Chapter

Adverse Drug Reactions and Pharmacovigilance

Md. Shah Amran

Abstract

The discovery of a new drug usually takes 10-15 years. Within this time period, the candidate drug is thoroughly screened for its beneficial as well as side effects. But the side, adverse or toxic effects cannot be detected to a full scale due to some special reasons. The beneficial effects and toxicity of new drugs and vaccines are usually studied by "Clinical trials", which are divided into four categories ranging from clinical trial phases I to IV. During clinical trial phase-III, about 4,000-10,000 patients are involved and after passing this phase, the drug is allowed to enter into the global market. Then, billions of people, including those who were excluded in phase-III, may be administered with this drug. It is worthy to mention that these 4,000-10,000 patients may not show many of the side effects or toxic actions. The undetected adverse drug reactions (ADRs) are studied in clinical trial phase-IV, which is also known as post market surveillance. For this reason, the ADRs are compared with the tip of the iceberg, as it indicates the minor part of a major event. This phenomenon gave birth to a new branch of the pharmacology known as Pharmacovigilance.

Keywords: Adverse drug reaction, Drug safety, Pharmacovigilance, Phocomelia, Post market surveillance

1. Introduction

The discovery of a new drug can usually take 10-15 years [1, 2]. Within this time period, the candidate drug is screened for its beneficial as well as for its side effects (**Figure 1**). But the side, adverse or toxic effects cannot be detected to a full scale due to some special reasons.

Adverse Drug Reaction (ADR) is a damage or injury response caused due to intake of medication [3]. The ADRs may arise after administration of a single dose, or long-term administration of any drug or consequence of the administration of two or more drugs as a combination product or separately [4]. The study of ADRs has turned to be a separate field of science and is known as Pharmacovigilance (PV), which is defined by the World Health Organization (WHO) as, "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [5]. The Program for International Drug Monitoring (PIDM) was established by WHO in 1968 in response to the tragedy caused by thalidomide in 1961. The "Thalidomide Tragedy" was related to the birth of children with deformed limbs, also known as phocomelia [6], and it became one of the most known tragedies in the history of medical and pharmaceutical sciences. The WHO encourages, supports and promotes PV at

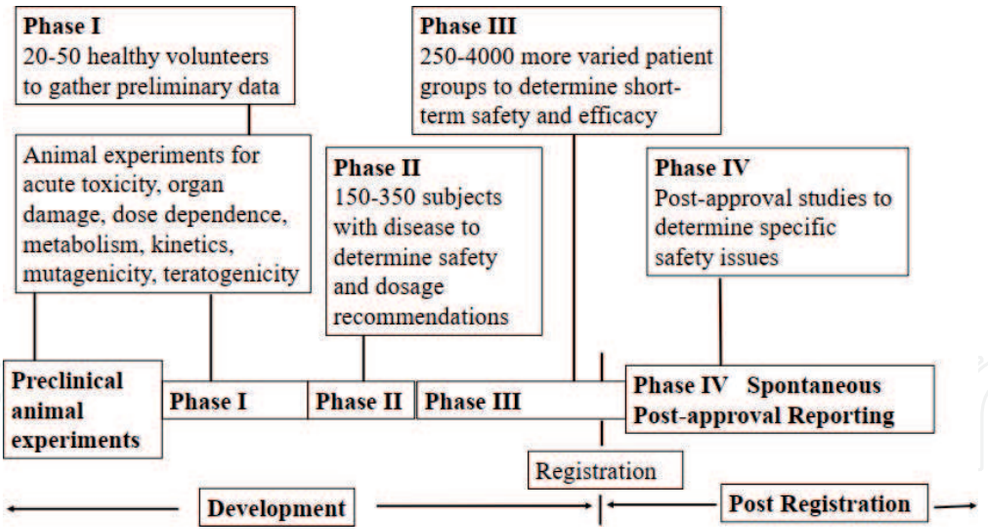


Figure 1.
Steps of drug development and commercialization.

the country level for its member countries, and offers collaboration through its Collaborating Centre for International Drug Monitoring in Uppsala, Sweden [7]. Until March 2019, the total number of member states which have enrolled in the WHO PIDM as a member corresponds to 142 and, additionally 29 associate members are expecting full membership [8].

To prevent tragedies such as the thalidomide disaster, governments all over the world took necessary ethical and legal actions and strengthened their drug regulatory authorities (DRAs) to keep alert and to ensure the marketing of relatively safe drugs.

2. Adverse drug reaction

An ADR can be defined as "any response to a drug which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" [9].

2.1 The importance of studying ADRs

As we have mentioned earlier, the overall toxicity of a drug is clearly understood during the whole life cycle of a drug, while only a minor portion of these toxicities are unveiled during clinical trial phases. After global launching, the post market surveillance studies help to assess the information leading to drug withdrawals, safety alerts from regulatory authorities and changes in product labelling. This also triggers the advances in pharmacology and therapeutics. Directly or indirectly, reports of ADR studies have shaped much of the current drug regulatory framework and contributed significantly to drug regulatory decisions. Furthermore, some ADR reports have also proved to be valuable weapons in discoveries in pharmacology and in improving drug use [10]. Clinical trial phases [11] include a small number of population and many clinical trials usually exclude:

