

## Pharmacovigilance: An Overview

Santosh KC<sup>1,2</sup> and P. Tragulpiankit<sup>1\*</sup>

<sup>1</sup>Department of Pharmacy, Faculty of pharmacy, Mahidol University, Bangkok, Thailand

<sup>2</sup>Bir Hospital, Kathmandu, Nepal

### Abstract

The safety concern of drug is now becoming the priority area. The thalidomide tragedy of 1960's opened the eyes of drug regulators as well as other concern body to establish a way to ensure drug safety, previously the issues was in shadow. The drug safety issues were globalised, strengthen and systematized after the establishment of World Health Organization (WHO) Programme for International Drug Monitoring in 1968. Every drug is associated with beneficial as well as undesirable or adverse effect. Adverse drug reactions (ADR) is the common clinical problem. The hospitalization due to ADRs in some countries is about or more than 10%. In addition, it is estimates that 10-20% of the hospital inpatient suffers from ADRs. Appropriate and effective monitoring of ADRs, i.e. pharmacovigilance, is the only best way to safeguard the public health. Spontaneous reporting system (SRS) is the first and most widely used method to report ADRs in spite of under-reporting as a major limitation. It is enable to early detection of new, rear and serious ADRs. Based on those reported cases signal is generated. Signal is new possible causal link between a suspected ADR and drug; which is previously unknown or incompletely documented. Disproportionality analysis is most commonly used method of data interrogation to figure out the association between drug and ADR of interest. The severity of under-reporting of ADRs is very high; it estimates that only 6% of ADRs are reported. There are many factors associated with under reporting of ADRs; categorized as personnel and professional characteristics of healthcare professional and their knowledge and attitude to ADR reporting. In terms of ADR reporting knowledge and attitudes of health professionals is strongly related. Under-reporting can be significantly improved by appropriate educational intervention.

**Key words:** Adverse drug reaction, Pharmacovigilance, Signal, Spontaneous reporting system, Under-reporting

## INTRODUCTION

The safety concern of drug is now becoming the priority area, and indeed is the first issues to address by pharmaceutical company to make available any drug in the market. It is now well understood the limitation of clinical trials, which cannot generate enough safety information to safeguard the public health. To ensure the safety of new drug product after marketing authorization, there are provisions to continuously monitor the safety of drug as a part of regulatory requirements. Pharmacovigilance emerged after much overlooked area of drug safety, which resulted tragic event of thalidomide at around 1960's<sup>1,2</sup>. After that, there has been lots of progress in the drug safety issues. Starting from spontaneous reporting system to the latest concept of risk management plan, they all are instrumented to ensure drug use safer and safer. As, adverse drug reaction (ADR) cannot be avoided, though some of them can be prevented, new knowledge on the new and rare type of ADRs and ADRs of new drug product is important to ensure the safety of public health. Pharmacovigilance is the ongoing process to monitor drug safety and to make available new information and knowledge about ADRs. In fact, this information is very important for the drug regulators to take appropriate decision about any marketed drug. It is well understood that drugs are always rated in terms of benefit risk ratio; the regulators take appropriate decision to restrict or withdraw any drug based on these information. This can be warning or label change as a restriction and withdraws from market as the final decision to any drug. Drug regulators and other stakeholders are always vigilant to drug safety issues. There are lots of example of restriction and withdraw of drug product based on the safety concern, rosiglitazone is the latest drug withdrawn from European market<sup>3</sup>. Previously, very well known drugs for example terfenadine, cisapride, phenylpropanolamine, refocoxib, cerivastatin were withdrawn because of the safety concern<sup>4</sup>. So, there is an immense role of drug safety monitoring that is pharmacovigilance.

