ЭКОНОМИКА

The Evaluation of the Drug Safety Monitoring System in RA and the Ways of Its Improvement

Papoyan Tatshat A.
PhD student, Department of Statistics, Faculty of Informatics and Statistics
Armenian State University of Economics (Yerevan, RA)
https://orcid.org/0009-0002-8525-110X
tajatpapoyan@gmail.com

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Դեղերի անվտանգության մոնիտորինգի համակարգի գնահատումը ՀՀ-ում և նրա կատարելագործման ուղիները

Պապոյան Տաճատ Ա.
Ասպիրանտ, Վիճակագրության ամբիոն, ինֆորմատիկայի և վիճակագրության ֆակուլտետ,
Հայաստանի պետական տնտեսագիտական համալսարան (Երևան, ՀՀ)

Ամփոփագիր. Ուսումնասիրության առարկա է դարձել ՀՀ-ում դեղերի անվտանգության դիտարկման համակարգի գնահատումը և դրա կատարելագործման ուղիները, քանի որ առանձին մարդկանց և ամբողջ հասարակության առողջության պահպանումը ցանկացած հասարակարգում սոցիալական և տնտեսական կարևորագույն նշանակություն ունի: Այս խնդրի կարգավորումը իրականացնում է երկրի առողջապահության համակարգը, որտեղ իր ուրույն տեղն ունի դեղերի անվտանգության դիտարկման համակարգը: Աշխարհում լուրջ հիմնախնդիր է դեղերի արդյունավետության և անվտանգության ապահովումը: Այն պայմանավորված է՝ բժշկական պրակտիկայում ուժեղ կենսաբանական ազդեցությամբ մեծ թվով դեղերի օգտագործմամբ, կենսաբանական և քիմիական նյութերի նկատմամբ բնակչության զգայունության բարձրացմամբ, դեղերի տարածված ոչ արդյունավետ կիրառմամբ, դեղերի դուրս գրման ժամանակ թույլ տրվող սխալներով:
Հաճախ դեղաբուժության բարդացումները հիվանդների հոսպիտալացման, հաշմանդամության կամ մահացության պատճառ են դառնում: Միաժամանակ դեղերի շուկայում աճում է որակի ստանդարտներին չհամապատասխանող (անորակ) և կեղծ դեղերի շրջանառությունը: Կեղծ բժշկական արտադրանքը զգալիորեն տարածված է ամբողջ աշխարհում, իսկ այս ամենից զերծ մնալու համար հարկավոր է ճիշտ վարել ՀՀ-ում դեղերի անվտանգության դիտարկման համակարգի գնահատումը և գտնել դրա կատարելագործման ուղիները: Հենց սրանով էլ պայմանավորված է թեմայի արդիականությունը:
Հանգուցաբառեր և բառակապակցություններ՝ դեղ, անվտանգություն, համակարգ, գնահատում, կատարելագործում, ուղի

Оценка системы мониторинга безопасности лекарственных средств в РА и пути ее улучшения

Папоян Тачат А.
Аспирант, Кафедра статистики, Факультет информатики и статистики,
Армянский государственный экономический университет (Ереван, РА)

Аннотация. Оценка системы мониторинга безопасности лекарственных средств в Республике Армения и пути ее совершенствования стали предметом исследования, поскольку в любой системе обеспечения безопасности общества забота о здоровье отдельных людей и всего общества имеет социально-экономическое значение. Эффективность и безопасность лекарственных средств является серьезной проблемой в мире. Это связано с использованием в медицинской практике большого количества лекарственных средств, биологических и химических веществ. с повышенной чувствительностью, распространенным неэффективным применением лекарств, ошибками при назначении лекарств.
Осложнения наркологического лечения часто становятся причиной госпитализации, инвалидности или смерти пациентов. В то же время на фармацевтическом рынке наблюдается увеличение оборота некачественных и поддельных препаратов. Контрафактная медицинская продукция широко распространена во всем мире, и ее следует избегать. Для этого необходимо управлять РА-оценкой системы мониторинга безопасности лекарственных средств и поиском путей ее совершенствования.
Ключевые слова и словосочетания: лекарственный препарат, безопасность, система, оценка, улучшение, путь действия

Introduction

The efficacy of disease prevention and treatment relies heavily on the existence and the effectiveness of certain high-quality drugs and their efficient use as well. The availability of medications has an important bearing on the economic aspects of health care within a country. In various countries, the household heads purchase medication after food which becomes the next biggest budgeted item and in the health sector, the second cost item is these costs next to salary costs. Therefore, medication plays both a healthcare and developmental (economic) role in any healthcare delivery system.

Clinicians have come up with the phrase 'safety of drug' as related to clinical practice. Considering that in most cases, drug studies in general are quite focused on therapeutic reasoning by demonstrating only the main pharmacological effect of the given drug, its therapeutic usefulness, often little attention is paid with respect to how these drugs may affect the functional system of the body.

