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A REVIEW ON ADVERSE DRUG REACTION AND ITS HISTORICAL BACKGROUND

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ABSTRACT

Adverse drugs reactions (ADRs), put simply, are noxious, unintended, and undesirable effects that occur as a result of drug tre atment at doses normally used in man for diagnosis, prophylaxis, and treatment. Although there are many terms indicating the harmful and undesirable effects of drug treatment, the term ‘adverse drug reaction’ describes them best. During the course of treatment, drugs prescribed to patients produce certain effects other than the desired or expected effects. An adverse event is harm that occurs while a patient is taking a drug, irrespective of whether the drug is suspected to be the cause. A side-effect is any effect caused by a drug other than the intended therapeutic effect, whether beneficial, neutral or harmful. The term ‘side-effect’ is often used interchangeably with ‘ADR’ although the former usually implies an effect that is less harmful, predictable and may not even require discontinuation of therapy (e.g. ankle oedema with vasodilators). Drug toxicity describes adverse effects of a drug that occur because the dose or plasma concentration has risen above the therapeutic range, either unintentionally or intentionally (drug overdose). Drug abuse is the misuse of recreational or therapeutic drugs that may lead to addiction or dependence, serious physiological injury (such as damage to kidneys, liver, heart), psychological harm (abnormal behavior patterns, hallucinations, memory loss), or death.

KEYWORDS: Adverse drug reaction, Drug abuse, Side effects.

INTRODUCTION

Adverse drugs reactions (ADRs), put simply, are noxious, unintended, and undesirable effects that occur as a result of drug tre atment at doses normally used in man for diagnosis, prophylaxis, and treatment. Although there are many terms indicating the harmful and undesirable effects of drug treatment, the term 'adverse drug reaction' describes them best. During the course of treatment, drugs prescribed to patients produce certain effects other than the desired or expected effects. These cause concern both to th e physician and the patient.[1] They not only add to spiralling costs of medical treatments, but also cause a great deal of morbidit y and mortality. These are generally referred to as 'side effects'. People usually attribute these abnormal effects to either overdos e or inappropriate medications prescribed by the doctor or the attending specialists. The unwanted effects are categorised into many types such as toxic effects, side effects, adverse reactions, and adverse drug events etc., depending upon the taxonomic classi fication used. Worldwide, studies have shown them to be a major cause of morbidity and mortality. Though Indian studies in this regard are very few, the pattern of reactions seems to be similar. Moreover, we have certain peculiarities of drug use such as[1,2] large number of patients, poor doctor-patient ratio, self-medication, drugs of alternative systems of medicine, malnutrition, widespread ana emias, presence of counterfeit drugs, and presence of the highest number of drug combinational products in the world. Therefore, incid ence of the adverse drug reactions is likely to be same as that of the West, or more.

Adverse drug reactions

An adverse drug reaction (**ADR**)**:** Is an injury caused by taking medication. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial. The study of ADRs is the concern of the field known as *pharmacovigilance*. An adverse drug event (ADE) refers to any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury. An ADR is a special type of ADE in which a causative relationship can be shown. ADRs are only one type of medication-related harm, as harm can also be caused by omitting to take indicated medications.[2]

History of adverse drug reaction

Pharmacovigilance (PV) is defined by the European Commission (EU) as the "Process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines". The international PV systems aim to monitor the risk/benefit ratio of drugs as well as improve patients' safety and their quality of life. PV activities include: collecting and managing data on the safety of medicines, looking at individual case reports to detect new "signals", *pro-active* risk management to minimize any potential risk associated with the use of medicines, communicating and informing stakeholders and patients. This seamless post-marketing surveillance, which is primarily aimed at protecting the public, allows CAs (Controlling Authorities) to modify—on the basis of newly discovered signals—the Summary Product Characteristics (SPC), released by the Marketing Authorization Holder (MAH) for any new medicinal product at the first boot into the market.[3]

The etymological roots for the word "pharmacovigilance" are: *Pharmakon* (Greek) = medicinal substance, and *Vigilia* (Latin) = to keep watch.