## HISTORICAL BACKGROUND

The safety of drug was not the early concern in the history of drug. The thalidomide tragedy of 1960's opened the eyes of drug regulators as well as other concern healthcare professionals to establish a way to ensure drug safety<sup>1,2</sup>. The mile stone in the drug safety was the publication of chloroform related death on *The Lancet* journal for the first time in 1893<sup>1</sup>. Onwards, safety of drug became the global concern and different initiatives were taken by different country to safeguard the public health safety. The US Federal, Food and Drug (US FDA) act was passed in 1906 for the first time, but it was amended to control misbranding of ingredients and false advertising claims after the deaths associated with sulphanilamide elixir<sup>1</sup>. There were 107 deaths by the use of diethylene glycol as a solvent for sulphanilamide elixir. There were radical changes in the drug safety issues after the worldwide thalidomide tragedy which was first reported by an Australian obstetrician, William McBride in 1961<sup>1</sup>. He reported thalidomide associated "seal limbs" in the baby, used in pregnancy. This drug had not been adequately screened for teratogenic effects, but similar malformations were subsequently shown in the rabbit and (at high dose) in the rat. In West Germany 4000 individuals were affected. The tragedy made the world to be more concern about the drug safety, as efficacy was only the parameter to see the effect of drugs. Immediately after the tragedy the US FDA act was amended to compulsory premarketing submission of both efficacy and safety data in 1962<sup>1</sup>. The UK Medicines act was enforced in 1968, however, safety monitoring via "yellow card system" was introduced in 1964<sup>1</sup>. The drug safety issues were globalised, strengthen and systematized after the establishment of World Health Organization (WHO) Programme for International Drug Monitoring in 1968<sup>5,6</sup>. The Uppsala Monitoring Centre (UMC) located at Uppsala, Sweden co-ordinates the International Drug Monitoring program. Till now there are 104 official member countries and 33 associate members throughout the world, including developed, developing and under-developed country<sup>6</sup>.

## PHARMACOVIGILANCE AND DRUG SAFETY MONITORING

Every drug is associated with beneficial as well as undesirable or adverse effect. ADR as defined by WHO is “noxious or unintended response to a drug occurs at a usual dose”<sup>7</sup>. ADR is broadly classified as Type A and Type B<sup>8</sup>. Type A reaction is associated with the pharmacological actions of the drug and is predictable while Type B reaction is not associated with the pharmacological actions of the drug and is not predictable. It is also known as idiosyncratic reaction. Type A reaction is more prevalent, accounts for more than 80%, than the Type B reaction<sup>8</sup>. ADRs are associated with significant morbidity and mortality. Recent estimates suggest ADRs are the fourth to sixth major cause of death in the United States of America (USA)<sup>9</sup>. The hospitalization due to ADRs in some countries is about or more than 10%, which means ADRs as a major cause of hospitalization<sup>7</sup>. In addition, it is estimated that 10-20% of the hospital inpatient suffers from ADRs<sup>8</sup>. That’s why ADRs is the common clinical problem. Appropriate monitoring of ADRs is the only best way to safeguard the patients and even prevents ADRs.

The term pharmacovigilance is a French word, which has been described by Professor Bernard Begaud as “a discipline involving detection, evaluation and prevention of undesirable effects of medicines”<sup>10</sup>. Another definition as described by Professor Lawson is as “part of the science of pharmacoepidemiology”<sup>10</sup>. The 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”<sup>5</sup>. The pharmacovigilance aims to early recognition of previously unknown ADRs, recognition of frequency of known ADRs, identification of risk factors and mechanism of ADRs, quantitative analysis of benefit/risk ratio and dissemination of safety information for rational drug prescribing and regulation. The safety data generated during the clinical trials is always not

enough to rule out all possible adverse effect of the drug, when they introduced in the real world. The major limitations of clinical trial are: animal tests are insufficient to predict the human safety, only selected patients are exposed and limited time frame, limited human subject, in almost all cases less than 5,000, which is favorable to detect only the more common ADRs<sup>7</sup>. For the detection of rare and very rare ADRs large sample size is required. Rough estimation of the power to detect adverse events is generally calculated by ‘rule of 3’. For example, to find out the incidence of 1 in 10,000 at least 30,000 people need to be treated with a drug<sup>8</sup>. To detect the incidence of 1 in 100,000, we can imagine the sample size, which are almost beyond the scope of clinical trials. This in turn, the safety information available even by the well designed clinical trials is not adequate to answer the safety concern. As a result, the pharmacovigilance; often indicates as post marketing surveillance by pharmaceutical companies, as a systematic monitoring can be an effective ways to identify drug related safety issues throughout the life cycle of any drug.

