Review Article

Spontaneous Reporting in Pharmacovigilance: Strengths, Weaknesses and Recent Methods of Analysis

Rachna Kasliwal, MBBS, MSc, DLSHTM, *Berkshire, UK*

ABSTRACT

Use of medicines in real-life clinical setting is very different to the controlled clinical trial environment in which drugs are tested prior to marketing. As not all adverse effects of a drug may be identified from pre-marketing clinical trials, the continuous safety monitoring of drugs is essential to ensure a favourable benefit-risk profile of the drug. The spontaneous reporting system is a method whereby healthcare professionals (HCPs) report suspected adverse drug reactions (ADRs) to drug regulatory bodies or pharmaceutical companies. It is a widely employed and effective method of collecting information on suspected ADRs. It helps to detect previously unknown effects of a drug and provides information from real-life clinical practice, throughout the life of the drug. In spite of its limitations such as under-reporting, spontaneous reporting forms the backbone of a Pharmacovigilance system. As the spontaneous reporting system is a passive method that relies on HCPs to report suspected ADRs, HCPs can contribute immensely in enhancing knowledge about the safety profile of a drug. More recently a number of different statistical tools have been developed to discern meaningful drug safety signals from the background 'noise' within large databases comprising of spontaneous reports. These tools have to be used cautiously and in conjunction with other methods of causality assessment. (J Clin Prev Cardiol 2012;1:20–3)

Key Words: Spontaneous reporting, Pharmacovigilance, Signal detection

Introduction

Real-life use of drugs is very different from the controlled clinical trial environment in which drugs are tested prior to marketing. Clinical trials are short in duration and exclude vulnerable individuals such as the elderly, women of child-bearing age, children, and those with concurrent illnesses. Therefore, when a drug is launched in the market not all of its adverse effects may be known, thereby making post-marketing surveillance of drugs extremely important. An example is that of cardiovascular events with rofecoxib, a drug which was indicated for the treatment of osteoarthritis. After being marketed for 5 years and being used by millions of patients, the drug was withdrawn as a result of the APPROVe trial that showed a doubling of risk of myocardial infarctions and ischemic cerebrovascular events in patients taking rofecoxib as compared to those taking placebo (1).

From: Central Department of Pharmacovigilance, IPSEN Biopharma Ltd, Berkshire, SL (R.K.)

Corresponding Author: Rachna Kasliwal, Central Department of Pharmacovigilance, IPSEN Biopharma Ltd, 190, Bath Road, Slough, Berkshire, SL1 3XE, U.K.
Email: rachnakasliwal@hotmail.com

The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" (2). The science is essential for maintaining optimal risk–benefit profile of marketed drugs and hence for safeguarding public health.

The thalidomide disaster in the 1960s provided the impetus for the establishment of pharmacovigilance centers in a number of countries, for the systematic collection of suspected adverse drug reactions (ADRs) through what is now known as the spontaneous reporting system. Although a wide variety of methods are available for conducting drug safety studies, the spontaneous reporting system is one method that is used throughout the life of a drug and is now operational in most developed and many developing countries. This paper describes this method, its strengths and weaknesses, and recent advances in detecting signals from databases containing spontaneous reports.

The Spontaneous Reporting System

When a physician suspects a serious clinical event to be an ADR, they are encouraged to complete a questionnaire and notify the country's drug regulatory agency about

the suspected ADR. An adverse event is serious when it results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (3). In some countries, the spontaneous reporting scheme has been extended to reporting from pharmacists, nurses, and even patients.

Although the spontaneous reporting questionnaire differs from country to country, in general the information collected includes patient details (such as age, sex, weight), details on the suspected drug (such as dose, duration of treatment), details on the suspected reaction(s) (such as description of the event, seriousness, outcome), medical history of the patient, and other concomitant medication that the patient was taking. Examples of spontaneous reporting systems include the "Yellow card scheme" operated by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines, and the Adverse Event Reporting System (AERS) which is a database of spontaneous reports received by the US Food and Drug Administration (FDA) through the MedWatch form. In India the suspected ADR reporting scheme is undertaken by the Central Drugs Standard Control Organization (CDSCO).

The pharmaceutical industry and regulatory bodies collect and analyze these reports and utilize them in identifying previously unknown adverse reactions and where appropriate take action to minimize the risk due to the drug. Action taken may be in the form of change(s) to the product label (e.g., change in dosage regime or addition of a contraindication) providing information to physicians through "health professional letters," publication in the medical literature, changes in the patient information leaflet, restricted drug distribution, or drug withdrawal (4).

A study by Wysowski and Swartz (4) recorded a total of 24 drug withdrawals (between 1978 and 2003) where the identification/evidence of the safety issue had originated from spontaneous case reports to the US FDA. These include phenformin (indicated for diabetes mellitus and withdrawn due to lactic acidosis), fenfluramine (indicated for diet aid for obesity and withdrawn due to cardiac valvulopathy), trogliatzone (indicated for diabetes mellitus and withdrawn due to hepatotoxicity), cisapride (indicated for nocturnal heartburn and withdrawn due to drug interaction/ventricular arrhythmias), and cerivastatin (indicated for hypercholesterolemia and withdrawn due to rhabdomyolysis) (4). Furthermore, two recent examples where spontaneous reports have identified new safety issues and lead to changes in the drug label include the following: rhabdomyolysis with rosuvastatin (lead to revised dosing instructions and improved warning) and hepatic disorders with atomoxetine (lead to warning) (5).

