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Pharmacovigilance as an imperative of modern medicine – experience from Montenegro

Farmakovigilanca kao imperativ moderne medicine: iskustvo iz Crne Gore

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Introduction

According to the definition of World Health Organization (WHO), pharmacovigilance is a science that comprises activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem [1]. The specific aims of pharmacovigilance are to improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions, improve public health and safety in relation to the use of medicines, contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public [2].

According to the latest definition, denounced in 2010, adverse effect is harmful and unintentionally caused reaction to a medicine [3]. Previous definitions of adverse effects [4] (since 1972) meant "adverse and unexpected response to a drug, which occurs in the application of the dose conventionally used for the prophylaxis, diagnosis or treatment of diseases or modifying the physiological functions". The latest definition implies harmful and unintended effects caused by a medicine at any dose [3].

Since its founding the WHO has the mandate to establish international standards for medicines. The realization of this task seriously started during the late sixties, after the discovery of the reproductive toxicity of thalidomide. A pilot project to establish an international system of monitoring adverse drug reactions (1968) made very quick recommendations on the establishment of national centers to deal with this issue and stressed the necessity of setting uniform guidelines. The WHO Collaborating Center for International Drug Monitoring was founded in 1978 and located in Uppsala (Sweden) [5], and contact with this center is the most important task of national pharmacovigilance centres. Today this center has 118 regular members and 30 affiliated member states. The most important sources of information on adverse drug reaction (ADR) are spontaneous reporting by healthcare workers, systematic study on the whole population and analysis of health statistics and information on the consumption of medicines. Data from these sources would be poured in a reference center. At this point, Uppsala base has over ten million reported cases of adverse effects of medicines from around the world [6].

The importance of monitoring of the safe use of medicines

The aim of the activities on monitoring and collecting data on ADRs is rationalization of pharmacotherapy, use of the most effective medicine with the least ADR upon the establishment of the proper diagnosis.

ADRs may be observed during preclinical and clinical trials. Data collected during these phases of drug development cannot predict a possible adverse ADR that may manifest only after placing a medicinal product on the market. The reasons are as follows: animal studies are insufficient to predict the safety of medicines in humans; in clinical trials a limited number of selected patients is included, conditions of

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administration of medicine are different from those in normal clinical practice, and duration of trials is limited; less than 5,000 patients would be exposed to medicine during clinical trials before its placing on the market and only ADRs with higher incidence of manifestation could have been observed; at least 30,000 patients need to take medicine to observe ADR with the incidence of 1 : 10,000; data on rare serious adverse events, toxic effects of chronic treatment, the use of a medicine in specific categories of patients (children, the elderly, pregnant women) or interactions with other medicines are often incomplete or not available [7].

It is estimated that in the first three phases of clinical trials of the medicine less than 0.1% of all ADRs would be detected, although there are opinions that the number is higher, up to 2% [8].

The most important source of new information on the unknown effects of medicines before its registration represents the fourth phase of clinical testing or monitoring of medicines. It starts after placing a medicine on the market and indicates that the medicine is in widespread, general use. This phase lasts indefinitely. In this open-ended period, both harmful and beneficial unknown aspects of the drug will be revealed. In the fourth phase, ADRs which rarely occur are registered, for example, thrombocytopenia caused by sulfonamides (only in one in 15,800 patients); thrombocytopenic purpura, which follows the use of clopidogrel, occurs in one in a million of those who use it [9]. This low frequency of purpura is not the reason for restrictions of routine use of clopidogrel, unlike ticlopidine, a medicine of the same group, in which purpura occurs in one of 2,000 to 4,000 patients who receive it. These examples show that the correct conclusion regarding frequency of ADRs need many patients and a very long period of monitoring the effects of the drug.

After placing a medicine on the market, manufacturers are obliged to monitor its safety, but this does not necessarily imply the organization of prospective studies about its ADRs. These data manufacturers receive mostly from physicians who prescribe/apply medicine, pharmacists and other healthcare workers. If they do not participate in these activities, physicians and pharmacists eliminate their personal contribution to the extension of knowledge of ADRs. Reporting ADRs, healthcare workers can protect health of their patients.