It is also necessary to be aware of the fact that the absence of appropriate governance regarding this kind of research in the preclinical stages of drug development brings about the deterioration of important functional characteristics. Sterility Studies of drugs are of primary importance in estimating the chances of critical alterations in body functions. This is also because the scope of the studies, which involve the participation of patients suffering from various diseases, includes the assessment of the cellular response of patients to chemotherapy drugs within the range of pharmacologically active compounds. Undesirable pharmacological side effects of new chemical entities or drug substances in development on animals or man might involve alterations of the body's structural, biochemical, or physiological compensatory mechanisms. The focus of traditional toxicological assessments on structural and biochemical changes has been primarily targeted at the response of internal organ clinical pathology and histopathology.

Literature Review

It was in the inception documents of the ICHM3 guidelines and the ICHS6 guidelines that the concept of "drug safety" was introduced.

The first ICHS7A guideline on general principles for drug safety studies was released in the year 2000 while its counterpart including study of drug cardiotoxicity, the ICHS7B, came out in 2005. Drug safety studies are hence defined as studies which assess the safety of a new drug or drug maker by determining the potentially unacceptable pharmacodynamic effects of that new drug or drug maker's product – administration or overdose of the drug at therapeutic or higher doses.

Drug safety studies are carried out in compliance with the international requirement because of concern to:

- To detect any potential pharmacodynamics that could be clinically adverse and important to the drug's safety in clinical trials,
- To quantify and bring forward any adverse events arising from toxicological or clinical investigations,
- To understand the reasons for adverse events conducted or forecasted in the investigations.

Clinical research on the safety of the drug includes compulsory and additional safety studies (Table 1). The first step is to consider aspects of the drug that would alter the functional activities of several systems in the body, in this case, the cardiovascular system, respiratory system and central nervous system.

The additional ones concentrate on the drug's effects on the organs and systems which may be functionally affected temporarily but are not related to causing irreversible damage to the body [**7**, pp. 139-144].

Considering the peculiarities of specific clinical research programs, it must be emphasized that evaluation of the effects of the studied drugs on any specific system may be of paramount importance and should be given first place in the review.

Additional drug safety studies will be carried out when:

- The drug materia medica, based on a specific drug is classified in such a manner as a certain pharmacotherapeutic group, there is always a chance that some unwanted reactions may be produced.
- There are other sources of information that have been found which are significant in the safety of the drug to humans.
- From the stepped up development of basic drugs.
- From undertaking clinical trials.
- From sources of pharmaceutical control.
- From literary sources etc.

The studies on safety of drugs must be applied to all new drugs including those that are developed through chemical synthesis and those through biological technologies.

These types of studies of drugs approved for medical use are needed if unwanted effects are discovered, or if the drug is intended to be used in new patients, or the route of administration is changed.

The experience of expert work shows that large foreign companies, in order to consider the possibility of conducting a clinical trial, must provide information on the study of the safety of drugs. In the past, studies on the effects on the

central nervous, respiratory and cardiovascular systems were carried out for innovative drugs [**1**, pp. 133-137].

Table 1. *Types of drug safety studies*

Studies	Problems
Mandatory	Impact on vital systems. cardiovascular, respiratory, central nervous
Additional	An in-depth study of the effects identified Effects on organs and systems, the functions of which may be temporarily impaired

Research Methodology

It is an underestimation to state that the choice of the research method is a straightforward work. When research methods are selected for any type of the work we do, choices were taken on the basis of convenience. It is possible to say that a number of ways were applied during the investigation, which can be delimited in a more precise way as a complex group. Here, it is the division of goals or their formulation or reformulation, activity of each subgroups of each complex group, and the identification of particular constraints, which acts as the link between the objective and the means of achievement. It begs the question, why did we elect this or that method, in other words, what was that made us elect, let's say, the analytical method as opposed to the comparative method? To answer these and similar questions, let's note that the choice of methods in different periods depended on the specific object of study and the defined target segmentation. According to necessity and effectiveness, which method would be more relevant to the studied area was taken into account.

Using analytical and comparative methods, we were able to identify and analyze the indicators characterizing the evaluation of the drug safety monitoring system in the Republic of Armenia and ways to improve it.

In order to collect quantitative data, to carry out qualitative analysis on them, we used the statistical method. The peculiarity of the statistical method lies in the fact that it is possible to study not only individual facts, but also to examine statistical data with general properties that are specific to mass combinations. In the work, we also used such methods, through which we collected and studied the literature related to the topic. Combination is the linking of different aspects of the phenomenon into an overall structure. This is not mere joining together but joining together of thoughts. No phenomenon is made solely on using either an analysis or its opposite juxtaposition. With the help of the combined method, studying the interrelation of these elements helps to understand the nature of this phenomenon. If one of such components were to be modified, the overall aspect of the phenomenon would immediately be impacted. Patterns of economic systems can be delineated by the use of analysis and combination methods by looking at economic phenomena in isolation and in abstraction.

