

Adverse Drug Reaction: An Impediment to Patent Compliance

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Abstract- The high incidence of Adverse drug reactions (ADRs) is a global health problem requiring the attention of all healthcare professionals. Adverse drug reactions have been reported as a significant cause of morbidity and mortality among all age groups, with prolonged hospitalisation imposing a substantial financial burden on society. This review provides a detailed overview of the adverse reactions and factors contributing to adverse reactions. Additionally, we discussed the role of healthcare professionals in reporting ADR. A review of the literature was done on PubMed, EMBASE and SCOPUS using keywords such as Adverse drug reactions, Pharmacovigilance, factors affecting ADR etc. Healthcare professionals play a crucial role in Pharmacovigilance system & require considerable knowledge and expertise in the field of medication safety, especially for early detection, management and reporting of ADRs. Drug safety assessment must be considered an integral part of the daily clinical practice of healthcare professionals. The two primary steps to be followed for prevention of ADR is to identify the patients likely susceptible to ADR and modify the treatment accordingly.

Keywords- Adverse drug reactions, Hospitalization, Pharmacovigilance, Medication, Treatment.

INTRODUCTION

According to World Health Organization (WHO), ADR is a response to a medicinal product which is noxious, unintended & occurs at doses typically used in man for prophylaxis, diagnosis or therapy of disease or the restoration, correction or modification of physiological function. It is universally accepted that No Drug is free from side effects.^{1,2} The aetiology and nature of adverse drug events are often complex and multifactorial. ADR can be divided into immunological and non-immunological etiologies. Most ADR (75% to 80%) are predictable, non-immunological effects. The remaining 20% to 25% of ADR are unpredictable effects that may or may not be immune-mediated. Immune-mediated reactions account for 5% to 10% of all drug reactions and establish true drug hypersensitivity, with IgE-mediated drug allergies falling into this group.³ Type A and B drug reactions Adverse drug reactions can be categorised into two main categories: type A and type B. Type A reactions are the most common and predictable and can develop in any individual. Type B reactions are unusual and unpredictable and only occur in susceptible individuals.⁴ Type A reactions are the most frequent, observed in 25–45% of patients. These represent an exacerbation of the Drug's known primary and secondary pharmacological effects. They are dose-dependent and could probably be avoided or foreseen.⁵ In contrast, type B or idiosyncratic drug reactions could not be explained based on the drug's pharmacology and do not have an apparent dose-response relationship in susceptible individuals. They are often undetected until the drug has been marketed and are generally correlated with high mortality. Genetically determined changes in drug-metabolizing enzymes can predispose to pharmacological and idiosyncratic toxicity. Defect in a single gene account for only a minority of ADRs. The predisposition of adverse reactions, particularly of a distinctive nature, seems to be multifactorial, involving defects in multiple genes and environmental factors such as concurrent infections.⁶

Most adverse medication events are associated with prescription errors. The awareness of the risk factors of ADRs can help physicians to recognise the patients with increased risk of ADRs. This review focused on the analysing and reporting of ADR. A review of the pieces of literature was made based on PubMed, the Cochrane database of systematic reviews, and EMBASE. Keywords used were: medication error, adverse drug reaction, factors affecting ADR, prevention of ADR, and Pharmacovigilance.

Factors affecting the incidence of ADR

Contributing factors affecting the incidence of ADRs are subdivided into five groups; Patient-related factors, social factors, Drug-related factors, Disease-related factors and ADR-related factors.

1. Patient-related factors

1.1 Age

All medicines can induce side effects, but not all patients develop the same level and type of side effects. Age is a crucial factor which contributes to the occurrence of side effects. Elderly patients with multiple medical conditions, those with polypharmacy, those with a history of adverse effects, and patients with reduced ability to eliminate medications have an increased risk of adverse effects.⁷ Infants and very young children have an increased chance for ADRs because the ability to metabolise the Drug is not thoroughly evaluated. Below are some factors that may influence the development of ADR in newborns.⁸

★ Newborns have an immature renal tubular function; digoxin, aminoglycosides, ACE inhibitors and NSAIDs should be avoided when they are less than eight weeks old.⁹

- ★ Physiological hypoalbuminemia in newborns influences the dosage of drugs. Caution should be taken when handling drugs with high protein content, such as NSAIDs.¹⁰
- ★ Newborns have low body fat; may be affected by fat-soluble drug.¹¹
- ★ Increased effect of anaesthetics due to immature blood-brain barrier at <8 weeks of age.¹²

1.2 Gender

Drug effects are influenced by the biological differences between males and females. The anatomical and physiological differences are body weight, composition, gastrointestinal tract factors, liver metabolism, and kidney function. Women have lower body weight and organ size, more body fat, different gastric motility and lower glomerular filtration rate than men. These differences can alter the pharmacokinetics and pharmacodynamics of drugs, including absorption, distribution, metabolism, and elimination.⁷