In this short article, we describe the milestones (as represented in Fig. 1) that led to the evolution of Pharmacovigilance activities in the last century.

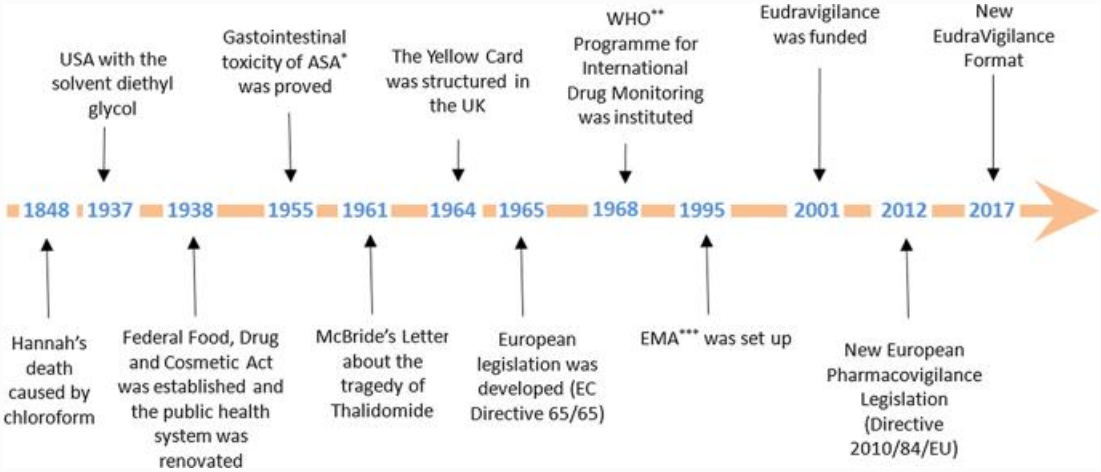

Fig. 1.

Timeline of the historical evolution of Pharmacovigilance. *ASA: acetylsalicylic acid; **WHO: World Health Orgnaisation; ***EMA: European Medicines Agency

We intentionally excluded a part of scandals (e.g. inhibitors of cyclooxygenase types 2 because of cardiovascular adverse reactions), because they were mainly due to incorrect marketing or inappropriate information campaigns by pharmaceutical companies.[3]

The history of Pharmacovigilance started 169 years ago, on Jan 29, 1848, when a young girl (Hannah Greener) from the north of England died after receiving chloroform anesthetic before removal of an infected toenail. Sir James Simpson had discovered that chloroform was a safer and powerful anesthetic, and he had introduced it in clinical practice. The causes of Hannah's death was investigated to understand what happened to Hannah, but it was impossible to identify what killed her. Probably she died of a lethal arrhythmia or pulmonary aspiration.[3,4]

As a result of other deaths and alerts raised by the clinicians and the public about the safety of anesthesia, *The Lancet* Journal established a commission to take on this problem. The commission exhorted English doctors, including the doctor in colonies, to report deaths caused by the anesthesia. The results were published in The Lancet in 1893.[4]

The US Federal Food and Drug Act was formed on June 30, 1906, and it established that drugs must be pure and free of any contamination. Furthermore, in 1911, this organization forbade false therapeutic indications of drugs.[4,5] In 1937, there were 107 deaths in the USA, because of the use of sulfanilamide elixir, containing diethyl glycol as the solvent. This solvent was considered the cause of deaths, but the manufactory companies were not aware about its toxicity at that time.[3,5,6] Consequently, the Federal Food, Drug and Cosmetic Act was established in 1938; its aim was to renovate the public health system. Indeed, the new system foresaw that the safety of drugs should be demonstrated before their market approval, and introduced the possibility of conducting factory inspections.[7] In 1938, Douthwaite supposed that acetylsalicylic acid (ASA) could cause melena.[8] The study of the gastrointestinal toxicity of ASA showed different outcomes. However, in 1955, it was proved that ASA can cause gastrointestinal diseases and therefore it is currently contraindicated in patients with gastrointestinal ulcers.[9]

