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ADVERSE DRUG REACTIONS: A REVIEW

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ABSTRACT

Adverse drug reactions (ADRs) are types of adverse drug events (ADEs). ADEs include ADRs, medication errors, and other drug-related problems. Adverse drug reaction can be defined as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.” Such reactions are currently reported by use of WHO's Adverse Reaction Terminology, which will eventually become a subset of the International Classification of Diseases. Adverse drug reactions are classified into six types (with mnemonics): dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure). Timing, the pattern of illness, the results of investigations, and rechallenge can help attribute causality to a suspected adverse drug reaction. Management includes withdrawal of the drug if possible and specific treatment of its effects. Suspected adverse drug reactions should be reported. Surveillance methods can detect reactions and prove associations.

INTRODUCTION

Definitions

According to World health organization (WHO) an Adverse drug reaction (ADR) is any response to a drug that is noxious and unintended, and occurs at doses used for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose[1]. The Food and Drug Administration (FDA) focuses on ADRs that have unexpected reactions and/or those of more significant morbidity. These ADRs would include those where the patient outcome is death, life-threatening, hospitalization, disability, congenital anomaly, or required intervention to prevent permanent impairment or damage[2]. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) is concerned with the reporting of significant ADRs. Those that result in morbidity, require additional treatment, require an increased length of stay, temporarily or permanently cause disability, or cause death must be reported to the FDA[3]. The American Society of Health-System Pharmacists (ASHP) defines significant ADRs as any unexpected, unintended, undesired, or excessive response to a drug that includes the following:

- Requires discontinuing the drug
- Requires changing the drug therapy
- Requires modifying the dose
- Necessitates admission to the hospital
- Prolongs stay in a health care facility
- Necessitates supportive treatment
- Significantly complicates diagnosis
- Negatively affects prognosis/results in temporary or permanent harm, disability, death[4]

The ASHP definition does not include reactions due to drug withdrawal, drug abuse, poisoning, or drug complications.

Other terms that may be included as ADRs are side effects, drug intolerance, idiosyncratic reactions, toxic reactions, allergic reactions, or hypersensitivity reactions[5]. Side effects are reactions that are unintended and unwanted but are known pharmacologic effects of the drug and occur with predictable frequency. Drug intolerance is a mild reaction to a drug that results in little or no change in patient management. Idiosyncratic reaction is an unexpected response that occurs with usual dose of a drug. Toxic reaction is a predictable response that results from greater than recommended drug dosages or drug concentration in the body. Allergic or hypersensitivity reaction is an unusual sensitivity to a drug of an immunologic nature.

Classification of ADR

ADRs can be classified according to the pharmacologic effect of the drug.

Type A, B, C, and D reactions.

Type A reactions Are exaggerated but normal pharmacologic actions of a drug. They are predictable and dose dependent.

Type B reactions Are not predictable given the known pharmacologic action of a drug and are not dose related. Many of these Type B reactions are hypersensitivity or immune-based. These reactions can be further subdivided into type I (IgE-mediated reaction), II (IgG or IgM-mediated cytotoxic reaction), III (IgG-mediated immune complex reactions), and IV (cell-mediated immune reaction).