1. Children,

2. Old people,

3. Pregnant and lactating women,

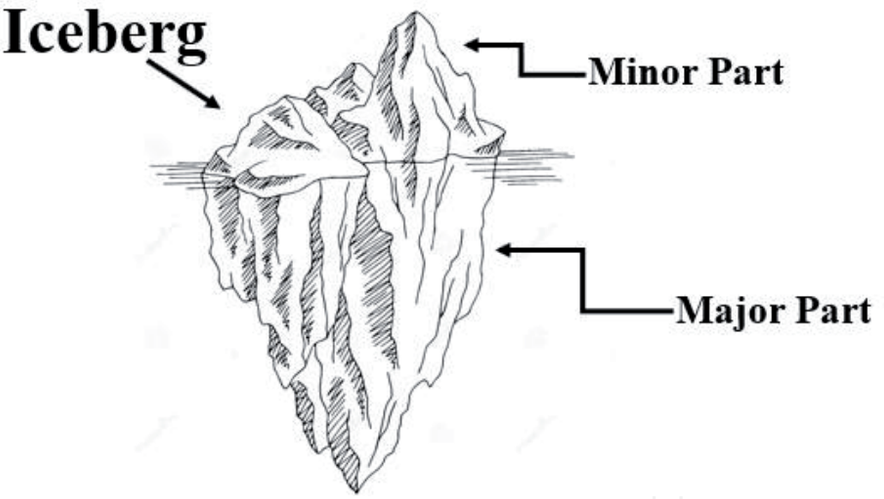


Figure 2.
The schematic diagram of an iceberg [12].

4. Ethnic groups,

5. Peoples with genetic disorders and,

6. People with liver and kidney insufficiency.

During the development of a drug, only less than 50% of ADRs can usually be detected, with the remaining more than 50% being detected after global launching, during the whole life cycle of the product. This can be compared with tip of the iceberg, which indicates a minor part of a major problem (**Figure 2**).

That is why it is very important to study the ADRs after launching of a new drug or vaccine.

3. Drug tragedies abroad and at home

As will be mentioned and described below, the "Thalidomide-induced Phocomelia" led the drug regulatory authority to take rigorous actions, including regulatory actions against the drug and promulgation of regulatory guidelines, as well as legislation. This and other reports have helped to discover a number of major drug disasters, such as the Benoxaprofen (known to cause severe hepatotoxicity and a variety of cutaneous reactions), Torsadogenic Drugs (e.g., prenylamine, terfenadine, cisapride that caused QT prolongation), Practolol (known to cause exfoliative dermatitis, systemic lupus syndrome, drug eruption, psoriasiform eruptions, skin reactions with eye signs consisting of atypical conjunctival shrinkage and xerosis, and keratoconjunctivitis sicca) [10]. In Bangladesh, the "Paracetamol tragedy" led the Directorate General of Drug Administration (DGDA) to take strict regulatory actions in the manufacture and quality control of drugs by the manufacturers. A few examples of those drug tragedies that occurred abroad and in Bangladesh are discussed below.

3.1 The thalidomide tragedy in Europe

In December 1961, William McBride, an Australian obstetrician, alerted in a letter to the *Lancet* that he had seen "multiple severe abnormalities" in babies born from ladies who had been administered with 'thalidomide' at the time of their

pregnancy (**Figure 3**) [13]. Dr. McBride summarized his report by questioning if any of their readers had seen similar abnormalities in babies born from women who had taken this drug during pregnancy.

The letter the first printed and published suggestion from a medical doctor about the teratogenic effect of thalidomide in women and it was a brief publication containing only five sentences. Dr. McBride's apprehensions about the drug thalidomide were eventually settled by numerous babies who were born with birth defects [14, 15].

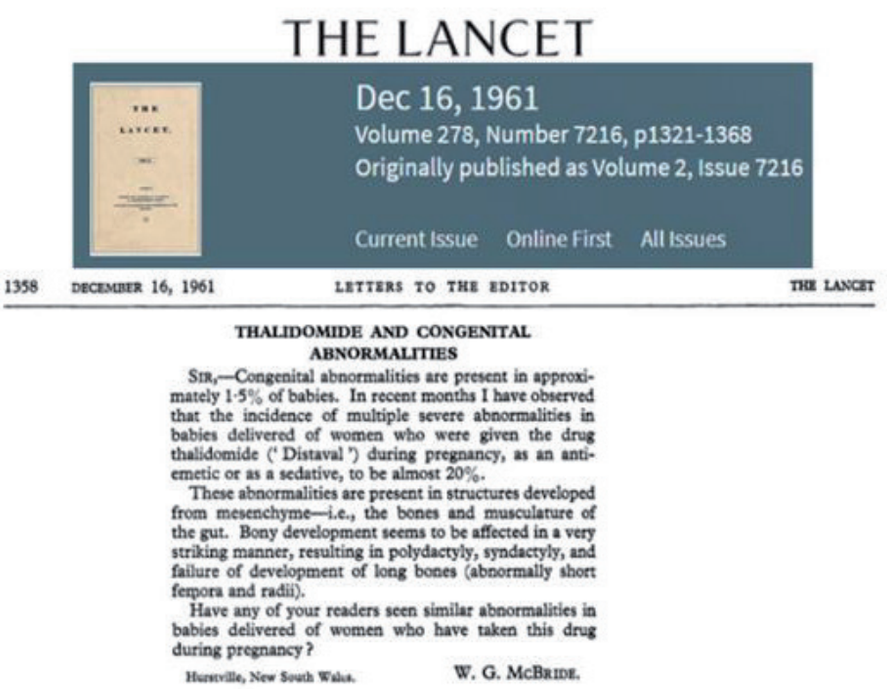
In 2016, a *BMJ* publication about a chronicled film, describing the lives of persons born with birth defects as a consequence of the administration of the medicines narrated, reported the following: "The thalidomide scandal stands as one of the worst ever medical disasters" [16, 17].