Strengths and Weaknesses

The spontaneous reporting system is a widely used, effective, and relatively inexpensive method of collecting information on suspected ADRs. Its main function is the detection of new, rare, and serious ADRs (6), which remained undetected in the pre-marketing clinical trials. Spontaneous reporting operates throughout a drug's life, starting from the day it is launched in the market. The system also merits from the fact that it provides information from real-life clinical practice as opposed to clinical trials where vulnerable individuals are excluded and the duration of treatment is limited.

However, the spontaneous reporting system has a number of shortcomings, under-reporting being one of the major ones; this is discussed in detail below. Another weakness of the system is that it only provides a numerator; information on population exposed to the drug is lacking. Therefore, the risk associated with a drug is difficult to quantify accurately. Moreover, the numerator is also subject to reporting bias (6,7). Other weaknesses include variations in the quality of information provided and missing data.

However, in spite of the limitations spontaneous reporting is the backbone of pharmacovigilance and provides valuable information on the safety of a drug throughout its life.

Under-reporting and Methods to Improve Reporting

The spontaneous reporting system is a passive surveillance method that solely relies on the healthcare professionals to detect and take the initiative to report an ADR. Reporting varies with the reporters' skill and experience to detect the ADR, their level of understanding of the spontaneous reporting system, and their workload (7). Furthermore, ADR reporting is also influenced by other factors such as the media, published literature, and age of the drug. A higher number of reports are seen in the first two years after drug launch.

A survey conducted to assess doctors' attitudes toward reporting of ADRs in Netherlands showed that uncertain causality, the ADR being trivial, and the ADR being too well known were the most frequent reasons for not reporting. Other reasons for not reporting were lack of knowledge, for example, not knowing how to report, and lack of awareness of the existence of a reporting scheme. This survey also showed that general practitioners (GPs) were more likely to report an ADR than specialists (51% vs 35%) (8). Another study looking at reporting of ADRs by GPs showed that GPs who actively report ADRs had more knowledge on ADR reporting and were more interested in pharmacotherapy than their nonreporting colleagues (9).

In an attempt to improve reporting of suspected ADRs, studies have been conducted to examine the impact of interventions on ADR reporting; one such study was undertaken in a large teaching hospital in Spain (10). A multifaceted intervention approach to improving spontaneous ADR reporting was undertaken, and interventions included economic incentives, physician training and education (about spontaneous reporting/ pharmacovigilance, selection of serious ADRs, etc.), providing feedback to physicians about signals identified by the pharmacovigilance program, and distribution of list of the most important ADRs to be reported. The result of the interventions was a quantitative and qualitative improvement of spontaneous reporting of ADRs by hospital physicians. Other studies analyzing the effects of educational interventions on spontaneous reporting of ADRs have also shown improvement in reporting as a result of these interventions (11,12).

Data-Mining Techniques

As the pharmaceutical industries and regulatory bodies receive a large number of spontaneous reports each year, their databases are often large and complex; consequently a case-by-case analysis becomes extremely time-consuming and inefficient. This has lead to the development of statistical tools, known as data-mining algorithms (DMAs) to discern meaningful drug safety signals from the background "noise" within large databases (13). The CIOMS VI working group defines a signal as "a report of any event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance" (5). Data-mining tools act as a quick method for screening these large databases which then help in hypothesis-generation and prioritization of safety issues (14). The US FDA's Adverse Drug Reporting System (AERS) and the WHO safety database are two large databases with a large variety of products, which are available in the public domain (14).

A number of different data-mining techniques are available; these are the proportional reporting ratios (PRRs, employed by the UK MHRA), the Bayesian confidence propagation neural network (BCPNN, employed by the WHO Uppsala Monitoring Center), and the multi-item Gamma Poisson Shrinker (MGPS, used by the US FDA). These methods, however, share the basic principle that they express the extent to which the number of observed cases differs from the number of expected cases (15). The MHRA utilizes the Yellow Card database to calculate PRRs, which gives the proportion of all reactions to a drug for a particular medical condition of interest, compared to the same proportion for all drugs in the database (16). The BCPNN implements Bayesian statistics within a neural network architecture; the measure of disproportionality used by the WHO Uppsala Monitoring Center is the information component (IC) and it gives the strength of dependency between a drug and an adverse reaction (17). The MGPS used by the US FDA utilizes Baysiean shrinkage, and was first described by DuMouchel. MGPS computes signal scores for pairs, and higher order combinations of drugs and events that are significantly more frequent than their pair-wise associations would predict (18).