1.3 Allergy

Drug-independent cross-reacting antigens can lead to sensitisation, which can develop into drug allergy. The medical literature supports the existence of such cross-reactivity.¹³ After Primary sensitisation to the inducing drug, a second exposure to the drug cause affected T cells and antibodies to enter the elicitation phase, corresponding to types I to IV immune responses. The most common drug allergies are type I or IV reactions; type II and III reactions are rarely encountered.¹⁴ Immune complex formation, a joint event in a normal immune response, usually occurs without symptoms. Rarely do immune complexes bind to endothelial cells and lead to the deposition of complement-activated immune complexes in small blood vessels.¹⁵ Clinical manifestations of a type III reaction include serum sickness (e.g., lactams), medication-induced lupus erythematosus (e.g. quinidine), and vasculitis (e.g. minocycline).¹⁶ T-cell-mediated drug hypersensitivity can have a variety of clinical manifestations, from the involvement of the skin itself to fulminant systemic disease. These are often sulfa antibiotics and b-lactams.¹⁷

2. Social factors

2.1. Alcohol drinking

The metabolism of many drugs is influenced by alcohol and facilitates the occurrence of side effects. Alcohol-drug interactions refer to the possibility that alcohol may alter the severity of the development of adverse effects, making it more toxic or harmful to the patient, either in a pharmacokinetic or pharmacodynamic manner.¹⁸ Co-administration of alcohol with some medications may induce side effects like nausea, headaches, drowsiness, vomiting, fainting, and hypotension.¹⁹ A patient with peptic ulcer, ex-peptic ulcer, or gastritis who takes alcohol with NSAIDs can cause internal bleeding due to severe ulceration.²⁰

2.2 Smoking

Smoking is one of the risk factors for many diseases, such as peptic ulcer, cancer and cardiovascular disease.²¹ Effect of tobacco on liver enzymes can alter the metabolic process as it is a potent inducer of isoenzymes 1A1, 1A2 and eventually 2E1 of liver cytochrome P-450 (CYP).²² Induction of metabolism of the drugs, which are substrates for hepatic CYP1A2 in smokers, leads to a clinically significant reduction in pharmacological effects.²³ These drug interactions are not caused by nicotine. They are caused by tobacco. Because nicotine stimulates the sympathetic nervous system, it can counteract the pharmacological effects of some drugs.²⁴

3 Drug-related factors

3.1 Polypharmacy

Taking several prescription or over-the-counter medications contributes to increased ADR risk. The number and severity of ADRs increase disproportionately with the increasing number of drugs administered.²⁵ Many conditions can result in polypharmacy; patients may suffer from more than one disease, especially among the elderly. Patients may seek multiple prescribers for different illnesses, acute or chronic conditions. Adverse effects may develop due to drug interaction, synergism, duplication, additive effect, discontinuation of treatment, change of dose to save money, omission of certain drugs and physiological antagonism. One important reason for the development of adverse effects from polypharmacy is the inability of some patients, especially the elderly, to follow their medication, regardless of how well the Drug may work when given alone.⁷

3.2 Drug doses and frequency

Drug dosage influences the development of adverse effects in many ways; e.g. some medicines should be administered in the morning and others in the evening, some at bedtime. Taking bisphosphonates at bedtime can lead to esophagitis. The antiplatelet effect of aspirin, when taken in the evening, is more vital than in the morning.²⁶ Dosage should be considered as a factor that may have a specific influence on the occurrence of adverse effects.

3.3 Disease-related factors (accompanied diseases)

A patient's co-morbidity may also affect susceptibility to ADRs. For example, increased frequency of idiosyncratic toxicity with anti-infectives such as trimethoprim-sulfamethoxazole.²⁷ Multiple diseases make patients more vulnerable to adverse effects due to multiple medications. If other conditions accompany hypertension, these diseases can affect the body's response to antihypertensive drugs because metabolic processes in the body will be negatively affected. In patients with renal failure, the effect of drugs on the kidneys is reduced due to the loss of the site of action of these drugs. This leads to an increase in the dose, leading to more side effects.

Preventing Adverse Drug Reactions

While some adverse events are unpredictable—such as anaphylactic reaction in a patient following a single prior accidental exposure to a penicillin-containing antibiotic—many are preventable with reasonable anticipation and monitoring. Prevention (or avoidability) typically refers to situations where a drug treatment plan is not consistent with current evidence practice or is unrealistic due to known circumstances.²⁸ Epidemiological studies usually find that a third to a half of adverse events are (at least potentially) preventable, although preventability is much easier to diagnose in hindsight. However, interventions that reduce the

likelihood of ADRs are crucial to reducing the risk of patient harm. The two primary steps that can be followed to prevent an ADR from occurring:

- a. Identify the patients likely susceptible to ADR and modify the treatment accordingly.
- b. Ensure the treatment plan mitigates any adverse effects.