In 1961, a big change of European Pharmacovigilance happened following the tragedy of Thalidomide. Dr. McBride, an Australian doctor, wrote a letter to the editor of the Lancet Journal, in which he suggested a connection between congenital malformation of babies and thalidomide. In fact, he observed that the incidence of congenital malformations of babies

(1.5%) had increased up to 20% in women who had taken thalidomide during pregnancy. At the same time, during a Pediatric Convention in Germany Dr. Lenz suggested a correlation between malformations and thalidomide and his suspect was published in a German Journal (Welt am Sonnatag). In 1973, a retrospective study showed the correlation between the congenital malformations of babies and the ingestion of thalidomide during pregnancy. In USA, the tragedy of thalidomide was not observed, because Dr. Kelsey showed strong doubts about the safety of thalidomide during pregnancy.[5] The tragedy of thalidomide brought to light many problems and critical issues, in particular, the reliability of animal tests, the behavior of the industrial company, and the importance of monitoring the drugs after their marketing. In particular, this tragedy changes the system of Pharmacovigilance, because the spontaneous reporting of adverse drug reactions became systematic, organized, and regulated. This letter already contained all of the elements needed to generate a spontaneous reporting and to establish a cause-effect relationship between the adverse event and the drug (Fig. 2). In 1964, the "Yellow card" (YC) was structured in the UK. YC is a specific form to compile a spontaneous report of drug toxicity. In USA (1962), the amendment, requiring safety and efficacy data of drugs before premarketing submission, was approved. As a result of this amendment, the safety data have to include also teratogenicity test in three different animals.[5] In Europe (1965), the disaster of thalidomide stimulated the development of a European legislation with the EC Directive 65/65.[5] In 1966, a pilot study of Boston Collaborative Drug Surveillance Program started. It was the first group to conduct epidemiologic researches to quantify the potential adverse effects of drugs utilizing in-hospital monitoring and had an essential role in the development and application of methods in drug epidemiology. In 1968, the WHO Programme for International Drug Monitoring was instituted and ten members participated in this program (Australia, UK, USA, Germany, Canada, Ireland, Sweden, Denmark, New Zealand, and Netherlands). Italy participated in this program in 1975. Many studies of observed adverse drug reactions were conducted between 1968 and 1982.[3] In 1992, the European Society of Pharmacovigilance (ESoP) was funded, turned into the International Society of Pharmacovigilance (IsoP). The aims of this society were to promote Pharmacovigilance, and enhance all aspects of the safe and proper use of medicines.[8] In 1995, the European Medicines Agency (EMA) was set up. In 2001, EudraVigilance was funded. It is the official European database for managing and analyzing information on suspected adverse reactions to medicines which have been authorized for the market or being studied in European clinical trials. A major change in European

Pharmacovigilance was observed with the new legislation (Directive 2010/84/EU), in 2012. The main changes in the new legislation were

- Modification of the definition of adverse drug reactions (ADR);
- Greater involvement of patients and citizens in Pharmacovigilance activities;
- Strengthening of the Eudravigilance database containing reports of suspected reactions reported by all EU Member States;
- Increasing transparency and timeliness of important information on Pharmacovigilance problems;
- Obligation of "additional monitoring" for the products contained in the specific list kept by the EMA;
- Possibility to impose further safety and/or efficacy studies on the certificates of marketing authorization at the time of granting the trust;
- Establishment within the EMA of the Pharmacovigilance Risk Assessment Committee (PRAC)