## SIGNAL AND METHODOLOGY IN PHARMACOVIGILANCE

Signal is a potential and established indicator of new ADR. Signal is referred as any new possible causal link between a suspected ADR and drug; which is previously unknown or incompletely documented<sup>7</sup>. It is generated by reported cases of ADRs. However, careful judgment and establishment of possible causal relationship is always warranted to exclude the misinterpretation of the signal. Usually more than one report is required to generate a signal depending upon the seriousness of the event and quality of the information. A signal may not be definitive but it indicates the need for further enquiry or action. There are different sources of signal. Observation in patient, often called as qualitative signal, observation in population, often called as quantitative signal and the experimental findings are the main sources of signal<sup>11</sup>. The widely

used methods to find out the signal are spontaneous reporting system (SRS), active surveillance, cohort studies, case control studies<sup>12,13</sup>. SRS is the basic and most widely used method since decades to report ADRs. It can be used to identify rare ADRs however under-reporting remains the major limitation, accounts for 90-95%<sup>12-14</sup>. Besides that, quality of report, reporting bias and reporting only short latency events are the other limitations. Even though, there is evidence that SRS has proved to be an effective way for ADRs reporting and able to safeguard the patient safety. For example, trovofloxacin was withdrawn tolcapone was suspended, cerivastatin was withdrawn in Europe because of the evidence of SRS<sup>12</sup>. Active surveillance is another method of ADRs reporting. It is non-interventional observational study and aims to monitor selected drugs during certain period of time. It is conducted within specific structures, for example, hospitals or a well defined geographical region. Patient registry, intensive medicine monitoring program of New Zealand and prescription event monitoring of UK are the example of active surveillance. Active surveillance enables quantification of risk of certain ADRs and doesn't have selection bias. However, an event not reported to the doctors is unknown. In addition, it produces reported events rather than true incidence rates. Cohort studies are an epidemiological study, which is conducted to determine the true incidence of ADRs under real life conditions. It is drug specific and only one drug is studied at one time. Case control studies are fast to set and less expensive than Cohort studies. It is useful for measuring risk. Selection of control and bias in collecting drug exposure may limit their validity of the results.

Pharmacovigilance is a cyclic process of signal detection, signal strengthening and follow up<sup>11</sup>. Signal detection involves the process of selection of drug-adverse event association of possible interest. As, it is something new even, careful judgment and analysis on the ground of chemical, pharmacological and therapeutic point of view is necessary to establish the association. Unknown ADR, strong statistical

connection, serious but unlabelled, low background noise, high potential relevance are the positive indicator of the signal. Once the signal is detected, it is strengthened by available evidence. Case reports from different countries on the event, 'best case-worst case scenario', nested case control studies provide balanced view on the signal strength<sup>11</sup>. Signal strengthening is the process of making signal more evidence based and reliable. Follow up is the process of searching for the presence of similar association from other sources, e.g literature, registration file, spontaneous reporting etc. Follow up of signal is necessary to ensure both scientific credibility and clinical and regulatory relevance.

Data interrogation of different pharmacoepidemiological studies to find out the relationship of particular ADR to the drug in the large database is carried out by different methods. However, disproportionality analysis is the most commonly used method<sup>15,16</sup>. This analysis involves the '2x2' contingency table (see Table 1), which classifies report according to the presence or absence of the suspect drug of interest and the presence or absence of the event of interest in reports. It measures the association in terms of relative reporting (RR), proportional reporting rate ratio (PRR), reporting odds ratio (ROR) and information component (IC)<sup>15,16</sup>. Table 2 shows common measures of association and the way to calculate those associations.