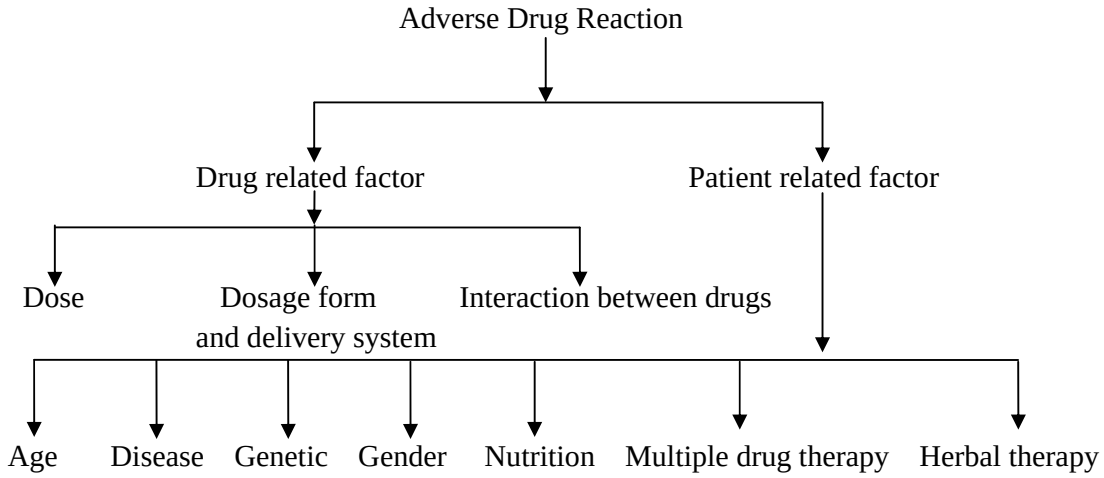
Type C reactions Are those due to long-term use of a drug.

Type D reactions Are delayed drug effects, such as due to carcinogenicity or teratogenicity.

ADRs can also be classified according to the dose relationship, i.e., dose-related and non-dose-related reactions. Another classification system is based on the causal relationship between the reaction and the drug. One of the most widely used causality classifications is based on Naranjo's descriptions. These categories include definite (drug is likely the true cause), probable (drug is the apparent cause), possible (drug appears to be associated), and remote (drug is not likely to be the cause). The fourth classification system is based on degree of injury or severity of reaction. There are mild reactions (temporary discomfort and tolerable), moderate (significant discomfort), and severe (potentially life threatening or causing permanent disability or death)

Factors related to ADRs

Factors related to ADRs are classified as below:



Drug related factor includes

a) **Dose** ADRs may be the result by taking increased amounts of a drug. Dosing issues are especially likely with narrow therapeutic index drugs. Examples can be digoxin, anticoagulants, anticonvulsants, antiarrhythmics, antineoplastic agents, bronchodilators, sedatives, and hypnotics[6].

b) **Dosage form and delivery system** Many of the ADRs related to the dosage form and delivery system are the result of local irritation or hypersensitivity reactions[7]. Local irritation to the gastrointestinal (GI) tract can occur with oral dosages. For example, toxicity resulting in mouth ulcerations is associated with antineoplastic drugs. In addition, the use of certain formulations, such as sustained release preparations, can increase esophageal injury if esophageal transit is delayed. For example, a controlled release wax matrix of potassium chloride has been associated with significant esophageal erosions. Factors identified to predispose to esophageal injury include large film-coated tablets, capsules, large sustained-release preparations, rapidly dissolving formulations, and ingestion of solid oral dosage forms before bed rest with very little water intake[7].

c) **Interaction between drugs** It has been estimated that 6.9% of ADRs are due to drug–drug interactions[5]. The most likely reason for an adverse drug interaction is the pharmacokinetic changes that result in altered metabolism or excretion of drugs, or the pharmacodynamic changes that result in synergistic or additive effects of drugs.

2) Patient related factor Age, disease states, genetics, gender, nutrition, multidrug therapy use, and herbal therapies use are patient-related factors that influence the likelihood of adverse drug reactions.

a) **Age** Age-related alterations in pharmacokinetics and pharmacodynamics may affect the response of elderly patients to certain medications, and may increase the susceptibility for ADRs among elderly patients[8,9]. The risk of ADRs among elderly patients is probably not due to age alone. ADRs may be related more to the degree of frailty and medical conditions of the patient[9]. On average, older persons have five or more coexisting diseases that may increase the risk of adverse events. Polypharmacy seems to be more of a common problem among the elderly. The average elderly patient takes 4.5 chronic medications and fills 13 prescriptions yearly[9]. Elderly patients appear to have a decline in homeostatic mechanisms. The imbalance of homeostatic mechanisms and the decline in function reserves may put a patient at greater risk for ADEs due to decreased tolerance of medications and the ability to handle stressful situations[10].