When using these tools, it should be kept in mind that all the limitations of the spontaneous reporting system also apply to data-mining techniques. DMAs do not provide estimates of incidence of adverse events and a statistical association is not equivalent to a causal relationship. Therefore, signals generated by data mining should be used for hypothesis-generation, which should be investigated further (14).

Pharmacovigilance in India

The National Pharmacovigilance program began in 2005 with the establishment of several pharmacovigilance centers; the program was launched by the Central Drugs Standard Control Organization (CDSCO) of the Government of India (19). Information on suspected ADRs is reported to the peripheral Adverse Drug Reaction Monitoring Centres (AMC) or to the National Coordinating Centre.

CDSCO is initiating a nation-wide program (Pharmacovigilance Programme of India [PvPI]) in

collaboration with the Indian Pharmacopeia commission. Forthcoming targets of the PvPI include initiating software development for the National Drug Safety Database, pharmacovigilance training, and collaborating/ receiving technical support from the WHO Uppsala Monitoring Center (UMC), Sweden (20).

Conclusion

Post-marketing safety surveillance of drugs is essential as not all adverse effects of a drug may be identified from pre-marketing clinical trials. The spontaneous reporting system plays an important role in pharmacovigilance by providing information from real-life clinical setting throughout the life of a drug. Physicians and other healthcare professionals can contribute immensely to improving public health by reporting suspected ADRs. Although limitations such as under-reporting of ADR exists, reporting can be improved by education and training of healthcare professionals. A number of statistical tools are being tested for efficient signal detection in pharmacovigilance. These tools have to be used cautiously and in conjunction with other methods of causality assessment.

Acknowledgments

I would like to thank Mrs Lorna Hazell and Dr Sumit Munjal for reviewing this manuscript and for their constructive comments.

Conflict of Interest

This is a personal communication and is unrelated to my affiliation to Ipsen BioPharma. I have no conflict of interest. No sources of funding were used to assist in the preparation of this manuscript.

References

1. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med.* 2005; 352(11):1092–102.
2. World Health Organisation Collaborating Centre for International Drug Monitoring. The Importance of Pharmacovigilance, WHO 2002. Available from: http://www.who-umc.org
3. European Medicines Agency. ICH Topic E2A. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. June 1995.
4. Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969–2001. The importance of reporting suspected reactions. *Arch Intern Med.* 2005; 165:1363–9.
5. Mann R, Andrews E (ed). Pharmacovigilance, ed 2. Chichester: Wiley, 2007.
6. Storm BL. Pharmacoepidemiology, ed 4. Chichester: Wiley, 2005.
7. Hazell L, Shakir S. Under-reporting of adverse drug reactions. A systematic review. *Drug Saf.* 2006; 29(5):385–96.
8. Eland IA, Belton KJ, van Grootheest AC, Meiners AP, Rawlins MD, Stricker BH. Attitudinal survey of voluntary reporting of adverse drug reactions. *Br J Clin Pharmacol.* 1999; 48(4):623–7.
9. Passier A, ten Napel M, van Grootheest K, van Puijenbroek E. Reporting of adverse drug reactions by general practitioners: a questionnaire-based study in the Netherlands. *Drug Saf.* 2009; 32(10):851–8.
10. Vallano A, Cereza G, Pedros C, Agustí A, Danés I, Aguilera C, Arnau JM. Obstacles and solutions for spontaneous reporting of adverse drug reactions in the hospital. *Br J Clin Pharmacol.* 2005; 60(6):653–8.
11. Castel JM, Figueras A, Pedros C, Laporte JR, Capellà D. Stimulating adverse drug reaction reporting. Effect of a drug safety bulletin and of including Yellow cards in prescription pads. *Drug Saf.* 2003; 26(14):1049–55.
12. Figueiras A, Herdeiro MT, Polonia J, Gestal-Otero JJ. An educational intervention to improve physician reporting of adverse drug reactions. A cluster-randomised controlled trial. *JAMA* 2006; 296(9):1086–93.
13. Hauben M, Madigan D, Gerrits CM, Walsh L, Van Puijenbroek EP. The role of data mining in pharmacovigilance. Expert Opin *Drug Saf.* 2005; 4(5):929–48.
14. Almenoff JS, Pattishall EN, Gibbs TG, DuMouchel W, Evans SJ, Yuen N. Novel statistical tools for monitoring the safety of marketed drugs. *Clin Pharmacol Ther.* 2007; 82(2):157–66.
15. Härmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. *Eur J Clin Pharmacol.* 2008; 64(8):743–52.
16. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol. *Drug Saf.* 2001; 10:483–6.
17. Bate A, Lindquist M, Edwards IR, Orre R. A data mining approach for signal detection and analysis. *Drug Saf.* 2001; 25:393–7.
18. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf.* 2002; 25(6):381–92.
19. Joshi SR, Sapatnekar SM. Pharmacovigilance in India: how safe are the new drugs? How sure are we? *J Assoc Phys India.* 2008; 56:933–4
20. CDSCO official website. http://cdsco.nic.in/ [Accessed 1 December 2011].