Pharmacovigilance is the need and obligation of every country, because there are differences in the incidence of ADRs (and other problems caused by medicines) among different communities. Causes may be as follows: differences in the prevalence of certain diseases; different practice of prescribing medicines; genetic factors, diet, habits; different manufacturing process which affects the quality and composition of medicines; differences in the use of the drug, including the therapeutic indication and the dosage regimen; co-administration of the traditional and herbal products which may cause specific toxicological problems, whether administered alone or in combination with other medicines [10].

Information collected in one country (for example in the country of the manufacturer) may not be relevant to other regions of the world, because the conditions of administration could be different [7].

Monitoring the safety of medicines on the market is a valuable tool for detecting ADRs that are the result of counterfeiting or inadequate quality of a medicine.

An organized and permanent monitoring of the effects of medicines after obtaining marketing authorisation is necessary to recognize and prevent ADRs on time.

In consideration of aforementioned, the greatest importance in obtaining information about ADRs after granting marketing authorization has spontaneous reporting of adverse reactions.

Some of numerous recent examples experiencing contemporary pharmacotherapy with its accompanying risks manifested in the form of ADRs are shown in Table 1.

Decision of withdrawal of these medicines from the market due to the unfavourable ratio of benefits and risks was made by the national regulatory authorities based on data collected by spontaneous reporting of adverse reactions.

Table 1

Examples of medicines withdrawn from the market on the basis of decisions made by regulatory authorities as the result of spontaneous reporting of adverse drug reactions (ADRs) [11–13]

Year	Medicine	Pharmacotherapeutic group	Reason of withrawal
2000	astemizole	histamine H_1-receptor antagonist	QT prolongation
2000	troglitazone	antidiabetic (thiazolidinedione)	hepatotoxicity
2000	cisapride	serotonin 5-HT4 agonist histamine H_2-receptor antagonist	QT prolongation
2001	cerivastatin	statin	rhabdomyolysis
2001	trovafloxacin	fluoroquinolone antibiotic	acute liver failure
2001	rapacuronium	neuromuscular blocker	bronchospasm
2004	rofecoxib	(COX-2) inhibitor	myocardial infarction
2005	hydromorphone	opioid analgesic	the risk of overdose
2005	thioridazine	typical antipsychotic	cardiotoxicity
2006	ximelagatran	anticoagulant	hepatotoxicity
2007	pergolide	dopamine receptor agonist	defect of heart valves
2007	aprotinin	phospholipase A2 inhibitor	cardiac death
2007	insulin inhaled	antidiabetic	unsafe
2009	efalizumab	monoclonal antibody	multifocal leukoencephalopathy
2010	sibutramine	anorexiant	cardiotoxicity
2010	rosiglitazone	antidiabetic (thiazolidinedione)	myocardial infarction
2013	hexoprenaline	β_2-adrenergic receptor agonist	cardiac disorders

COX-2 – cyclooxygenase 2.

The frequency and significance of adverse drug reactions

In the last few decades, numerous studies showed an increase in morbidity and mortality caused by medicines. It is estimated that the adverse effects of medicines are the fourth to sixth leading cause of mortality in the United States [14, 15].

ADRs appear more frequently than actually reported and registered, and the consequences are complex and mostly have a medical, economic and social importance [7].

In some countries, the number of hospitalizations due to ADRs is about 10% [16–18]. In the European Union (EU), the average frequency of ADRs in adults is 1 *per* 30–60 visits to the doctor, or 1 *per* 30–40 patients [19]. In children, the incidence of ADRs varies between 1/60 and 1/83. Data on the frequency of ADRs depend on local legislation, the accepted definition in the field of pharmacovigilance, the national policy of prescribing drugs, the methods used in the detection of ADR, the institution of the origin of information (hospital or outpatient facilities) and other factors. Thus, drugs are significantly more often prescribed in France and Germany than in other EU countries (90% of visits to a doctor in France, followed by prescribing an average of 4.2 prescriptions, while the average for the EU is 0.8) [20].

ADRs that can be avoided or prevented make up a significant portion (28–80%) of ADRs. In Italy, ADRs that could be prevented caused 1.4% of all hospital admissions. Other authors note that 35.5% of hospital admissions caused by ADRs could be prevented [20]. Generally, it is estimated that ADRs could have been prevented in about 50% of cases [21–24].

ADRs are, also, a common cause of morbidity and mortality within the hospital setting. The hospital environment, with its clearly defined patient population, is an ideal setting to identify potential ADR signals [25].

