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Medical Law

Risk Management for the Use of Medicinal Products

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Summary:

Risk management for the use of medicinal products is a process of result assessment for quality, non-clinical and clinical studies. It is also understood as a constant monitoring of a medicinal product after its marketing authorization. In the process of risk management it is crucial to provide the healthcare professional environment with the specified data concerning the drug risk. It is vital to implement such tools as notifications in medicinal product descriptions and pharmaceutical compendia as well as safety announcements and educational materials designed especially for newly introduced drugs.

Key words: medicinal products, risk management, drug information

In certain circumstances use of drugs cannot be avoided. Practice proves that aside from the unquestionable indication of drug's effectiveness it is vital to implement such products that will cause the slightest possible complications in the course of a treatment. Clinical studies are inefficient in the detection of rarely occurring adverse events which, in turn, pose the most frequent case for drug withdrawal.

The following products may serve as the examples of such drugs: dexfenfluramine, terfenadine, cerivastatin or rofecoxib. Recent years provided the example of rimonabant.

Dexfenfluramine, a locally effective, appetite reducing drug which has been withdrawn from health care after such side-effects as heart valves damage were observed.

Cerivastatin, for the first time marketed worldwide in 1997, it was withdrawn in 2001 due to muscular complications of a severe course, i.e. rhabdomyolysis.

It emerged that the drug had been frequently prescribed along with the other product used in lipid disorders treatment, i.e. gemfibrozil, which in turn effected in an interaction. Eventually the risk of muscular complications would grow 1000 times. Although the company has noticed the risk and directly apprised the specialist of drug's safety conditions, the medical practice could not be altered and medicaments containing cerivastatin have been eventually withdrawn from the market.

Rofecoxib, a selective cyclooxygenase inhibitor, used in treatment of rheumatoid arthritis. It has been withdrawn after it was proved (in APPROVE clinical trial) that the risk of vascular complications (coronary attacks, brain strokes) doubled when treated with rofecoxib as compared to a group o patients treated with placebo.

Potentially new application of rofecoxib has been tested and analyzed for colorectal polyposis.

Rimonabant is the final example of a drug withdrawal due to safety concerns. Ancillary, anti-obesity drug was withdrawn due to suicides and suicidal attempts observed among patients. The drug caused more severe depression than obesity or therapy itself.

The examples illustrate the vitality of risk assessment and proper management accompanying drug use. Risk management is understood as every kind of action taken for the benefit of hazard detection and characterisation as well as informing the professionals and patients about potential complications. It is critical to take such course of action that will minimalize the risk, i.e. narrow down the adverse medication effects.

The first stage is hazard detection. In the course of drug development from a chemical molecule to completed and ready to use medicinal product a series of studies is conducted.

Quality verification studies are not in the scope of interest of this work as the assumption was made that good quality is a prerequisite for drug authorization.

In a non-clinical phase of studies a drug's effect on living organisms of various animal species is analyzed. Conducted studies are meant to evaluate drug toxicity, its effects on cardiovascular system, heart or nervous system, and to determine potential genotoxicity and carcinogenicity. The effect of a given substance on fertility, embryo and young animal specimen's development is also studied. There is a number of specified guidelines for the types of a necessary non-clinical studies. (http://www.ich.org) [1]

In this stage of research drug properties are already known to the extent that enables conducting Phase I clinical studies. In the successive stages of clinical trials it is possible to gather data concerning potential side effects. However, considering the size of population taking part in the study, observable side effects are only of types: frequent (ranging from 1% to 10% of patients) and very frequent (over 10% of patients).

Hence the still apposite opinion of an American pharmacologist Louis Lasagna who claimed that: when new drug is authorised on market one may be positive that not everything (both good and bad) is known about it. There are always some surprises lurking around the corner. [2]

What logically follows is that the importance of monitoring drug safety after a product being marketed becomes more obvious. It is also a legal obligation, with a substantial part of tasks assigned to a manufacturer.