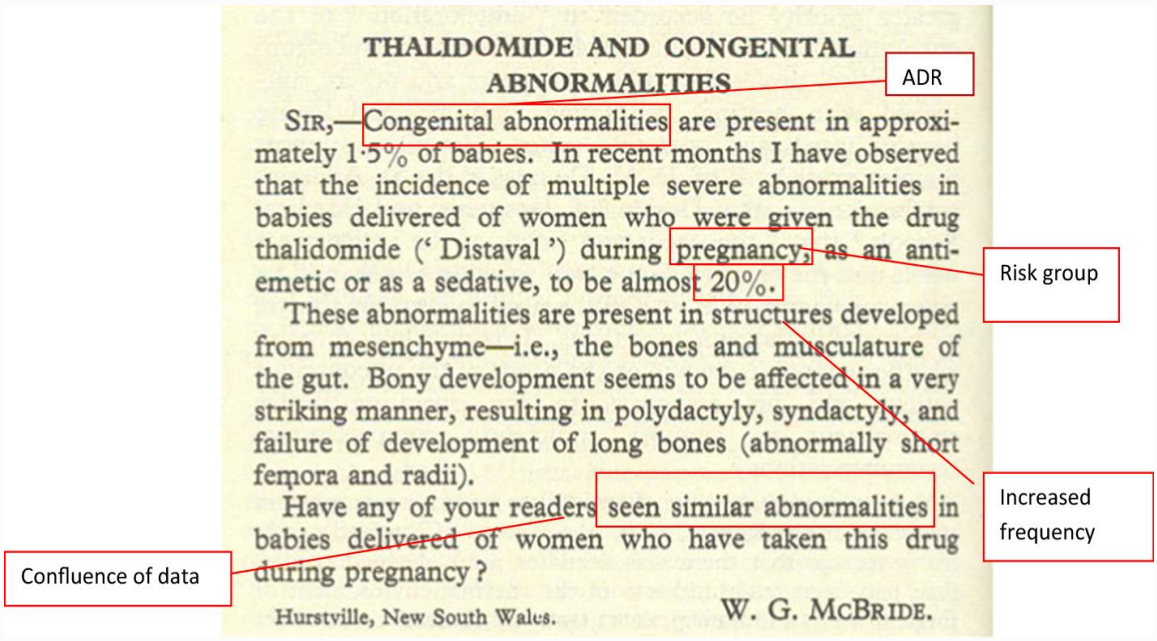

Fig. 2.

McBride's letter and important elements for generating spontaneous reporting.

In particular, the most relevant change consists in the new definition of ADR: "A response to a medicinal product which is noxious and unintended". In fact, with this definition were covering any adverse event following the use of a medicine, also medication errors and uses

outside the terms of the marketing authorization, including the misuse and abuse of the medicinal product.

Furthermore, the new legislation set-up measures to facilitate the performance of PV, called the Good Pharmacovigilance Practices (GVP). The guideline on GVP is divided into two categories: modules covering major Pharmacovigilance processes and product- or population-specific considerations. This last category is available for vaccines and biological medicinal products. In this guideline there are also special chapters dedicated to special areas, namely pregnancy and breast-feeding (P III) and geriatric population (P V).

In November 2017, the new EudraVigilance format was launched; in particular, the marketing authorizations will have extended access to the EudraVigilance database to support the fulfillment of their Pharmacovigilance obligations. These obligations include the continuous monitoring of EudraVigilance data and the communication of validated signals to the Agency and national regulatory authorities, as outlined in Commission Implementing Regulation (EU) N. 520/20121.

History of pharmacovigilance in india

The origin of pharmacovigilance in India goes back to 1986, when a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India.[3] However, nothing much happened until a decade later when in 1997, India joined the WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. This attempt was unsuccessful and hence, from 1January 2005, the WHOsponsored and World Bank-funded National Pharmacovigilance Program for India was made operational.[4]

The National Pharmacovigilance Program established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi. Two zonal centers-the South-West zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the NorthEast zonal centre (located in the Department of Pharmacology, AIIMS, New Delhi), were to collate information from all over the country and send it to the Committee as well as to the Uppsala monitoring centre in Sweden. Three regional centers would report to the Mumbai center and two to the New Delhi one. Each regional center in turn would have several peripheral centers reporting to it. Presently there

are 26 peripheral centers. The program has three broad objectives: the short-term objective is to foster a reporting culture, the intermediate objective is to involve a large number of healthcare professionals in the system in information dissemination and the long-term objective is for the program to be a benchmark for global drug monitoring.