3.1.1 Worldwide recognition

William Griffith McBride was born on the 25th of May 1927 in Sydney, Australia. As his mother was sick, he had to spend much of his early living with an aunt on a dairy farm. He pursued his study of medical sciences at Sydney University Medical School.

Dr. McBride attained global recognition for his contribution to alert everyone worldwide about the danger of the drug thalidomide, which have caused defects in the development of the limbs of the fetus and, ultimately, gave rise to the birth of truncated babies. In Australia, his own country, Dr. McBride was praised as a national hero, and a radiance of honor fell over him over the next three decades. He had a blooming practice in Sydney, and he was awarded with both the 'Commander of the Order of the British Empire' in 1969 and the Order of Australia in 1977.

But a later part of McBride's life and work was not so pleasing. In 1993, when he was 65, McBride was found guilty of scientific deception by a medical court for the consciously publishing of erroneous and fallacious research. Consequently, his name was cut from the medical register [18–20].



THE LANCET

Dec 16, 1961
Volume 278, Number 7216, p1321-1368
Originally published as Volume 2, Issue 7216

Current Issue Online First All Issues

1358 DECEMBER 16, 1961 LETTERS TO THE EDITOR THE LANCET

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

Figure 3.
The first page of the letter to the editor published in the scientific journal 'The Lancet', in 1961, on the adverse effects of thalidomide.

3.2 Sulfonamide tragedy in Chicago, USA

An article reporting to the "Sulfanilamide Disaster" was published in June 1981 in an issue from the FDA Consumer magazine, and was entitled "Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident" [21]. The incident was described as: "By the 1930s it was widely recognized that the Food and Drugs Act of 1906 was obsolete, but bitter disagreement arose as to what should replace it. By 1937 most of the arguments had been resolved but Congressional action was stalled. Then came a shocking development: the deaths of more than 100 people after using a drug that was clearly unsafe. The incident hastened final enactment in 1938 of the Federal Food, Drug, and Cosmetic Act, the statute that today remains the basis for FDA regulation of these products".

Sulfanilamide is used to treat streptococcal infections due to its curative effects and, at that time, was available in the form of tablet and powder dosage. The demand for the liquid dosage form was raised by a salesman of the S.E. Massengill Co., in Bristol, Tenn., and the company's principal chemist and pharmacist, Harold Cole Watkins, who used diethylene glycol to dissolve sulfonamide and prepare an elixir. The quality control laboratory of the company analyzed the product for flavor, appearance and fragrance, and certified it as satisfactory. Instantly, the company considered it as a safe product, manufactured a certain quantity of it and sent product shipments to the whole country [21]. The new dosage form had not been analyzed for its toxicity and no pharmacological evaluation had been performed on the new sulfanilamide preparation. Watkins failed to record one feature of the elixir made by using diethylene glycol, which is applied as an antifreeze and is a lethal poison, causing renal damage followed by death [21].

3.3 Tylenol tragedy

Tylenol (Paracetamol) tragedy occurred in 1982 [22]. Tylenol was a product of of Johnson & Johnson and a trade-named drug intended for lessening pain, decreasing fever, and alleviating the symptoms of cough, cold, headache, allergies and influenza. The active pharmaceutical ingredient of this preparation is paracetamol (in the US it is known as acetaminophen), which is prescribed as an analgesic and antipyretic. The branded name (market name) Tylenol is accrued from a chemical name for the compound, N-acetyl-para-aminophenol (APAP). The branded name is possessed by McNeil Consumer Healthcare [22].

In 1982, in Chicago, US, Tylenol capsules laced with potassium cyanide caused the death of at least seven persons and raised a big concern about the safety of the marketed product. Potassium cyanide looks like normal table sugar, is water soluble but very toxic, being usually used for suicide (it is also known as suicide pills) [23].

This accident guided to the reforms in the packaging of over-the-counter drugs and to central anti-tampering laws. Johnson & Johnson took some necessary actions in their packaging and marketing policy that led to a reduction in the number of deaths and warned the public about potential poisoning risks. This action has been widely glorified as an exemplary public relation response to such a big crisis. Thus, Johnson & Johnson became able to regain their market share, which had been lost due to the Tylenol incident [22–24].

3.4 Paracetamol tragedy in Bangladesh

Two critical mishaps happened with paracetamol in Bangladesh. The first one occurred during 1990 to 1993, with the paracetamol produced by Adflame Pharmaceuticals Limited, and the second one took place during 2009 to 2010,

with the paracetamol manufactured by Rid Pharmaceuticals Limited. These two incidents are described below.

i. Adflame Pharmaceuticals Limited (1990 – 1993)

From 1990 to 1992, about 339 children developed renal failure in Bangladesh, and most of them died, after being given paracetamol (acetaminophen) solution using diethylene glycol [25]. The drug was manufactured by the "Adflame Pharmaceuticals Limited", Savar, Dhaka. The incident compelled the national government to forbid the trading of paracetamol preparations. Consequently, a decrease of 53% in the admission of victims with kidney failure and of 84% in admissions by unexplored kidney failure was observed in December 1992. This drug-related accident was reported in BMJ (**Figure 4**) in 1995 [25].

