of medicinal products. This obligation concerns all employees of marketing authorisation holders and similar stakeholders.

Types of data collected

All suspected adverse reactions occurring during the use of the medicine should be reported and recorded. Examples of such suspected adverse reactions are skin rash, fever, malaise, abnormal laboratory findings, etc.

Data to be collected includes various user experiences which do not necessarily entail a suspicion on an adverse reaction. Such user experiences include e.g. the use of a medicinal product during pregnancy or breast-feeding, contraindicated use or off-label use, overdose or incorrect use, occupational exposure, and medication errors. A medication error can be any event which may lead to incorrect use of the medicinal product or cause harm to the patient when the medicinal product is used under the supervision of a health care professional or when the medicinal product is used by the patient or consumer. Reports on adverse reactions and user experiences should contain details of the patient, the medicinal product, the suspected adverse reaction, and the reporter. The batch number and the trade name of the medicinal product would be useful as well. The batch number is particularly important for biological medicines.

The data should be comprehensive to allow as accurate assessment as possible of the causal relationship between the suspected adverse reaction and the medicinal product, and to allow determination of adverse reactions typical to specific patient populations. Reports with exhaustive data reduce the need for further clarifications.

For what purpose is data collected?

The collected data is saved in Adverse Reaction Registers kept by companies and the authorities and can be utilized e.g. for periodic safety update reports on medicinal products. Each adverse reaction report is assessed by experts of both the company concerned and drug regulatory authorities.

Some medicines may have very long summaries of product characteristics, containing all reported suspected adverse reactions. Inclusion of such data does not however mean that the medicinal product will always cause the listed adverse reactions or will cause them to all users.

Occasionally, a decision is made to withdraw the medicinal product from the market due to safety reasons. Such measures are fairly rare and mostly adopted on new medicinal products which have been on the market only for a short period of time. Early detection of adverse reactions and appropriate response to them, e.g. by restricting the use of the medicinal product to a specific patient population, reinforce the safe and correct use of medicines.

From the point of view of drug safety, the combination of personalized medicine / individualized therapies and pharmacotherapies will reduce prevalence of adverse reactions as precision diagnostics used in the diagnosing of patients will enable targeting of medicines only to those individuals who will benefit from them.

Openness and transparency are imperative

EudraVigilance, the European database of suspected adverse drug reactions, is managed by the European Medicines Agency (EMA) and partly accessible to the users of medicinal products as well. Data on certain medicines in the database is available in Finnish, too. Furthermore, safety evaluations of medicinal products are published on the EMA website, and certain drug safety hearings of the regulatory network are open to the public. Also summaries of risk management plans of medicinal products are available on the website. A risk management plan describes the actions to be taken to gain more information on the potential risks of the medicinal product and to reduce the already known risks related to the use of the medicinal product in question.
All collected and analysed safety data will be reviewed in terms of patient safety. Marketing authorisation holders and drug regulatory authorities will always report all data essential to patient safety.

In Finland, the social and health care services reform has drawn the attention to the benefits and costs of these services. Treatment effectiveness relies on, among other things, an appropriately selected and appropriately implemented pharmacotherapy and the monitoring of clinical effectiveness. Efficient pharmacovigilance serves a function even in this context.

Pharmaceutical companies work diligently to ensure efficiency of pharmacovigilance activities and to improve patient safety.

Pharmaceutical companies must follow all applicable laws and operate in an ethically sound manner. Their pharmacovigilance activities are subject to regular and continuous inspections by both internal auditors and those acting on behalf of the authorities. Deficiencies detected in pharmacovigilance can have serious consequences on both patient safety and the company reputation.

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