Aside from gathering, analyzing and distributing single notifications about side effects, a pharmaceutical company prepares a summary report on data concerning the drug safety. These are known as Periodic Safety Update Reports (PSUR). Risk Management Plan is yet another type of summary report which is especially required for new therapies when (bearing in mind the lack of knowledge about a new drug being just marketed) the most effective method of hazard detection is being developed, basing on available non-clinical and clinical studies' results. [3] The latter document is simply a survey of collected data on potential complications on various stages of Research and Development and a description of actions taken by the manufacturer, which most efficiently provide data on new potential complications. As stated above this document is required for medicinal products containing new molecular entity, having new effective mechanism etc.

It is accounted for by insufficient knowledge on drug use in normal conditions among large scale population and not in the course of clinical study.

The following notifications may serve as the example of those, that would have never been received in the course of clinical study, yet they have been noticed during spontaneous monitoring:

1) Death of a 74-year-old male who had been administered with perineural and infiltration anaesthesia of articaine hydrochloride and adrenaline during a procedure of dental extraction.

It has been noted in contraindications to the use of medication that the drug cannot be administered to patients with advanced atherosclerosis.

As the cause of death, post-mortem examination indicated pulmonary embolism caused by highly advanced general arterial disease. The interference of the drug has been ruled out. However, there is a remaining question of adrenaline being a factor that might have contributed to the fatal complications.

2) A case of tongue and lips edema of a 23-year-old male with a prescription to mouthwash with a suspension of a tablet of acetylsalicylic acid and water as a treatment of pharyngitis

Hipersensivity to acetylsalicylic acid was a likely cause of such reaction. What needs to be stressed is that the action was not in accordance to indications.

3) Symptoms of gastrointestinal bleeding of an elderly male who has been simultaneously taking 3 anti-inflammatory drugs: piroxicam, naklofen and meloxicam as a treatment of osteoarthritis of knees.

The procedure here is faulty. By administering 3 drugs of the same anchor point the synergistic effect is not achieved. Instead there is a significant growth of side effect hazard.

Each notification of an adverse effect of a drug sent by a company or health care professional in the form of whichever blank or letter undergoes a formal and substantive evaluation conducted by a Registration Agency

The formal evaluation is meant to determine whether a notification includes required minimum data allowing the identification of a patient, drug, and at least one adverse effect as well as personal data of a person notifying, as the anonymous notifications are not acknowledged.

The evaluation of a cause and effect relationship is far more difficult and is meant to determine probability level of a notified drug that might have caused a given complication. It is very rare to determine it with 100% accuracy and certainty. In most cases the evaluation of the cause and effect relationship leads to designation of the level of probability up to which the drug might have caused complication.

For over 40 years World Health Organization, which has been gathering data on worldwide adverse effects, has developed categories of cause and effect relationship which can be assigned to a given notification about an adverse effect. It is crucial for the evaluated notifications to contain as much vital information as possible which, in turn, facilitates the process of evaluation.

The evaluation of cause and effect relationship uses also algorithms of series of inquiries with assigned scoring system. A specified score indicates relationship between a drug and a complication.

In case of large data sets, the quantitative value methods may be applied in the evaluation of cause and effect relationship. They use mathematical models which in turn are meant to "cut off" a set of notified adverse effects as randomly or accidentally related to administration of a drug from the set of those, where the relation is marked with higher probability.

Process of risk analysis is thus conducted on many levels of drug development, through its whole market life-span.

It is also important to properly distribute information about hazard. There are number of channels via which the information may reach the health care society and patients themselves. These are as follows:

- medicinal product specification
- a leaflet
- statements addressed directly to the health care professionals
- bulletins compiled by Registration Agencies
- review articles
- drugs monograph (i.e. Micomedex and other databases, databases of Drug Information Centers)
- educational materials prepared and compiled by the pharmaceutical industry, consulted with Registration Agencies, as implementation of European Commission's decision.