Three persons of the Adflame Pharmaceutical company were given 10-years of rigorous jail for producing a spurious drug which slaughtered 76 children in the 1990s. These convicted persons were Helena Pasha (Director), Mizanur Rahman (Manager) and Nigendra Nath Bala (production officer).

The prosecution against the manufacturing entity Adflame was only one of the four others also involved in this petition. Three other pharmaceutical producers were also accused of manufacturing the same contaminated liquid

Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic

Mohammed Hanif, M Reaz Mobarak, Anne Ronan, Dilruba Rahman, John J Donovan Jr, Michael L Bennish

Department of Nephrology, Dhaka Shishu Hospital, Dhaka, Bangladesh
Mohammed Hanif, *associate professor*
M Reaz Mobarak, *medical officer*
Dilruba Rahman, *registrar*

International Centre for Diarrhoeal Disease Research, Bangladesh
Anne Ronan, *international research fellow*

State Laboratory Institute, Massachusetts Department of Public Health, Boston, MA, USA
John J Donovan Jr, *senior chemist*

Division of Geographic Medicine and Infectious Diseases, New England Medical Center, NEMC 750 Washington Street, NEMC Box 321, Boston, MA 02111, USA
Michael L Bennish, *associate professor*

Correspondence and reprint requests to: Dr Bennish

Abstract

***Objective*—To determine the cause of a large increase in the number of children with unexplained renal failure.**

***Design*—Case-control study.**

***Setting*—Children's hospital in Dhaka, Bangladesh.**

***Subjects*—Cases were all 339 children with initially unexplained renal failure; controls were 90 children with cause of renal failure identified; all were admitted to hospital during 35 months after January 1990.**

***Main outcome measures*—Differences between the case and control patients in clinical and histological features and outcome; toxicological examination of 69 bottles of paracetamol from patients and pharmacies.**

***Results*—Compared with children with an identified cause for their renal failure, children with initially unexplained renal failure were significantly ($P<0.05$) more likely to have hepatomegaly (58% *v* 33%), oedema (37% *v* 20%), and hypertension (58% *v* 23%); to have a higher serum creatinine concentration (mean 519 μmol/l *v* 347 μmol/l) and lower serum bicarbonate concentration (10·1 mmol/l *v* 12·4 mmol/l); to have been given a drug for fever (91% *v* 31%); to have ingested a brand of paracetamol shown to contain diethylene glycol (20% *v* 0%); and to have died in hospital (70% *v* 33%). Diethylene glycol was identified in 19 bottles of paracetamol, from 7 of 28 brands tested. In the 12 months after a government ban on the sale of paracetamol elixir, new cases of renal failure decreased by 54%, and cases of unexplained renal failure decreased by 84%.**

***Conclusion*—Paracetamol elixirs with diethylene glycol as a diluent were responsible for a large outbreak of fatal renal failure in Bangladesh.**

Introduction

Diethylene glycol is a highly toxic organic solvent that causes acute renal failure and death when ingested.[1-3] Its toxicity became apparent when in the 1930s it was used to prepare a sulphanilamide elixir in the United States.[3] The deaths of at least 76 people from ingestion of this sulphanilamide elixir prompted the passage of the United States Food, Drugs, and Cosmetics Act in 1938, which regulates the evaluation and use of new drugs or foods.[4]

Diethylene glycol is still occasionally identified in medical preparations or foods, though rarely in lethal concentrations.[5-8] This report presents the results of investigations carried out in response to a large, initially unexplained epidemic of acute renal failure that was due to diethylene glycol poisoning.

Methods

PATIENTS

This study was conducted by Dhaka Shishu Hospital, the major children's hospital in the capital of Bangladesh. A dramatic increase in the number of patients with unexplained renal failure was noted in October 1990. Beginning in November 1990 possible causes for this increase were sought. Case records of patients admitted with renal failure from January 1990 onwards were reviewed, and information on all newly diagnosed patients with renal failure was recorded. Information obtained from patients' charts included history and physical examination findings and the results of complete blood counts, serum electrolyte and creatinine concentrations, and blood culture, if performed. Nutritional status was assessed with standard criteria.[9] Hypertension was defined as mean arterial blood pressure above the 95th centile for age.[10]

Because toxin ingestion was suspected as the cause of the epidemic of renal failure, special attention was paid to identifying medicines taken before renal failure developed. This was done by questioning the child's parents and asking them to bring to the hospital for verification any medicines given to the child.

The most commonly identified causes of acute renal failure at Shishu Hospital are the haemolytic-uraemic syndrome, poststreptococcal glomerulonephritis, and acute tubular necrosis. All three conditions are usually readily diagnosed on the basis of history, physical examination, and laboratory findings. Patients in whom the cause of renal failure was not identified were considered to have unexplained renal failure.

