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Adverse Drug Reaction Monitoring In India

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Abstract

Adverse drugs reactions (ADRs), put simply, are noxious, unintended, and undesirable effects that occur as a result of drug treatment 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 the physician and the patient. They not only add to spiralling costs of medical treatments, but also cause a great deal of morbidity and mortality. These are generally referred to as 'side effects'. People usually attribute these abnormal effects to either overdose 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 classification 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: large number of patients, poor doctor-patient ratio, self-medication, drugs of alternative systems of medicine, malnutrition, widespread anaemias, presence of counterfeit drugs, and presence of the highest number of drug combinational products in the world. Therefore, incidence of the adverse drug reactions is likely to be same as that of the West, or more. Unfortunately, inspite of presence of five well-organised centres for drug monitoring in the country, the number of reports sent annually are dismal. Most of the adverse drug reactions are, fortunately, preventable. This calls for the urgent need to reinforce the monitoring of adverse reactions to drugs; public education against self-medication, inclusion of reaction monitoring, and an introduction to drug-safety in the curriculum of medical undergraduates, and systemic and periodic continuing medical education of health professionals. This multi-pronged strategy can lead to reduction in the incidence of adverse drug reactions.

The gem cannot be polished without friction, nor medicines perfected without trials. – Chinese proverb.

The Joint Commission on the Accreditation of Healthcare Organisations (JCAHO) defines an adverse drug reaction (ADR) as an undesired effect of a medication that either increases toxicity, decreases desired therapeutic effect, or both[1]. This term covers drug reactions of all degrees of severity and is used with a fair degree of uniformity throughout the world. However, for convenience, other commonly used terms are also described. In European countries, adverse drug monitoring is commonly referred to as pharmacovigilance. The Americans use this term in a broader sense and call it, pharmacoepidemiology. Following the thalidomide disaster of 1961, when Dr. McBride of Australia reported increased frequency of birth defects (seal limbs) that left 10,000 babies disabled for life, monitoring centres were started the world over.

A 1998 report estimated that 1,06,000 Americans die each year as a result of adverse reactions to prescription medications[2]. This figure represents three times the number of people killed by automobiles and is the fourth leading cause of death in the United States. Only heart disease, cancer, and stroke kill more people than adverse reactions to drugs. This staggering figure does not include drugs administered in error, nor those taken as a suicidal intent[3-4]. ADRs increase health care cost by an estimated US $ 1,900 per case.

If medication errors were included in this statistic, the death toll would probably be as high as 1,40,000 deaths per year. As a result of 39 separate studies in the USA, it was found that 3.2 out of every 1,000 hospitalised patients die each year as the result of adverse reactions to prescription drugs[4].

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 in

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India, 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 physicians[3]. 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 missed[4]. 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 release[6]. 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.

Table I : Adverse drug reactions[8].

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.

If adverse drug reactions are considered as any other medical illness and approached in the same way, then many questions would appear like :

What is an adverse drug reaction (Definition)?

What is its importance in the current medical practice (Epidemiology)?

What are the factors related to its occurrence (Aetiology)?

What are the mechanisms of its causation (Pathogenesis)?

What can be done to prevent it (Prevention)?

The last question is indeed the most important one. Many studies from different parts of the world have shown that with timely intervention, many of the adverse drug reactions can be prevented. Focus of the studies in the pharmacovigilance has now shifted from knowing the incidence, patterns, severity, and predictability to prevention. Many programmes and approaches are being tried in the western countries to know what can be done to prevent the adverse drug reactions. This has made the study of pharmacovigilance more relevant than ever before.

Spontaneous adverse drug reaction monitoring is the structured countrywide system of reporting of suspected effects of the drugs. This has at many times served to be the early warning system for regulatory action related to the particular drug. The vigilant clinicians during their routine clinical work might encounter many adverse drug reactions worth reporting. Publications of series of cases or individual case reports in the medical journals are examples of spontaneous drug monitoring. Intensive adverse drug monitoring on the other hand, is a systematic method of data collection of reports of ADRs in the hospital setting.