Age related factor in children The two factors responsible for increasing risks of ADRs in children are pharmacokinetic changes and dose delivery issues[11]. It is important to note that only one-fourth of the drugs approved by the FDA have indications specific for use in a pediatric population[11]. Medications used in adults are often given to children without FDA safety and efficacy data. Compatibility and stability issues with dosage forms intended for adults that have been altered (e.g., dilution or reformulation) can increase risks for ADRs. Information on pediatric age-related difference in neonates, children, and adolescents may aid in prevention of pediatric ADRs[12]. Further studies of drug use in pediatrics are needed in order to prevent ADRs

b) Disease Such as hepatic or renal diseases can influence the incidence of ADRs by altering the pharmacokinetics of drugs, such as absorption, distribution, metabolism, or excretion[5]. Hepatic disease Patients with liver disease have an increased susceptibility to certain drugs due to decreased hepatic clearance for drugs metabolized by the liver or due to enhanced sensitivit[y5]. For example, impaired hepatic metabolism can precipitate central nervous system (CNS) toxicity in patients on theophylline, phenytoin, or lidocaine; or ergot poisoning on ergotamin[e13]. Increased sensitivity to drugs is also encountered in liver diseas[e13]. The use of anticoagulants increases the risk of bleeding due to the reduced absorption of vitamin K or decreased production of vitamin K-dependent clotting factors. There is an enhanced risk for respiratory depression and hepatic encephalopathy due to morphine or barbiturates in patients with severe liver disease. Vigorous use of diuretics can precipitate hepatic coma due to potassium loss in liver disease. There is an increased risk of hypoglycemia with sulphonyl urea antidiabetic drugs due to decreased glycogenesis in liver disease. Liver disease can also cause hypoalbuminemia due to decreased liver synthesis of albumin. For drugs that are extensively bound to albumin, such as phenytoin, an enhanced risk of drug toxicity could occur because of the increase in free drug concentration. There are no useful methods to quantify the degree of liver disease that can assist in dosage adjustment. A practical approach involves checking patients for elevated prothrombin time, rising bilirubin levels, and/or falling albumin levels. In such instances, drugs that have an altered response in liver disease or cause hepatotoxicity need to be avoided.

Renal disease Impaired renal function increases the incidence of ADRs for drugs that depend on the kidney for their elimination. Unlike liver disease, use of pharmacokinetic dosing principles can minimize the risk for adverse effects. Mechanisms responsible for enhanced ADRs in renal disease include delayed drug excretion, decreased protein binding due to

hypoalbuminemia, and increased drug sensitivity[5]. Delayed renal excretion is responsible for enhanced toxicity with drugs such as aminoglycosides, digoxin, vancomycin, chlorpropamide, H2-antagonists, allopurinol, lithium, insulin, and methotrexate[14]. For some drugs, the accumulation of a toxic metabolite during renal failure is responsible for ADRs. This is the case with meperidine, where a toxic metabolite, normeperidine, accumulates in renal failure[14]. Patients with accumulation of uremic toxins have increased sensitivity to certain drugs. There may be an enhanced response to CNS depressants (such as barbiturates and benzodiazepines), hemorrhagic effects from aspirin or warfarin, and other bleeding effects from antibiotics that inhibit platelet aggregation, such as carbenicillin, ticarcillin, and piperacillin.

Other diseases On theoretical grounds, other diseases associated with hypoalbuminemia could predispose patients to adverse reactions and to altered responses to drugs that are highly protein bound.

c) **Genetics** Genetic factors account for some ADRs due to either altered pharmacokinetics or by altering tissue responsiveness. Altered metabolism of drugs occurs due to differences in hydrolysis, acetylation, and hepatic oxidation of drugs. Altered pharmacodynamic reactions could be either an exaggerated response or a qualitative response. These types of reactions are unpredictable[5].

d) **Gender** A higher incidence of ADRs has been reported for women in comparison to men[5]. One reason for this observation is that women take more drugs than men. Yet, no sex-linked differences in drug pharmacokinetics have been documented. Other reports have not supported a higher incidence of ADRs in women as compared to men. Thus, sex alone is unlikely to be a major determinant of ADRs.