It has been estimated that 10–30% of hospitalized patients experience ADRs [26–30] and 0.3–10% of all hospital admissions are actually the results of ADRs [17, 22, 31]. In hospital environment, 3% of all fatal outcomes are caused by ADRs [28]. ADRs also cause prolongation of the hospitalization period and increase of hospital costs [27].

Varieties in frequency of ADR occurrence during hospitalization among different studies could be explained by different investigation methods. While in some studies only spontaneously reported ADRs were recorded, in others, ADRs were recorded by using intensive monitoring systems [17, 32]. Furthermore, there are significant differences between stimulated *versus* non-stimulated reporting systems, as well as between manual and electronic active monitoring systems [32]. Prospective collection of ADRs has many advantages over retrospective data collection (which rely on chart review) mostly due to most often daily visits by trained healthcare professionals on selected departments, over a restricted time period, in order to obtain records of all patients and suspected events [33–35].

Furthermore, earlier studies emphasised that ADRs could often be prevented if physicians had had possible risk factors in mind [36–38].

Pharmacovigilance legislation in Montenegro

The role of the Agency for Medicines and Medical Devices

Appalling statistics at the level of EU countries, in which the pharmacovigilance system was building through decades, especially when it comes to proven fatalities caused by irrational use of medicines (200,000 deaths annually in the EU due to adverse effects of medicines) [39] and the enormous costs of their treatment (about 709 billion € annually) [39] were the trigger for proposal, final approval by the European Parliament and entry into the force of the new EU regulation on pharmacovigilance.

The Agency for Medicines and Medical Devices of Montenegro (*Crnogorska agencija za lekove i medicinska sredstva* - CALIMS), as a full member of the WHO-Uppsala Monitoring Centre, in order to protect public health by monitoring the safety of medicines, collects, assesses and manages all reported suspected ADRs into the national database, and forwards them to this center.

Reporting of ADR based on the principle of spontaneity means that healthcare workers report any suspected ADR; they should inform the Agency or manufacturer's representative who will forward the report to the Agency. Healthcare workers have moral and professional, but also a legal obligation to do so [40]. Fulfilled reporting form could be submitted to the Agency in one of the following manners: by post, in person, by fax or by e-mail. In 2013 the possibility of reporting through the information system of primary healthcare institutions and general hospitals was introduced. This is expected to be the principal method when it comes to report ADR, because it is an easy, safe and fast way to transfer data from a healthcare institution to the CALIMS.

According to the Law on Medicines, the CALIMS publishes annual report [40] on the results of spontaneous reporting of ADRs. Each new report that arrives at the CALIMS represents important information about medicines and in this sense the CALIMS makes further efforts to work together with other participants in the system of pharmacovigilance in order to build an effective national surveillance system in Montenegro. Special attention is directed towards increasing the number of reports sent by pharmaceutical companies over the person responsible for pharmacovigilance, legally obliged to take an active role in the reporting of ADRs of their medicines placed on the market in Montenegro.

As other agencies for medicines and medical devices, the CALIMS prepares Direct Healthcare Professional Communication (DHPC) [41] – information important for safe and effective use of medicines, which is sent to healthcare professionals by Marketing Authorization Holder (MAH) or the CALIMS. The Agency sends Dear Doctor Letters in case of significant changes in the Summary of product characteristics (new contraindications, lowering recommended dose of medicines, limitations in the indications, limitations in dispensing mode of a medicine, new precautionary measures, etc.), termination of marketing authorization or its temporarily suspension due to safety reasons, or in other similar situations in which it is necessary to inform healthcare

professionals on safe medicine use. Providing information about safe and effective use of medicines is one of the preconditions for their rational use and is considered a public health responsibility. In case Dear Doctor Letter is to be sent by MAH, the content of the letter, as well as plan for communication with healthcare professional must previously be approved by the Agency.

When it appears that a drug leads to frequent and/or unacceptable adverse effects, appropriate regulatory action should be taken: correction of Summary of product characteristics and Patient information leaflet (Level I warning) or withdrawal of the medicine from the market (Level II warning).