TESTING OF SAMPLES

Paracetamol elixir was identified as the medicine most commonly taken before admission by patients developing unexplained renal failure. Samples tested by laboratories in Bangladesh did not identify the presence of toxic substances, so 69 samples of 28 brands of paracetamol were submitted on four occasions for analysis to the State Laboratory Institute of the Commonwealth of Massachusetts in Boston. Samples for analysis included three bottles from the stocks of the hospital pharmacy, 49 bottles purchased

Figure 4.
Publication in BMJ on the 'paracetamol tragedy' in Bangladesh by Hanif et al., in 1995 [25].

paracetamol, including Polychem Laboratories Ltd., BCI (Bangladesh) Ltd., and Rex Pharmaceuticals. The fifth pharmaceutical industry - City Chemical and Pharmaceutical Works Ltd., was also sued but not trialed.

ii. Rid Pharmaceuticals Limited, Brahmanbaria (2009–2010)

Once more, in 2009, 28 children died due to the diethylene glycol toxicity [26]. The national government started to constitute a probe committee which detected the presence of the toxic substance diethylene glycol in the liquid paracetamol of one pharmaceutical company, after investigating 300 samples of liquid paracetamol and liquid vitamins of 10 industries. This company was supposed to use propylene glycol, but instead used the toxic diethylene glycol, a component applied in tannery and battery industries. Consequently, its manufactory was completely sealed off and its goods were re-called from the market [26].

In 2016, the drug court (at Dhaka) decided to exonerate all five persons from the Rid Pharmaceutical Industry Ltd., in the case where a poisonous paracetamol was produced and authorized by this company, leading to the death of 28 children all over the country in 2009. The Dhaka drug court judge Mr. Atoar Rahman issued the order on a Monday afternoon. In the verdict, the judge slammed the drug authority for "their inefficiency in handling the case before the drug court". The judge said the prosecution had failed to demonstrate the charges due to the inability and inefficiency of the case investigation officer. Of the five officials, only Mizanur Rahman and his wife Sheuli were present during the delivery of the verdict. The rest of the accused persons are still absconding. The public prosecutor of this case, Dr. Nadim Miah, expressed his disappointment over the verdict by saying to the Dhaka Tribune: "We will decide on moving against the verdict after receiving the copy of the full verdict" [27]. Five prosecution witnesses gave depositions before the court during the trial, sources said. Twenty-eight children across Bangladesh died from renal failure during the period between June and August 2009, after consuming a paracetamol syrup manufactured by Rid Pharma. As the number of deaths was spread around the population, the government published notices in national daily newspapers warning people to not consume any drugs manufactured by this pharma company. A case was filed on August 10th, 2009, by the drug superintendent Shafiqul Islam with the Dhaka drug court against the five accused. Four more petitions were signed in Brahmanbaria, Comilla, Narayanganj and Sylhet. On July 22nd, 2009, the Directorate General of Drug Administration took steps to seal off the Rid Pharma's factory at Brahmanbaria. The national government also constituted a seven-member enquiry committee to probe the matter. On July 29th, 2009, the enquiry committee submitted its report, referring that a poisonous chemical named diethylene glycol was used to manufacture the paracetamol syrup. The report also said that Rid Pharma used diethylene glycol, mainly applied in tannery and rubber industries, as a cheaper substitute of propylene glycol, since diethylene glycol costed Tk. 200 per liter, while propylene glycol costed Tk. 1,100 [26–29].

4. WHO's program on global patient safety challenge (also known as well-being program)

The WHO has the responsibility to promote the health and hygiene of the people of its member countries. To perform this responsibility, WHO has taken a few programs. One of such programs is the Global Patient Safety Challenge. Till date, WHO has undertaken three Global Patient Safety Challenges, which are popularly known as '**Well-being Programs**'. These include [30]:

i. First Global Patient Safety Challenge**: Wash your Hands**

ii. Second Global Patient Safety Challenge: **Safe Surgery** and

iii. 3rd Global Patient Safety/Security Challenge: **Medication without Harm**

These programs are almost self-explanatory, and a detailed description is out of the scope of this chapter.

5. Pharmacovigilance (PV)

According to WHO, PV can be defined as: "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [31]. The term PV has been accrued from the Greek word *Pharmakon* meaning *drug* and from the Latin term *vigilare* meaning *to keep aware or, vigilant/alert or, to keep watch* [31]. Vigilance usually indicates:

- Aware/Alert;
- Restraint/Forbearance of sleep, wakefulness;
- Watchfulness in respect of jeopardy, care, caution;
- The procedure of giving close and continuous attention.

From the definition given above, we see that there are four pillars of PV. These include:

i. Detection

ii. Assessment

iii. Understanding (Analysis) and

iv. Prevention (Reporting) of ADR

5.1 Main aims

The general aims of PV are to promote both patient care and patient safety with respect to the use of drugs and medical devices; and to bolster the public health programs (PHP) by giving reliable and equalized information for the productive estimation of the benefit–risk quotient of medicines [32].

The most important aims and purposes of PV are [32];

i. to alert people, not to scare them;

ii. to boost the care and safety of the patient with respect to the consumption of medicines, medical devices and other healthcare interventions;

iii. to improve the public health and safety, while using medicines;

iv. to detect problems of medicine usage, reduce risks and communicate the observations in a disciplined way;

v. to contribute to the evaluation of benefit, hazard, effectiveness and dangers of medicines, directing to the curbing of harm and maximization of beneficial effects;

vi. to embolden the safe, effective (i.e., cost-effective) and rational applications of medicines;

vii. to enhance the understanding, education and the scientific and clinical tutelage in PV and its fruitful communication to the people.

6. PV analytical tools

It is well-known that PV is a risk management procedure for drugs. The process begins with identification of a possible danger, which is then assessed and investigated, ultimately resulting in actions that are taken to minimize those risks. The PV implementation requires the use of specific tools (**Figures 5** and **6**) that will help to communicate with the prescribers and end-users, and the last step should be an evaluation of the effectiveness of the process. The overall process of risk management is iterative due to new proofs that may emerge, or to certain measures taken that may be inadequate. A drug safety issue is rarely considered complete and the safety study goes on until the life cycle completion of the drug.

