The complexity of pharmacovigilance

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Abstract

This article will discuss some general considerations on the complexity of pharmacovigilance: the real scope of pharmacovigilance, the many actors involved in this process, the peculiarity of drug monitoring and the issue of feedback to healthcare professionals from collection and collation of safety data of medicines.

Introduction

Modern drug safety, in the sense of widespread, routine, post-marketing surveillance of drugs for new safety issues, came into being following the unpredicted teratogenic outcomes from the use of thalidomide in the mid-1960s. During the intervening years, pharmacovigilance has been defined in many ways, sometimes with divergent concepts and aims (see Box), but the recent 'pharmaceutical package' issued by the European Commission in December 2008[1] gives a concise yet comprehensive definition, describing the pharmacovigilance system as the supervision and monitoring of adverse drug reactions (ADRs).

Technical details about the activities inherent to pharmacovigilance will not be discussed here, since they are the focus of many articles in this issue and in future issues of *Regulatory Rapporteur*. However, some general considerations will be briefly mentioned to introduce the complexity of the process: the real scope of pharmacovigilance, the many actors involved, the peculiarity of drug monitoring and the issue of feedback from collection and collation of safety data of medicines to the final users.

The real scope of pharmacovigilance

In general, pharmacovigilance is a multidisciplinary issue: basic and clinical pharmacology; clinical medicine; toxicology; epidemiology; and (pharmaco)genetics are the major disciplines involved in this scientific process, which is coordinated by a stringent regulatory framework. The ultimate aim of pharmacovigilance is the optimisation of the risk–benefit ratio of marketed drugs at the individual level (ie, the choice of the most suitable treatment for a given patient) and at the population level (ie, maintenance or removal of a drug from the market, informing prescribers of its potential risks, etc). This process relies heavily on the reporting and analysis of ADRs. Unfortunately, there is no consensus on ADR definitions. Consensus has been reached in the industry and the regulatory arena with the efforts of ICH (International Conference of Harmonisation) and CIOMS (Council for International Organizations of Medical Sciences). However, there is no agreement on the meaning of an ADR between healthcare professionals and patients, and the emotional involvement of patients and sometimes the physician in defining any drug-related effect creates difficulties in many cases.

Moreover, even the unique focus on ADRs which encompasses all pharmacovigilance activities may be misleading. Not every 'adverse' side-effect (ie, 'unwanted' in respect of the approved indication or the desire of the physician and/or the patient) is necessarily 'adverse' in the broader perspective: the case of the antithrombotic action of aspirin at a population level is an example of an ADR which became a useful novel indication for this drug. So in addition to assessing a drug's safety over and above what is known at the time of a marketing authorisation, pharmacovigilance can also be a major tool to better understand the actions of human medicines on a larger scale, in real life settings and with varied conditions of use.

The many actors involved

As outlined by the WHO Foundation Collaborating Centre for International Drug Monitoring,[2] drug products are not like other products by virtue of their heavy dependence on a 'learned intermediary' for the prescription and dispensing of the product between the manufacturer and the end users, at least in countries with heavily regulated healthcare. In such countries there can be as many as four such intermediaries, including the prescriber/dispenser; the healthcare maintenance authority (which issues general management plans for patients); and the regulatory authority (which decides on restrictions and availability of individual products). Each of these 'learned intermediaries' makes decisions about the benefits and risks of medicines, although in none of these decisions is there complete transparency for the end user. Moreover, the interests and responsibilities of each intermediary may be in conflict at times. For no other range of products is the technical complexity so great, the breadth of use universal, the impact so personal, and the responsibility for successful use so dispersed.

A single ADR may therefore arise from many different actions, some of them completely unrelated to the medicinal product involved. This dispersed chain of activities may pose serious problems when assessing the real value of an ADR.

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The peculiarity of drug monitoring

Safety of a medicinal product is generally evaluated during the clinical development phase (Phase II-III). This means that a controlled environment is used with stringent rules and criteria for the selection of patients, drug administration and monitoring. Studies must comply with GCP and safety assessment is a scientific and regulatory tool to generate sound and reproducible clinical data, but the results seldom mimic the real world situation. When compiling the proposed summary of product characteristics (SPC) required to obtain a marketing authorisation, an applicant aims to collect all safety information available at the time of the application, adding, where possible, considerations about the specific drug class. Of course, this is somewhat incomplete information, although every attempt should be made to get the best possible data. However, once authorised, a given medicinal product is then administered much of the time in a broader, more varied and less controlled manner. Clinical situations in real life medicine are much more complicated than in a clinical protocol. A practicing physician cannot generally apply such stringent criteria when treating a patient, and multitherapy is the rule rather than the exception. Here, pharmacovigilance has an immense value, being the only way to understand what reactions a drug may cause in the clinical setting. The question is, how can data from controlled studies be pooled with data coming from usage in the real world? How can we overcome the historical reluctance of physicians to report ADRs? How can we understand if a given event is part of a poorly understood illness or caused by a given drug? No clearcut answer has been found so far by health authorities and healthcare professionals, and I doubt these issues will have an easy and practical solution in the near future.

Feedback of pharmacovigilance reporting

There is considerable effort to collect, collate and transmit ADRs across the current EU pharmacovigilance system. The main accent is on the correct transmission from the field to the central repository (EudraVigilance), and the complexity of this activity is such that courses are mandatory to be a Qualified Person for Pharmacovigilance (QPPV) in the EEA. However, to be able to transmit information is just part of the problem, and very far from the solution. Even so-called and expensive pharmacovigilance software is no more than a user-friendly tool to comply with regulations. Is this compliance all we really need? The answer is 'No'.

Having been a physician before becoming a regulatory professional, my dissatisfaction is enormous. As a physician reporting ADRs, I never received any feedback on what I reported, nor did I receive any suggestions on how to improve my clinical practice. Yes, there are safety bulletins, drug alerts on some websites, useful clinical articles sometimes, but what I really needed in my day-to-day work was very simple: to get feedback on what I reported regarding my individual patient, the drug I prescribed, the conditions of its use. If a sound pharmacovigilance system is to be foreseen, then it should be able to answer these questions. If not, it may only be a good exercise for regulatory bodies without the active involvement of major stakeholders.

Conclusion

The complexity of pharmacovigilance is not only related to the increasing regulatory requirements but also to the number of factors involved. The regulatory framework, although greatly improved compared with the past, is still not able to include all stakeholders. The communication and related legislative proposal of the EU Commission on pharmacovigilance, issued on 10 December 2008, is a major step forward which takes into account medication errors as well as the prevention and control of healthcare-associated infections. In essence, improvement in the protection of public health will be achieved through clearer roles and responsibilities for key responsible parties (the learned intermediaries); more transparency and communication on medicine's safety issues (the feedback); and a simplification and rationalisation of the procedures in order to reach a proactive and proportionate collection of high quality data (the real scope of pharmacovigilance).

Definitions of pharmacovigilance
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. *World Health Organisation*
Pharmacovigilance is all observational (nonrandomised) post-approval scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic safety studies. *ISPE – International Society of Pharmaco-Epidemiology* (this is similar to the definition given by the US FDA)
The group of activities with the aim of the safe use of medicines. These include legislative, official, marketing authorisation holders' and public health authorities' activities. *InforMed, Hungary*
Pharmacovigilance is the process and science of monitoring the safety of medicines and taking action to reduce risks and increase benefits from medicines. It is a key public health function. *European Commission – Enterprise and Industry*

References

1 http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/pharmpack_en.htm

2 I R Edwards. 'The future of pharmacovigilance: a personal view', *Eur J Clin Pharmacol*, 64:173–181, 2008.