e) Nutrition Nutritional factors are also responsible for ADRs. These factors include the interaction of drugs and nutrients, and altered pharmacokinetics related to nutritional status.[15] Three mechanisms postulated for drug–nutrient interactions are interference with drug absorption, alteration of drug excretion, and affecting drug activity. For example, the absorption of tetracycline is reduced by chelation with iron, calcium, and magnesium. Foods that acidify or alkalinize the urine can affect drug excretion. Foods that contain a large amount of vitamin K can inhibit the activity of warfarin[15,16].

f) **Multi drug therapy use** According to several epidemiological studies, multiple drug use has a strong association in the causality of ADRs. It has been suggested that the more medications used, the higher the risk for ADRs[17]. Consistent drug regimen reviews by healthcare providers in order to reduce polypharmacy may decrease the risk of ADRs.

g) **Herbal therapies use** The use of herbal therapies increased dramatically during the 1990s. Herbal therapy sales are estimated to be $4 billion a year, with sales increasing at 20% per year since the early 1990s[18]. Patients often mistakenly believe that since these products are natural, they do not possess the potential harm as in prescription medications. Since herbal medications are sold and marketed without stringent FDA approval and guidelines, limited evidence-based data on efficacy, adverse effects, and drug interactions exist[18,19]. For most conditions, herbal products are not a replacement for proven prescription or nonprescription drugs. Patients should be aware that health care practitioners cannot guarantee the safety and consistency of herbal products. Patients should start with the recommended effective doses and report any unusual side effects to their health care practitioner. Patients should always consult with their pharmacist for possible drug–herbal interactions. Side effects and possible drug interactions for the ten most commonly used herbals are listed in Table 1.

Table 1: ADRs for the top ten herbal medicines

Herbal	Common use	Side effects and interactions
Echinacea	Treatment and prevention of upper respiratory infections, common cold.	Rash, pruritis, dizziness, unclear long-term effects on the immune system.
St. John's wort	Mild to moderate depression.	Gastrointestinal upset, photo-sensitivity. Mild serotonin syndrome with the following medications: paroxetine, trazodone, sertraline, and nefazodone. May decrease digoxin levels. May decrease cyclosporine serum concentrations. Combined oral contraceptives—breakthrough bleeding.
Gingko biloba	Dementia	Mild gastrointestinal distress, headache, may affect warfarin. Interaction with aspirin (spontaneous hyphema)
Garlic	Hypertension, hypercholesterolemia.	Gastrointestinal upset, gas, reflux, nausea, allergic reactions, and antiplatelet effects.
Saw palmetto	Benign prostatic hyperplasia.	Uncommon
Ginseng	General health promotion, sexual function, athletic ability, energy, fertility	High doses may cause diarrhea, hypertension, insomnia, nervousness, may affect warfarin.
Goldenseal	Upper respiratory infections, common cold.	Diarrhea, hypertension, vasoconstriction.
Aloe	Topical application for dermatitis, herpes, wound healing, and psoriasis, orally for constipation.	May delay wound healing after topical application. Diarrhea and hypokalemia with oral use.
Siberian ginseng	Similar to ginseng	May raise digoxin levels.
Valerian	Insomnia, anxiety	Fatigue, tremor, headache, paradoxical insomnia (not advised with other sedative-hypnotics)

Preventing Adverse Drug Reactions ADRs are problematic in that they cause significant morbidity and mortality. Almost 95% of ADRs are Type A (predictable) reactions, and thus with quality improvement measures, ADRs can be avoided and prevented[20]. Knowledge of causative factors and an increase in patient education may help prevent ADRs. Improvements in the documentation of allergic reactions (e.g., via computer tracking), development of tools to enhance compliance, and application of tools to improve prescribing and administration of drugs are other preventative approaches to ADRs.

DISCUSSION

Adverse drug reactions are of significant concern in the pharmaceutical technology arena. Various drug and patient factors that predispose to ADRs have been identified. Reporting systems used to screen and assess ADRs facilitate the understanding of risk factors and contribute to the development of systematic improvement in the prevention of ADRs.

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