Main goals that should be achieved are: providing data on specific hazard connected with the use of a given drug (e.g. occurrence of severe skin conditions or hypersensivity reactions), lowering the frequency of either occurrence or intensification of a given undesirable reaction, e.g. by early diagnosis of a side effect (e.g. observation of transaminase activity as a symptom of deteriorating liver function during the use of statins). The information should also help in an early detection and proper procedures when side effects occur, as with the administration of lamotrigine (an antiepileptic drug) which has to be discontinued after the occurrence of first skin conditions in order to prevent development of fatal erythema multiforme. It is especially important when administering the drug to children. Discontinuation of a drug suspected to bare a side effect on a patient usually causes symptoms withdrawal or, at least, its decrease.

It is not always possible to completely discontinue a drug, as in the case of statines in secondary prevention of cardiovascular diseases, yet adjusting a dosage or changing to another analog drug from a given group may e.g. reduce experienced myalgias. When distributing the information on hazard it is worth to focus the attention on contraindications, as they define known aspects of risk of side effects' occurrence. It is also important to enclose information on diagnostic procedures enabling detection of e.g. particular gene allele, the presence of which determines an occurrence of a complication for a given patient. Drug information is also understood as a description of its proper development and administration, e.g. in French children's wards the injected form of paracetamol with the enclosed description of product strength given in mg/ml was improperly dosed due to necessity of unit conversion, i.e. mg of paracetamol for kg of child's bodyweight to ml of the product.

Obviously among the recipients of drug specification (with information on possible side effects) are the medical doctors, nurses, pharmacists but also patients and their carers.

The latter may play a crucial role, as in case of wife taking care of her husband dialyzed with Extraneal. The fluid due to its physicochemical properties may falsify the results of glycemic index test. The man has been admitted to a hospital's admissions' from a different reason, however doctors, after glycemic

testing, wanted to administer hipoglycemic treatment as they were concerned with test results (glycemic index around 300mg/dl). The wife's initial explanations as to the fault of dialysis liquid met with little response and only due to her determination the administration of the drug has been cancelled, thereby avoiding eventual complications or even death. Nowadays patients dialysed with Extraneal carry charts or, as in some countries, special bracelets or type of a pendant with an information about possible, significantly overestimated glucose test results. Due to so doing doctors are aware not to administer hipoglycemic treatment after a single testing of glucose level, as it may lead even to patient's death.

Educational materials for medical doctors are a different way to note the peculiar type of hazard during the course of a treatment. The following drugs are the example of products for which these kind of materials are developed:

- isotretinoin: (used in severe skin conditions as acne) drug proved to have teratogenic properties and a programme preventing the exposure of pregnant women to that drug
- drugs used in pulmonary hypertension (endothelin II receptor antagonists such as ambrisentan or bosentan) and educational materials highlighting the teratogenic properties, but also liver complications including such damage to its function which may require transplantation.
- drugs used in age-related macular degeneration (pegaptanib, ranimizumab injected intravitreally) and educational materials including proper technique of administration as well as procedures necessary in case of delayed hypersensivity reactions

Drug safety messages are most often short (approximately 2 page-long documents) and aimed to draw medical personnel's attention to a specific problem concerning safety of a drug use. There are numerous examples of such messages including recent one on a safety of use for all products of external application containing ketoprofen. The drug status has been changed from the purchased over-the-counter to the available only when prescribed due to recorded cases of severe hyposensitivity reactions to sunlight and cross reaction with octocrylene (a UV filter). It became apparent that even during a cloudy weather the solar radiation is strong enough to cause severe skin irritation in case of some patients.

The most difficult problem in managing the risk of drug use is an assessment of applied system's efficiency. There is a question of determining parameters used in the process of efficiency verification. One possibility is do define such a parameter as a number of complications resulting from the use of a given drug. However, drugs administered in case of commonly occurring diseases may be automatically pushed to a default position if the scale of exposure to the drug would not be provided for.

Possibly the method in question should analyse the specific groups of complications for a given drug, especially those of a severe course. As a promising development one may see the implementation of services' data bases run by a withholding agent, as that would also allow to gather medical data. The process of creating the register indexing all patients would have to undergo extensive monitoring procedures in terms of personal and medical data.

Medication-induced complications are among the first ten causes of deaths and one of the most frequent reasons for patients hospitalisation. However, the most disturbing fact is that the majority of complications include those already known and possible to be prevent under the condition of effective risk management.

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