Spontaneous reporting and intensive monitoring of ADRs

The Pharmacovigilance Department of the Agency for Medicines and Medical Devices of Montenegro received a total of 106 spontaneous reports of suspected ADR (171 *per* million inhabitants) in 2014, of which 68 reports from healthcare workers, while 38 reports ensued from post-marketing noninterventional studies [42]. The total number of reports increased by 9.28% compared to the year 2013 [43]. Physicians have reported 82% of suspected ADRs, while the pharmacists reported 18% of suspected ADRs. Most reports were received from the Clinical Center of Montenegro (59%) and primary health care system (19%) [42]. The results of spontaneous reporting of ADRs, according to the latest CALIMS annual report [42], indicate that the largest number of reports, according to the the Anatomical Therapeutic Cemical (ATC) classification of suspected drugs, related to drugs belongs to the group of antineoplastic and immunomodulating agents, drugs for cardiovascular system and anti-infectives for systemic use. Reported ADRs [42] based on Medical Dictionary for Regulatory Activities (MedDRA) system organ classification (System Organ Class – SOC) at the most include: skin and subcutaneous tissue disorders (20%), general disorders and administration site conditions (17%), gastrointestinal disorders (11%), laboratory investigations (7%), respiratory, thoracic and mediastinal disorders (6%) and nervous system disorders (5%).

Similar data are listed in the Annual Report on spontaneous reporting of ADRs of Agency for Medicines and Medical Devices of Serbia [44]. According to this report from 2013 the number of reports is also too low, 162.9 *per* million inhabitants [44] (WHO Drug Monitoring Programme defines less than 200 reported ADRs *per* million inhabitants annually as underreporing [45]). Physicians have reported 69% of suspected ADRs, while the pharmacists reported 29%.

In contrast to Montenegro and Serbia, ADR spontaneous reporting in neighboring Croatia is far more common. According to the Annual Report on spontaneous reporting of ADR Agency for Medicinal Products and Medical Devices of Croatia for 2014 [46], a total of 3,112 suspected ADRs was reported, by which Croatia took 16th place out of 115 countries participating in the WHO program of monitoring drug safety [46]. In Croatia, most of the reports came from physicians and pharmacists (the largest number of reports reaches from pharmacies, 35%, followed by the primary health care level facilities and hospitals, 18%).

In order to analyze occurrence, characteristics and risk factors for developing ADRs using intensive monitoring system of ADRs, we conducted a prospective study in 2014, which included 200 patients, hospitalized at Cardiology Center of the Clinical Center of Montenegro [47]. ADRs were collected using a specially designed questionnaire, based on the list of symptoms and signs that could point out to the potential ADR. Data from patients' medical charts, laboratory tests and other available parameters were observed and combined with the data from questionnaire. The results show that 34% of all patients experience at least one ADR. The most common ADRs occurs as nervous system disorders, less frequent are cardiovascular disorders, while immune system disorders are the rarest. Sixteen percent of all ADRs are characterized as serious. The majority of patients (97.3%) recover without consequences. The multivariate analysis shows independent significant associations between ADR and age, gender, co-morbidities, polypragmasia and duration of hospitalization [47].

None of ADRs observed in this study was reported by health workers to the Department of Pharmacovigilance of the Agency, despite legal obligations. Considering a high incidence of ADR in this study and the fact that none observed suspicion of ADR was reported to the CALIMS by health workers, it can be concluded that the system of spontaneous reporting of ADR in Montenegro is deficient.

The CALIMS, as a national representative institution with contacts with European and international databases, remains deprived of valuable information on the safety of medicines that are placed on the market of Montenegro. As each ADR reported by a healthcare worker the CALIMS forwards to the MAH, with the protected data on the health worker who reported the adverse effect, in global document on the safety of drugs, leading pharmaceutical companies have not been included cases from Montenegro.

Futher directions for farmacovigilance development in Montenegro

The success of the pharmacovigilance system of each country depends on the participation of healthcare professionals in it. The CALIMS conducts many activities aimed at the promotion of pharmacovigilance, pointing to the importance of spontaneous reporting of ADR, as well as the training of healthcare professionals in this field. One of them is organizing workshops on pharmacovigilance for the development of a system of continuous monitoring of safety of medicines. The Agency will continue future organizing workshops of this type.

Conclusion

Reporting on ADRs by healthcare workers should be a part of everyday clinical practice, since it is one of the indicators of healthcare quality.

National ADR reporting system in Montenegro is organised by the Pharmacovigilance Department of the Agency for Medicines and Medical Devices of Montenegro, but the number of reports coming from healthcare professionals is quite low.

Therefore, it is necessary to conduct additional training of healthcare workers, to improve their awareness about the importance of ADRs and the risk factors that lead to them, as well as to increase the number of reported suspected ADRs.

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