Given this background on pharmacovigilance in India to date, things have definitely changed for the better but at a very slow pace. The Regulatory Authority for India should be commended for introducing and implementing the Schedule Y and for reporting of all serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARS) from clinical trials. However, there is a need of spontaneous adverse event reporting from post-marketed medicines to the zonal centers and in turn to the National Pharmacovigilance Centers to the WHO Uppsala Monitoring Center, which at the moment is woefully lacking. Therefore, in these circumstances, the questions that arise are whether the strategy should be changed and if so, how?

Why is the number of ADRs so high?

There are several reasons why the number of adverse drug reactions is so high. These include: 1) the number of drugs prescribed are high; 2) the ever-increasing number of new drugs in the market; and, 3) the lack of a formal system for monitoring adverse drug reactions.[5]

While the exact epidemiology remains to be known inIndia, ADRs have recently emerged as leading killers. The management of drug-induced illnesses requires more than 100 billion US dollars annually.[4] These astronomical figures are currently unmatched by money involved in any single disease management presently. Fortunately, several studies have shown that most ADRs are preventable, provided that the drugs are used rationally. But unfortunately, the most common system failure has been to disseminate the knowledge of pharmacovigilance to the individuals actually involved in prescribing, i.e., the physicians3. Principles and practice of pharmacovigilance seem to be more often discussed in an academic manner, rather than in a pragmatic or applied sense. Several times, such discussion is held amongst pharmacologists and pharmacists who are not directly involved in patient care; and physicians who treat cases and use drugs generally keep themselves uninvolved. Drug safety has been included in curriculum guidelines of Indian medical undergraduates (MCI Curriculum Guidelines,1997), but little is done in this regard. Prevention is considered to be better than cure, as elsewhere

in medicine; application of the same principle has given a new dimension to the study of pharmacovigilance.[6]

Why is ADR monitoring needed?

One of the most frequently asked questions in pharmacovigilance is: What is the need to monitor the adverse reactions to drugs, if their safety profiles have already been studied adequately before their commercial release? The answer is simple: To make the drugs safer. The next obvious question would be: How would drug monitoring for adverse reactions make the drugs safer, when, according to the general perception, safety is something that is inherent in the physiochemical properties of the drug molecules under consideration? This is because in the formal evaluation of the drug by clinical trials, many of the drug issues related to the safety are inadequately studied. In addition, the formal therapeutic trials are conducted in carefully controlled conditions; in highly selected and limited number of patients, so that the exact safety profile of the drug in the real life situations is not known. Moreover, prior to its release, a drug is studied in just 4,000 cases. Therefore, adverse reactions having frequency less than 0.5 to 1% are missed4. Children, pregnant women, and elderly are not included in clinical trials for ethical reasons. Therefore, the safety of the drug in these cases remains unknown until its release6. Another important drawback of clinical trials is that they can only report adverse reactions that appear within the finite duration of trial. Delayed reactions would be missed. Reporting of adverse drug reactions is done by mainly two methods: spontaneous and intensive. Though plagued by numerous problems like low yield of reports, sub-optimal quality and imperfect nature, these have often served to be a useful source of data or provided early warning signals for the drug related regulatory actions.

Aims of pharmacovigilance[5-7]

1. Detection of severe and unexpected adverse drug reactions to the established drugs and even the minor ones to newer drugs.
2. Identification of the risk factors associated with the development of adverse drug reactions and mechanisms of their causation like Type A, Type B, Type C, etc.
3. Quantitative estimation of the risk factors, incidence, and prevalence of adverse drug reactions. Estimation of the pharmacoeconomic data related to ADRs, e.g. :

- How much is the hospital stay prolonged by ADRs?
- How much is the total cost (direct and indirect) involved in the management of ADRs and what is the cost incurred by the hospital and the nation?