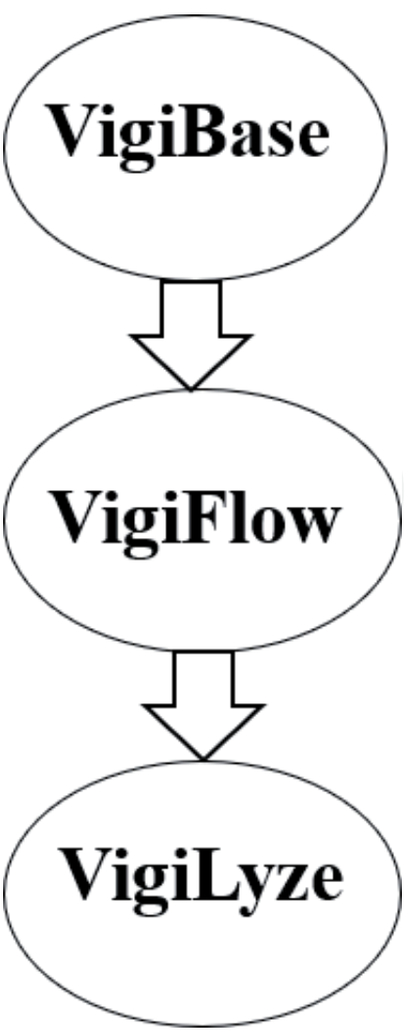


Figure 5.
PV tools to detect and assess the signals related to ADRs.

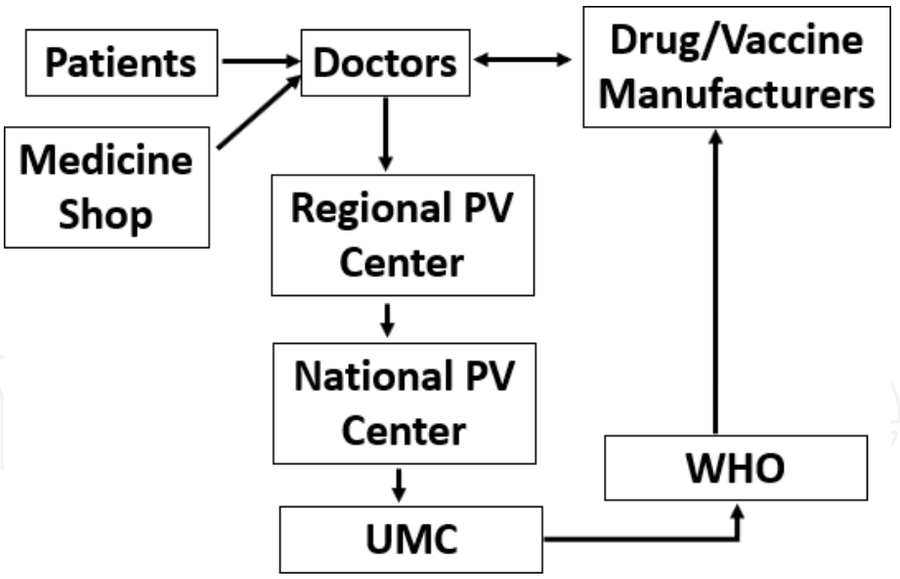


Figure 6.
Flow of information among PV centers and the global monitoring organizations by using PV analytical tools for ADRs analysis [33].

The beginning of the process is normally a 'signal' which is not often a real hazard. Before that can occur, there is a necessity to detect the signal.

The term 'signal' is defined by WHO as a "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely recorded previously" [34].

6.1 VigiBase

VigiBase is the starting point for the journey of Uppsala Monitoring Center (UMC) from data to wisdom regarding the safe use of drugs, as well as the sage therapeutic decisions in clinical practice. This is the motivating-force of the work of UMC and the WHO Program. The main aim of VigiBase is to make sure that initial signs of previously undetected, unknown, and unexplored drug-related safety problems are identified as quickly as possible.

VigiBase is one of the unique WHO global databases of individual case safety reports (ICSRs). This is the biggest database of its kind worldwide, with more than 20 million reported records of suspected adverse effects of drugs, which have been submitted since 1968 by member states of the WHO PIDM. VigiBase is continually updated with incoming reports from the member countries [35].

6.2 VigiFlow

VigiFlow stands as a management procedure for recording, processing, and sharing reports of ADRs. VigiFlow collects the domestic data and processes the ICSR, thus sharing the reports for instance with VigiBase. This allows maximum local control and gives effective ways for management review and data scanning coming from national sources [36].

6.3 VigiLyze

VigiLyze is a signal detection and management system using national, regional or global data as the launching point for quantitative signal detection. VigiLyze supports the overall signal management process, including the qualitative evaluation.

The major strengths of this signal detection tool are its capacity to re-estimate disproportionality based on any selected country or region background within seconds, and re-investigate those for certainty using different tools [37]. VigiLyze will enable the users to search for any drug or reaction that is shared with the program from UMC, other national centers, or their own centers.

VigiLyze is accessible free of cost to national pharmacovigilance centers in all member states of the WHO Program for IDM. Under-reporting is a familiar matter in pharmacovigilance. By distributing the national reports of adverse events to the global database, individual nations can help increase all countries' understanding of achievable safety concerns.