Analysis is regarded as a method of conducting scientific inquiry and it entails the separation of the subject being investigated into its elements. Combining, on the other hand, is the process of putting back together the separated elements from an analysis. As minified, these two approaches are dextrously intertwined in the course of the scientific endeavor and may take different forms at the other end of system under scrutiny and goal of the investigation.

The study of economic patterns takes place on the basis of a systematic method, as a comprehensive method that allows observing the cause-and-effect relationships between individual manifestations of many economic events.

In the course of the research, the methods of grouping, comparison, analysis and synthesis were employed.

The logical method of cognition has itself found practical application along with common sense by allowing the processes to be interpreted in such a manner and making pertinent conclusions as was required by the situation. In this way, such recommendations and measures were worked out, which could elevate the appraisal of the system of drug safety monitoring in RA and its ways to be improved, which stimulate economic growth. The evaluation method of the drug safety monitoring system in Republic of Armenia was also applied.

Therefore, we can conclude that the application of different types of research evidence broadens the scope of understanding of the issues under consideration as well as their extent and core theories. The use of various methods during the study increases the scope and content of the study. Often these methods complement and continue each other. It should be noted that research methods are formed during the expansion of new knowledge and understanding related to the given science. It is because of this that various methods are created for the study of different sciences, which make the study more reliable, accurate and comprehensive.

Analysis

Requirements to provide information on drug safety studies are not fundamentally new for RA. However, recently, domestic developers often do not pay enough attention to assessing the effect of new drugs on the functioning of vital systems. This

is sometimes due to the lack of domestic methodological documents regulating the conduct of drug safety studies [**3**, pp. 148-153].

The World Health Organization (WHO) implements a comprehensive policy to implement the principles of effective drug use. The analysis of the measures carried out by the WHO in that direction showed that although most of the countries are working to implement certain programs to increase the efficiency of drug use, in recent years there have been no significant improvements in the process of drug use in most countries, and the ineffective use of drugs continues. Remain a serious problem [**6**, pp. 803-806].

The effective use of drugs can be affected by such factors as: the presence of many registered drugs with the same therapeutic effect, the appearance of expensive new drugs on the market, sometimes with unproven clinical effectiveness, insufficient reliability and objectivity of the available reference literature on drugs, active marketing by pharmaceutical companies, including in violation of the ethical norms of drug promotion, the problem of the circulation of fake drugs in the pharmaceutical market, the development of the paid medical services market, the imperfection of the system of selection, prescription, purchase, distribution and use of drugs at all stages of drug consumption, the insufficient training of medical personnel for the effective use of drugs, the therapeutic process Inadequate use of treatment standards and scientifically based approaches when choosing drugs for treatment and diagnosis of diseases [**5**, pp. 6-10].

Accordingly, WHO recommends the following main components for the effective use of drugs:

1. existence of an interdisciplinary national body coordinating the use of drugs,
2. clinical guidelines, list of basic drugs,
3. introduction of the formulary system (FH) in preventive medical institutions,
4. problem-oriented training of pharmacotherapy at the pre-diploma stage,
5. a mandatory process of continuous improvement of qualifications,
6. monitoring, reporting and feedback;
7. independent information about drugs,
8. increasing the educational (pharmacological) level of patients in matters of the correct use of drugs,
9. refusal of wrong financial incentives,
10. Availability of sufficient funds to ensure access to medicines, ensure proper regulation of medicines.

In each country, the program for the effective use of drugs should have 3 structural elements (directions):

1. strategy and monitoring of rational use of drugs,
2. purposeful prescribing of drugs by doctors and proper dispensing by pharmacists,
3. Correct use of drugs by consumers, for which it is necessary to create an effective information system about drugs and increase the responsibility of patients in making decisions about treatment.

Long-term studies are carried out to determine the effect of the drug on the function of vital systems. Currently, there is a rich methodological and methodical base. Table 2 presents a comparative analysis of the methodological techniques used. According to international requirements, these types of studies are, as a rule, mandatory. Thus, according to international recommendations, in vitro and in vivo experiments for the assessment of the arrhythmogenic risk of the active substance of drugs are considered complementary and require mandatory implementation. In experimental practice, this type of in vitro study is usually performed only during the screening of cardiotropic drugs as part of the initial evaluation of their drug properties. The effect of the drug on blood pressure and ECG indicators, as a rule, is studied almost always. A similar situation is observed in connection with the study of the effect on the respiratory system. The study of the effect of drug substances on the central nervous system is the closest to international standards. Thus, domestic developers do not carry out special drug safety studies. In this regard, it is very relevant to create national methodological documents containing recommendations on planning, conducting and evaluating drug safety studies [**2**, p. 501].