- To what extent ADRs are the cause of hospital admissions?
- What is the total extent of morbidity and mortality caused by adverse drug reactions?

4. Systematic analysis of the obtained data and dissemination to the health agencies, regulatory authorities, pharmaceutical companies, physicians, and other members of the health care system (e.g., nurses, dentists, and paramedics, etc.), so that the safety of drugs and modification of the prescribing patterns can be ensured.

Types of adverse drug reactions

Type-A (Augmented): Commonest (up to 70%) - Dose dependent, severity increases with dose. Preventable in most part by slow introduction of low dosages. Predictable by the pharmacological mechanisms, e.g., hypotension by beta-blockers, hypoglycaemia caused by insulins or oral hypoglycaemics, or NSAID induced gastric ulcers.

Type-B (Bizarre): Rare, idiosyncratic, genetically determined, unpredictable, mechanisms are unknown, serious, can be fatal; unrelated to the dose, e.g. ,hepatitis caused by halothane, aplastic anaemia caused by chloramphenicol, neuroleptic malignant syndrome caused by some anaesthetics and antipsychotics.

Type-C (Continuous drug use): Occurs as a result of continuous drug use. May be irreversible, unexpected, unpredictable, e.g., tardive dyskinesias by antipsychotics, dementia by anticholinergic medications.

Type-D (Delayed): Delayed occurrence of ADRs, even after the cessation of treatment, e.g., corneal opacities after thioridazine, ophthalmopathy after chloroquine, or pulmonary/peritoneal fibrosis by methyserzide.

Type-E (End of dose): Withdrawal reactions. Occurs typically with the depressant drugs, e.g., hypertension and restlessness in opiate abstainer, seizures on alcohol or benzodiazepines withdrawal; first dose hypotension caused by alpha-blockers (Prazosin) or ACE inhibitors.

Type-F (Failure of therapy): Results from the ineffective treatment (previously excluded from analysis according to WHO definition), e.g., accelerated hypertension because of inefficient control.

Dose-related adverse drug reactions: Represent an exaggeration of the drug's therapeutic effects. For example, a person taking a drug to reduce high blood pressure may feel dizzy

or light-headed if the drug reduces blood pressure too much. A person with diabetes may develop weakness, sweating, nausea, and palpitations if insulin or an oral antidiabetic drug reduces the blood sugar level too much. This type of adverse drug reaction is usually predictable but sometimes unavoidable. It may occur if a drug dose is too high (overdose reaction), if the person is unusually sensitive to the drug, or if another drug slows the metabolism of the first drug and thus increases its level in the blood (see Drug Interactions). Dose-related reactions are usually not serious but are relatively common.

Allergic drug reactions: Are not dose-related but require prior exposure to a drug. Allergic reactions develop when the body's immune system develops an inappropriate reaction to a drug (sometimes referred to as sensitization). After a person is sensitized, later exposures to the drug produce one of several different types of allergic reaction. Sometimes doctors do skin tests to help predict allergic drug reactions.

Idiosyncratic adverse drug reactions: Result from mechanisms that are not currently understood. This type of adverse drug reaction is largely unpredictable. Examples of such adverse drug reactions include rashes, jaundice, anemia, a decrease in the white blood cell count, kidney damage, and nerve injury that may impair vision or hearing. These reactions tend to be more serious but typically occur in a very small number of people. Affected people may have genetic differences in the way their body metabolizes or responds to drugs.

Some adverse drug reactions are not related to the drug's therapeutic effect but are usually predictable, because the mechanisms involved are largely understood. For example, stomach irritation and bleeding often occur in people who regularly use aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). The reason is that these drugs reduce the production of prostaglandins, which help protect the digestive tract from stomach acid.

What constitute an ADR report?

1. All adverse drug reactions to both older and newer drugs.[9]

a) Unexpected, severe, and serious reactions to established drugs and minor ones to the newer ones.

b) ADRs to established drugs :

- Chloramphenicol induced aplastic anaemia.