VigiLyze provides a national, regional, and global aspects of the suspected adverse effects of a drug. This enormous collection of data enhances assessments of surfacing domestic issues. Through VigiLyze it is possible to obtain easy entrance to post-marketing safety information for medicines that are new to the national market, but that are already marketed in other parts of the globe [38].

It is important to mention that one of the major concerns of PV is the safety issue of the PHP [39], such as vaccination in the form of national immunization day, administration of anthelmintics, administration of vitamin A capsule, etc. In those cases, PV tools act as very essential weapons to analyze the situations or adverse effects arising from mass drug administration [40] to handle the pandemics.

7. Bangladesh perspective of PV activities

The Directorate General of Drug Administration (DGDA), under the ministry of Health and Family Welfare, is the national DRA of Bangladesh. The DGDA acts as the only PV center in Bangladesh. An Adverse Drug Reaction Monitoring (ADRM) cell has been set up under the DGDA in 1999 in Bangladesh [41]. The ADR reporting form was introduced in relevant medical institutions to collect information on ADRs. More recently, and under the ADRM, a PV cell was established to effectively monitor and collect the information on ADRs. However, PV is only one of the main components of effective medicine regulation by the national drug regulatory agencies. The vision of DGDA is to guarantee that effective, high-quality and safe drugs are available to the Bangladesh population. This can be achieved through

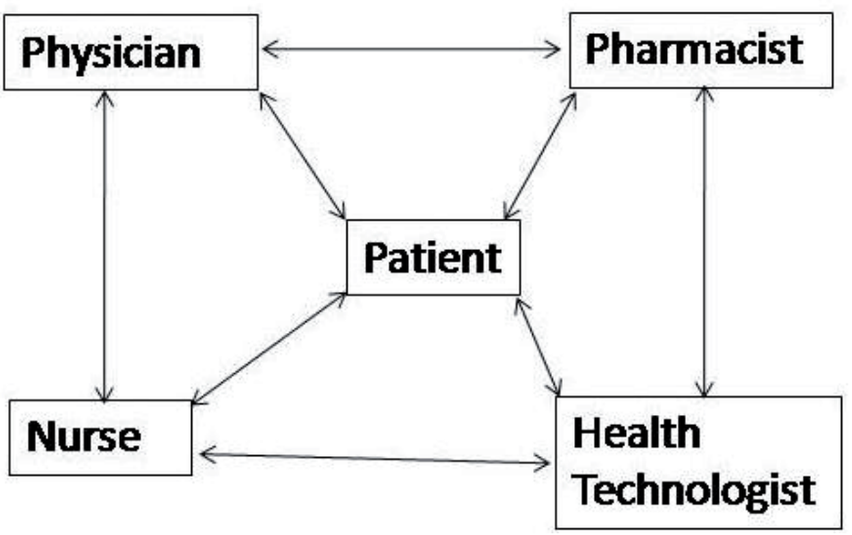


Figure 7.
Interrelationship among the different health professionals (physicians, pharmacists, nurses and health technologists) and the patients [42].

an effective dissemination of the PV cell activities all over the country, including all public and private medical institutes, hospitals, clinics, public and private practitioners, pharmacists, nurses, and other health professionals (**Figure 7**). However, it is very important to keep in mind that the patients should always remain at the center of all [41].

8. Conclusions

The main purpose of the PV study is to protect the future generations or the potential users from the harmful effects of a drug that has already launched in the market. Although the emergence of side effects resulting from the use of drugs are unavoidable, the incidence of morbidity and mortality caused by the occurrence of side effects can be reduced if proper measures are promptly adopted by the local, as well as by the global regulatory organizations. To this end, the main PV principles should be strictly followed by all the member countries of the WHO.

Acknowledgements

1. Dr. Md. Aktar Hossain, Assistant Director, Directorate General of Drug Administration (DGDA).

2. Mr. Ahmed Kamrul Alam, Director (Marketing), Square Pharmaceutical Industry Ltd., Dhaka, Bangladesh.

3. Ariful Karim, Department of Pharmacy, Southeast University, Dhaka, Bangladesh.

Conflict of interest

The author declares no conflict of interest.

Notes/Thanks/Other declarations

Special thank goes to my wife Shirotaz Begum for her cooperation to complete this write up.

Appendices and nomenclature

ADR	Adverse Drug Reaction
ADRM	Adverse Drug Reaction Monitoring
BMJ	British Medical Journal
DGDA	Directorate General of Drug Administration
DRA	Drug Regulatory Authorities
FDA	Food and Drug Administration
ICSR	Individual Case Safety Reports
IDM	International Drug Monitoring
GPSC	Global Patient Safety Challenge
PHP	Public Health Programs

PIDM	Program for International Drug Monitoring
PV	Pharmacovigilance
UMC	Uppsala Monitoring Center
WHO	World Health Organization

Author details

Md. Shah Amran
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Dhaka, Shahbag, Dhaka, Bangladesh

*Address all correspondence to: amranms@du.ac.bd

References

[1] Summarized narratives of Dr. Md. Shah Amran from his experience gained in specialized training on Pharmacovigilance [Specialized training on Pharmacovigilance, Delhi, India, March 03-15, 2019].

[2] Chung Chow Chan, Y C Lee, Herman Lam, Xue-Ming Zhang; Analytical method validation and Instrument performance verification, WILEY-INTERSCIENCE, 2004, 2p.