## **UNDER-REPORTING OF ADVERSE DRUG REACTIONS**

SRS is the most widely used method in the ADRs reporting, which is enable to early detect new, rare and serious ADRs. Spontaneous reports are generated during the healthcare professional routine diagnostic appraisal of the patients. However, under-reporting, reports of known reactions, false causality assessments are the major drawback of the SRS. Reporting of serious unlabelled reactions is the major concern to safeguard the public health. Under-reporting of ADRs is the major obstacle for rapid and relevant signal detection of new and/or serious ADRs.

The severity of under-reporting is very high; it estimates that only 6% of ADRs are reported<sup>17-19</sup>. There are different methods to estimate under-reporting rate. Determination of under-reporting coefficient (U); which is ratio of number of adverse effects actually observed and those spontaneously reported to the pharmacovigilance system, is one of the methods<sup>17</sup>. Estimates of under-reporting rate for all ADRs based on different studies showed that 36% to >99% in general practice settings and 59% to 100% in the hospital settings, respectively<sup>17</sup>. Under-reporting rate for serious ADRs are relatively lower than all ADRs and, it estimates 6% to 100%<sup>19</sup>. Thai study showed 44.5% of under reporting for serious ADRs<sup>20</sup>. Even the reporting of ADRs is compulsory in Sweden; study showed that under reporting of serious ADRs is 75% to 100%<sup>21</sup>. Different factors are associated with under reporting. Inman has proposed “seven deadly sin” for under-reporting, which are complacency, fear, guilt, ambition, ignorance, diffidence and lethargy<sup>22</sup>. In different studies, ignorance was reported

as a major cause associated with under-reporting in 95% followed by lethargy in 77%, diffidence in 72%, indifference in 67%, insecurity in 67%, complacency in 47% and fear in 24% of studies<sup>23</sup>.

Overall, lack of knowledge about ADRs and attitudes to ADRs are the major cause of under-reporting<sup>24-29</sup>. Under-reporting should be improved by three ways, non-interventional, interventional and other methods like guidelines, codes. Non-interventional method helps to facilitate the reporting in effective way. While, education intervention showed to be more effective way to improve the rate and quality of ADRs reporting<sup>30-32</sup>. However, its effect is temporary. Effect of periodic renewal of the intervention and/or continuous education is still unknown<sup>31,32</sup>. To counter the under-reporting of ADRs; different measure should be taken simultaneously such as educational intervention to upgrade the knowledge and attitudes of healthcare professional, compulsion of ADRs reporting, easy access to ADRs database, issue guidelines or codes regarding ADR reporting.

**Table 1.** Contingency table

Exposure to study drug	Adverse effects		Total
	Present	Absent	
Present	A	B	A+B
Absent	C	D	C+D
Total	A+C	B+D	A+B+C+D

**Table 2.** Common measures of association

Measures of association	Formula
Relative reporting (RR)	$\frac{A(A+B+C+D)}{(A+C)(A+B)}$
Proportional reporting rate ration (PRR)	$\frac{A(C+D)}{C(A+B)}$
Reporting odds ratio (ROR)	$\frac{AD}{CB}$
Information component (IC)	$\text{Log}_2 \frac{A(A+B+C+D)}{(A+C)(A+D)}$

## CONCLUSIONS

Pharmacovigilance is the only way to ensure the safety of drug throughout the lifecycle. Its importance is very much crucial as the clinical trials have limitation to detect the rare and very rare ADRs. The knowledge and information available regarding safety of any drug is very much important to take appropriate decision by drug regulators to safeguard public health. Healthcare professionals are the main reports of the ADRs; however, there are high percentages of under-reporting reported globally. It is the major challenges for today. In spite of those limitations, spontaneous reporting system remains as a most widely used method to report ADRs and is able to generate signal of rare and very rare types of ADRs. If all the healthcare professionals take ADR reporting as an ethical obligations and their major responsibilities, we can make our world safer than what is today. Every reporting by healthcare professionals is important; even though, focus on the serious unlabelled type of ADRs is more important. There are significant efforts on the pharmacovigilance to make it more functional after the concept has emerged, and day by day we are closer to the destiny. It is our responsibilities to ensure pharmacovigilance system is functioning well. ADR reporting should be taken as a very important duty; not as an extra clinical burden; by healthcare professions to ensure the safer drug use throughout the world.

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