- ACE inhibitor induced ARF in bilateral renal artery stenosis. NSAID induced hepatitis or nephritis (analgesic nephropathy).
- Antithyroid drugs induced granulocytopenia.
- Cisapride induced cardiac rhythm disturbances.
- Phenylpropanolamine induced cerebral haemorrhage.

c) ADRs to newer drugs

- Upper gastrointestinal haemorrhage to COX2 selective NSAIDs.
- Hepatitis by insulin receptor sensitisers- e.g., trogliatazone.
- Adrenal suppression and growth retardation by budesonide.
- Reduced libido by newer selective serotonin reuptake inhibitors like fluoxamine, paroxetine, or sertraline.
- Complete spectrum of ADRs including minor ones like rashes or gastrointestinal upset by herbal antidepressant St John Wort .
- Hypersensitivity reactions (Churg-Strauss syndrome) with montelukast and zafirlukast. Teratogenesis by both newer and older drugs and their safety in paediatric and geriatric population should be reported whenever encountered or systematically studied10.

2. Previously obscure adverse reactions, e.g.

- Hallucinations caused by fluoroquinolones.
- Constipation by clozapine. Oculogyric reactions by antipsychoticshaloperidol.
- Pedal oedema by selective COX-2 inhibitors; tracheoesophageal fistula caused by conventional NSAIDs.
- Hyperthyroidism and hypothyroidism by lithium in the same patient.

3. Unexpected therapeutic benefits that can occur to either newer or established drugs and can accidentally be discovered by careful clinical observations, e.g.

- Lipid lowering effects of paracetamol.
- NSAIDs reduced the risk of Alzheimer's disease.
- Amantidine reduced the manifestation of Parkinson's disease.
- Minoxidil produced hair growth. Sildenafil caused penile erection.
- Lithium increased neutrophil counts in the patients with bone marrow suppression.

4. Proof positive ADRs (ADRs that not only occur once a drug is given and subside on discontinuation, but reappear on readministration – positive re-challenge) e.g.

- Cotrimoxazole induced urticarial rashes.
- Penicillin or cephalosporin allergy.

- Bronchial asthma by NSAIDs in susceptible patients.
- Extrapyramidal disturbances by antipsychotics.
- Jaundice by barbiturates in patients with acute intermittent porphyria

5. Experiences of educational value, e.g.

- Ampicillin induced rashes in patients with infectious mononucleosis.
- NSAIDs may reduce the control of blood pressure by antihypertensives.
- Megaloblastic anaemia and reduced fertitility can occur in female health workers exposed to nitric oxide in anaesthetic care units.
- Indians are less prone to the bone marrow suppressing actions of thioacetazone.
- Asians require lesser doses of antipsychotics than their Caucasian counterparts in the management of schizophrenia. Moreover, adverse effects of antipsychotics in Asians appear at lower dosages than Caucasians.

Causality is assessed using WHO criteria. These ensure that the drug has caused the suspected reaction. There should be a temporal association between drug use and the appearance of an adverse reaction. It should disappear (maybe partially), once the drug is stopped (de-challenge). It should reappear when the drug is reintroduced (rechallenge). However, performing this de-challenge and rechallenge is not always possible in real clinical situations. In these cases, one should use the best judgement about the adverse effect profiles of the drug, underlying disease, concomitant medications, and pattern after removing the most likely offender.

Who can report? How to report? Whom to report to?

These are among the most frequently asked questions by a novice in pharmacovigilance. Health professionals working in the field of delivering the health care (both conventional and unconventional) like physicians, dentists, nurses, pharmacists, can report suspected adverse drug reactions by letter, phone, fax, e-mail, or by personal contact to any of the five adverse drug reaction monitoring centres located across the country.