When assessing the scientific justification of a particular drug's preclinical research program, it is important to bear in mind that such studies are discrete assessments of drug safety. However, in certain cases, these studies are included in the toxicology of a drug, studies of its kinetics, and its clinical trials.

When a particular study is being designed, the designer reviews every data that is available about safety, especially from secondary pharmacodynamic effects or from toxicity tests or when appropriate from the clinical use of the product. To make such a judgment, the developer analyzes the potential human safety profile of any adverse effect elicited from the intervention. Nevertheless, this information may do not exist during the early part of the development period (e.g., absence of comparative metabolism studies of such substances). In such instances, more general methodologies for deeper deepening analytical problems are recommendable.

Table 2. *The main types of studies of the effect of a new drug on the function of vital systems*

System	International practice	Native researchers
Cardiovascular	Mandatory research type	Performed only in the search for cardiotropic drugs
	In vivo, HR, ECG in anesthetized and unanesthetized animals	In vivo, HR, ECG
Respiratory	Mandatory research type	As a rule, they are evaluated within the framework of general poisoning effects
	Respiratory rate, tidal volume, blood oxygen saturation using quantitative techniques	Breathing rate
CNS	Mandatory research type	As a rule, they are evaluated within the framework of general poisoning effects
	Motor and research activity, coordination of movements, reflexes, body temperature	Motor and research activity, coordination of movements, reflexes, body temperature

Drug safety studies include both in vitro and in vivo research. There has to be an experimental confidence in the testing systems that have been developed to ensure that the acquired results are satisfactory and reproducible in every regard. The number of the samples should be enough such that the scientific message is not lost. For one reason or another, it is necessary to operationalize some of the drugs as per the management as well.

For reasons concerning the laws regulating the Federal Government it is customary to divide drug studies and their results into three categories – primary pharmacodynamics studies, secondary pharmacodynamic studies and safety studies.

Research shows the efficacy and safety during primary pharmacodynamics studies only carried out for registration purposes.

The studies performed for secondary pharmacodynamic purposes are about the pharmacological activity and properties of the agent that does not meet the intended therapeutic indication.

Studies carried out to establish the relationships between pharmaceuticals and pharmacological responses with respect to safety explore drug safety studies [**4**, pp. 132-144].

In other cases, it is essential for drug development that such primary and secondary assessment studies relate to the safety of a drug under development, in particular its antagonistic pharmacodynamics. This explains why such data is not overlooked, but is treated with the drug safety assessment studies.

Testing of safety of the marketed medications is necessary if new adverse event is found (these may include adverse effects registered for both the drug and its structural analogs), or if an indication of such drug provides new patient populations or fundamentally different routes of administration.

In attempting to clinically demonstrate the intended biomarkers in drug safety studies, it needs no explanation that these are constantly and increasingly carried out concurrently with drug administration. At any rate, it is important to understand that when appraising safety programs on the target medicines, the following questions must be answered.

- Therapeutic subclass-mediated effects.
- Adverse events normally attributed to the structural and functional counterparts.
- Adverse events pertaining to the receptor level.

For the purposes of drug safety studies, a single dose of the medicine is administered in most cases.

Conclusions

Thus, in order to meet those problems that are constantly faced by (the) health care workers, we can mention the following as the possible solutions for these challenges:

Limited resources for drug procurement,

- Drug procurement is constrained by a lack of funding,
- The increasing number of therapeutic options,
- Incompetent or unproductive drug prescribing,
- Unsafe, ineffective or questionable drugs that are available in the market,
- The absence of unbiased drug information,
- The large costs of obtaining, keeping and purchasing large amounts of drugs.

Taking into consideration such policies, the national drug provisions are focused on retaining the overall availability of the drug supplies and their optimal use. The presented methodological approaches to the assessment of the drug safety covered by this patent refine the subjective nature of

the experimental and expert evaluations of the new drug safety.

The specifics of preclinical drug safety assessment require drugs regulation of this nature because of the importance of such studies to clinical practice and the need to reconcile the 'inside' and the 'outside' requirements of drug safety regulation.

Table 3 presents international recommendations regarding the required scope of drug safety studies based on the clinical development stage of the drug.

Table 3. *The required amount of drug safety studies depending on the stage of clinical development*

Development stage	Necessary volume of research
Before the first administration of the drug by a person	Impact on CNS, cardiovascular system, respiratory system Additional studies if there are data on adverse effects on other systems and organs
During clinical trials	Additional pharmacologic safety studies are being conducted to clarify or explain identified or suspected adverse effects.
For medical use approval	Pharmacological safety studies should be carried out in full The absence of any type of research must be justified

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