[3] Guideline for Good Clinical Practice. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 10 June 1996. 2p.

[4] Nebeker JR, Barach P, Samore MH; Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Annals of Internal Medicine, 2004. 140 (10): 795-801.

[5] https://www.who.int/teams/regulation-prequalification/pharmacovigilance (Accessed on 15-01-2021)

[6] Neil Vargesson, Thalidomide-Induced Teratogenesis: History and Mechanisms, Birth Defects Research (Part C), 2015, 105:140-156.

[7] WHO Collaborating Centre for International Drug Monitoring, https://www.who.int/medicines/areas/quality_safety/safety_efficacy/collab-centre-uppsala/en/ (Accessed on 15-01-2021)

[8] Members of the WHO Programme for International Drug Monitoring, Full and associate member countries of the WHO Programme and the year they joined. Full member countries (143), https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring/who-programme-members/ (Accessed on 15-01-2021)

[9] Bangladesh National Formulary (BDNF), 2015, Volume 4, Pp759-768.

[10] Rashmi R. Shah, Importance of Publishing Adverse Drug Reaction Case Reports: Promoting Public Health and Advancing Pharmacology and Therapeutics, Drug Saf - Case Rep., 2017, 4:11 doi:10.1007/s40800-017-0053-0.

[11] Chung Chow Chan, Herman Lam, Y. C. Lee, Xue-Ming Zhang, Analytical method validation and instrument performance verification, Wiley interscience, 2004, P1-11.

[12] https://penlighten.com/meaning-origin-of-idiom-tip-of-iceberg (accessed on 15-01-2021)

[13] W.G. McBride, THALIDOMIDE AND CONGENITAL ABNORMALITIES, The Lancet, 1961, Volume 278, Issue 7216, 1358p.

[14] Papers of William McBride, ca. 1953-1996, National Library of Australia, accessed 26 July 2010.

[15] Bara Fintel, Athena T. Samaras, Edson Carias, The Thalidomide Tragedy: Lessons for drug safety and regulation, Helix Magazine, Jul 28, 2009.

[16] Attacking the devil: the thalidomide story, BMJ 2016; 352 [BMJ 2016;352:i353]

[17] Md. Shah Amran and Md. Aktar Hossain, Pharmacovigilance and Bangladesh perspective, Bangla Academy Science Journal, 2019, 1:88-95.

[18] "Time Magazine" Archived 3 September 2009 at the Wayback Machine.

[19] Medical Tribunal of New South Wales Archived 20 September 2009 at the Wayback Machine.

[20] Dr. McBride hails end of the affair – "The Australian".

[21] Carol Ballentine, Sulfanilamide Disaster, FDA Consumer magazine, June 1981 Issue.

[22] West, Nancy. "History of Tylenol" (PDF). Nancy West Communications. Retrieved July 26, 2014.

[23] Dan Fletcher, A Brief History of the Tylenol Poisonings, The Time, Monday, Feb 09, 2009.

[24] Euromonitor International. "Acetaminophen benefits from concerns surrounding safety of analgesics". Market Research World. Retrieved July 26, 2014.

[25] Hanif, M., Mobarak, M.R., Ronan, A., Rahman, D., Donovan, J.J. and Bennish, M.L. 1995. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. Bri. Med. J.311, 88-91.

[26] The Daily Star, Three Adflame officials jailed for 10yrs, 03:56 PM, July 22, 2014 / LAST MODIFIED: 01:53 AM, March 08, 2015.

[27] The Dhaka Tribune, All acquitted in Rid Pharma paracetamol case, 12:25 pm November 28th, 2016.

[28] The Daily Star, Rid's syrup unauthorized, toxic element found, 11:00 PM, July 29, 2009 / LAST MODIFIED: 11:00 PM, July 29, 2009.

[29] The Daily Star, The unfortunate case of Rid Pharma, 12:00 AM, December 06, 2016 / LAST MODIFIED: 12:00 AM, December 06, 2016.

[30] https://www.who.int/patientsafety/events/05/GPSC_Launch_ENGLISH_FINAL.pdf (Accessed on 01-12-2020)

[31] WHO / Pharmacovigilance (Accessed on 01-12-2020).

[32] WHO / Pharmacovigilance (Accessed on 16-06-2019).

[33] Maria Delaney, Improving pharmacovigilance through direct patient reporting, Cancerworld, March / April 2017. 77:28-32.

[34] https://www.who-umc.org/media/164092/general-information-about-signal-published-in-who-pn.pdf (21-05-2021)

[35] https://www.who-umc.org/vigibase/vigibase/

[36] https://www.who-umc.org/global-pharmacovigilance/vigiflow/

[37] WHOcausality_assessment.pdf (21-05-2021)

[38] https://www.who-umc.org/vigibase/vigilyze/

[39] The SAFETY of MEDICINES IN PUBLIC HEALTH PROGRAMMES: Pharmacovigilance an essential tool, 2006, Pp 9.

[40] https://en.wikipedia.org/wiki/Mass_drug_administration (Accessed on 17-01-2021)

[41] https://www.dgda.gov.bd/index.php/2013-03-31-04-35-57/adrm-news (21-05-2021)

[42] Md. Shah Amran, Introduction to Pharmacy, Published by Krishnachura Publications, Central Road, Dhaka-1205, Dhaka, Bangladesh, 2nd edition, 2015, Pp-7.