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 COX-2 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 studied[10].

2. Previously obscure adverse reactions, e.g.:
   - Hallucinations caused by fluoroquinolones.
   - Constipation by clozapine.
   - Oculogyric reactions by antipsychotics-haloperidol.
   - 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 (re-challenge). However, performing this de-challenge and re-challenge 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.

Indian scenario

Monitoring of adverse drug reactions started in India about two decades ago (1982). Under the chairmanship of the Drug Controller of India, five centres were established with the idea of starting a monitoring

programme nationwide. It consisted of three phases: the first one being monitoring of reactions in the institutes, second one in governmental bodies like CGHS, and the third phase proposed to include general practitioners. A multi-institutional pilot study involving 58,194 cases was done in 1987 under the aegis of Indian Council of Medical Research. Its nodal centre (National Pharmacovigilance Centre) is located in the Department of Pharmacology, All India Institute of Medical Sciences, New Delhi. It is affiliated to WHO collaborating Centre for ADR Monitoring, Uppsala, Sweden. The others are located in PGI (Chandigarh), JIPMER (Pondicherry), KGMC (Lucknow), and Seth GS Medical College (Mumbai) – special centre. It was envisaged to be a collaborative activity of both clinicians and pharmacologists; now in India, the pharmacologists with or without the involvement of clinicians usually do it[9]. Physicians, however, continue to play a meaningful role in the entire monitoring process, as the co-operation of the clinicians is needed to have an access to the patient data and at times in interpretation of the reports of suspected adverse drug reactions. In many other countries, the pharmacists or nurses usually carry it out under supervision[10-11]. They are specially recruited for this purpose; physicians and pharmacologists are involved in the interpretation of the collected data or hypothesis testing on the basis of the reports. These workers may involve a panel of the physicians in reviewing all the collected reports. Though the pattern of adverse reactions differs slightly from country to country, adverse reactions to analgesics (mainly, non-steroidal anti-inflammatory drugs) and antibiotics constitute about half of all such reports in India[9]. This may be partly due to the fact that these are the most commonly used drugs in therapeutics.

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 non-faculty 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' in

pharmacovigilance. 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.

What can be done to decrease ADRs?

The simplest way to prevent most adverse drug reactions is to use the minimum dosages of drugs[15]. The simple principle of 'start low and go slow' should be followed. Dosages should be individualised to the patients and drugs should be tailored to patient's need and not the *vice versa*[4]. Health professionals should periodically be educated about adverse reactions and should be encouraged to report the same. Students should be taught principles of drug safety and rational drug use in their undergraduate and postgraduate curriculum. History of drug allergy should be elicited, and renal and hepatic status of the patient should be known before drug use. This is because failure to adjust drug dosages results in adverse drug reactions in cases with renal/hepatic impairment[16].

Recently, the US FDA has developed a Med Watch Program (1993) specifically designed for the reporting of adverse events relating to medical products, equipment, and medication. Both, health professionals and consumers, are encouraged to use Med Watch. The purpose of reporting is to facilitate monitoring and investigation. The goal of an investigation by the FDA is to prevent the occurrence of further adverse reactions, some of which result in hospital admissions, permanent disabilities, birth defects and/or increased medical or surgical care to prevent permanent impairment or damage[17].

Another advantage of reporting to Med Watch is that this group aims to ensure that new safety information is quickly communicated to the health professionals, thus reducing further incidents. We in India, need to start a similar programme for online submission of drug reports. That will ensure anonymity as well, as many physicians think that such reporting may carry some legal obligation with it. It should be remembered that occurrence of adverse reactions are natural accompaniments of drug treatment due to their inherent properties. They can be prevented through diligent and rational use of drugs. A physician cannot, in any terms, be held responsible for occurrence of such reactions provided he has not been rash in using them, and drug usage is not in any way linked to negligence. Therefore, no clinician should refrain from reporting on this basis.

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, life-threatening 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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ANNOUNCEMENT

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