Identifying susceptibility

Knowing the susceptibility of patients can influence your prescription writing and reduce the adverse effect. The patient's medical history helps identify any previous adverse effects and prevents re-exposure to the Drug. In other cases, susceptibility factors such as age, gender, pregnancy status, and ethnicity may help predict ADR risk. For example, a NICE guideline suggested that patients of African or Caribbean descent should be prescribed an angiotensin-II receptor blocker in favour of an angiotensin-converting enzyme (ACE) inhibitor for hypertension because of ACE inhibitor-induced angioedema. Pharmacogenetics is beginning to yield more personalised drug selection by predicting who is more susceptible to a particular ADR. Clinical decision support systems can inform the physician of specific patient warnings for treatment or additional monitoring requirements to reduce harm. Practitioners should not rely on it for decision support as methods vary widely in providing information, ranging from no relevant alerts to information overload leading to alert fatigue.²⁹

Treatment plan

Treatment plans should attenuate the potential side effects. For example, co-prescribing folic acid with methotrexate will reduce the incidence of folate-related adverse effects. It is important to remember that judicious prescribing can also eliminate the use of drugs, and a treatment plan should always consider non-pharmacological or conservative options. Overall, a systemic approach involving multiple strategies and involving the patient and all healthcare professionals is needed to reduce the risk of adverse effects and to avoid these avoidable reactions in practice³⁰.

Analysis & Reporting Of Adverse Drug Reactions

According to the WHO, Pharmacovigilance is the science and activities relating to detecting, assessing, understanding, and preventing adverse effects or any other possible drug-related problem, especially long-term and short-term adverse effects.³¹⁻³⁴ Adverse events are more frequent with multidrug therapy, and with each additional Drug a patient takes, the chance of an ADR episode is multiplied by 1.14, directly extending the length of stay.^{35,36} Adverse reactions can also result in reduced quality of life, increased physician visits, hospitalisations, and even death. Early detection and effective communication by Pharmacovigilance help to minimise or prevent adverse events, which ultimately helps each patient to receive optimal treatment. Drug safety monitoring is, therefore, a crucial element of the health care system and high-quality medical care. The WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre) has a strong network of 194 Member States worldwide. These countries gather, review and report suspected adverse reactions to the Uppsala Monitoring Centre, which enters them into the WHO database (the most extensive database with more than 3.5 million case reports).³⁷ In India, the Ministry of Health and Welfare (MoHFW) launched the National Pharmacovigilance Program of India (PPI) in 2010. Criteria for Reporting ADR to the Regulatory Authority in India

What to report?

- ★ Life-threatening condition or death
- ★ Prolonged hospitalisation of the patient
- ★ Results of congenital anomaly
- ★ Medically significant conditions
- ★ Lack of efficacy related to a medical device or pharmaceutical product.
- ★ All drug interactions that are suspected
- ★ All adverse reactions arising from a vaccine or Drug [38].

When to report?

- ★ All spontaneous cases must be reported within ten days.
- ★ All suspected ADRs should be reported as soon as possible
- ★ Death incidents should be reported at the earliest, whereas all other severe ADRs/incidents must only be reported within seven days.
- ★ All non-serious cases must be reported within a month.
- ★ A delay in reporting may cause serious problems.³⁸

Who can report?

Professionals working in a healthcare team are the preferred sources of information in PV, for example, Medical specialists, Pharmacists, Dentists, and Midwives. The patient's relatives, witnesses or any familiar person may report along with the HCPs patient after medical confirmation.³⁸

Where to report?

Peripheral PV centre: It is a primary centre for collecting ADR. It comprises small medical centres, private hospitals, nursing homes, pharmacies etc. ADRs are recognised and integrated by RPCs or ZPCs. Every state and some primary medical colleges in India are part of the peripheral centre.³⁸

Regional PV centre: It is considered a secondary PV centre located in a medical college with more extensive facilities. They are identified and synchronised by zonal centres. There are five regional centres in India.³⁸

Zonal PV centres: This tertiary PV Centre is generally located in the metro city's medical college having sufficient facilities. It has been identified by CDSCO and serves as the first ADR data collection centre. The Zonal PV centre for both the North and East zone is AIIMS³⁸.

Healthcare Professionals in the Pharmacovigilance System

Healthcare professionals perform a crucial role in the Pharmacovigilance system. It requires significant knowledge and competence in drug safety to successfully contribute to the field through early recognition, management and reporting of drug safety issues. Furthermore, the healthcare team should be well-educated on the necessity and procedure of reporting adverse events. They should not have a combination of training and research skills in this area. Despite global drug safety concerns, healthcare professionals still lack awareness and knowledge of Pharmacovigilance and adverse event reporting. In addition, recent studies have shown that healthcare providers do not report adverse effects, especially in developing countries. It has been reported that only 2-4% of all adverse events and 10% of serious adverse events are reported worldwide. Healthcare professionals, including doctors, pharmacists and nurses, are strongly encouraged to report any suspected ADR, especially reactions to newly registered medicines and solemn events. Therefore, drug safety assessment must be considered an integral part of the daily clinical practice of healthcare professionals.³⁹

CONCLUSION

Elderly patients with comorbid conditions, polypharmacy, a history of adverse effects, and patients with reduced ability to eliminate medications have an increased risk of adverse effects. Attention to the contributing factors of ADR and Health professionals' knowledge and perception of the safety profile of drugs are essential for the prevention of unwanted drug actions. Reporting of suspected reactions to Drug Regulatory Authorities facilitates the detection and evaluation of drug safety.

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