In most countries, doctors report adverse drug reactions to the authorities concerned on purely voluntary basis. But in some they are required to do so legally. The number of such countries is increasing, following the realisation that clinicians reporting the adverse drug reactions are very low.[11] In many countries, it is mandatory to report all suspected ADRs that occurred in clinical trials to newer drugs to the competent authority.[12]

In India, the clinicians working in the tertiary care hospitals usually do the spontaneous monitoring. A recent study from a large tertiary care hospital from north India showed that in most instances, such reports are sent by the nonfaculty postgraduate students (junior doctors).[9] There are many problems associated with this kind of monitoring. The most important among them being under-reporting or biased reporting. For that matter, all the suspected ADRs should be reported and lack of the evidence of proof or certainty of causality should not be the reason for not reporting. This is because the reports sent by the clinicians are evaluated in a wider perspective, i.e., with the causality assessment criteria and the detailed assessment is done, with the help of all the available pharmacoepidemiological tools.[9-11]

Minor ADRs to the established drugs are given limited significance in pharmacovigilance, but is important in case of newly launched drugs as these are inadequately studied in clinical trials. In the developed countries, the specially designed proforma are sent to the medical practitioners and they in turn send the reports of all suspected ADRs to the concerned authorities. In India, the dissemination of such forms has not yet been started in a large-scale; small and sporadic efforts by individual institutions however continue to be done. The minimum requirements of the informations vary from country to country and institution to institution; most proforma of the ADRs are the variants of the original WHO proforma.[13] Although there is no evidence that the forms designed by individual institutions are better than the WHO proforma, they use their own variants according to their convenience. The information collected in this way is sent to Uppsala monitoring centre of WHO for entry into its global database.[14]

The experts also analyse these reports, and when put forward in the form of hypothesis it is called as ‘signal’ inpharmacovigilance. Thus, ‘signal’ is a hypothesis based upon certain collected reports, which need to be confirmed in subsequent systematic studies. The ultimate aim is to inform the prescribers about the outcome of the study in the form of some conclusion or recommendation, as they may not be aware of the reports sent by other clinicians.[16]

For example, individual physicians have reported 38 deaths to prokinetic agent cisapride and this led to the withdrawal of the drug from the market in the USA. Based upon this information, the drug was banned in Canada and Australia as well. Cisapride is under consideration for banning in India also. Similarly, phenylpropanolamine, an alpha-adrenergic

agonist commonly used in the cough and cold preparations, has been recently linked with increased incidence of stroke (brain haemorrhage). Astute observations have suggested that the risk is more in patients taking it in higher doses, e.g., those using it as an anorectic agent for promoting weight loss. The drug has also been banned in the USA. Thus reporting of the few cases as case reports or series of cases with ADRs are studied systematically and a conclusion is drawn as to whether the risk is considerable enough or whether other safe alternatives to the drug are available? If the answer to any of the above question is yes, the withdrawal of the drug from the market could be considered. The elderly are often the worst hit population by the drug reactions. Others include children and pregnant women, those severely ill, or having history of drug allergy, or taking multiple drugs.

CONCLUSION

Monitoring of adverse drug reactions is an ongoing, ceaseless, and continuing process. Though pharmacovigilance is still in its infancy in India, this is likely to expand in the times to come. This is because, as the newer and newer drugs hit the market, the need for pharmacovigilance grows more than ever before. Therefore, monitoring of the adverse effects of newer drugs particularly of serious nature is mandatory. Physicians should report death due to drugs, lifethreatening complications, hospitalisation (initial or prolonged), disability if significant, persistent, or permanent, congenital anomalies, a reaction which requires medical intervention to prevent damage, such as the administration of N-acetylcysteine following acetaminophen overdose. It is important to remember that most adverse drug reactions would subside once the offending agent is discontinued or dosage reduced; however, many result in permanent damage. The need is to spread awareness about using minimal doses of the drugs, at least in the beginning of the treatment.

For this, students (both undergraduates and postgraduates) need to be trained in drug safety and a habit of rational drug use should be inculcated in them from the beginning. Continuing medical education programmes for physicians and other health professionals should be conducted to make them aware of the methodologies and other technical aspects of the drug monitoring process.

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