Chapter ... 4

ADVERSE DRUG REACTIONS

♦ **LEARNING OBJECTIVES** ♦

After completing this unit, reader should be able to:

- ❖ Know adverse drug effects and its types.
- ❖ Describe the mechanism involved in drug interaction.
- ❖ Know different adverse effects and its management.

4.1 INTRODUCTION

Undesirable or harmful effects which can occur at therapeutic doses and need a reduction of dose or drug withdrawal. All drugs are poisons until used judicially. Every drug acts on all systems of the body, e.g. aspirin used for headache also acts on GIT and blood producing side effects. Preventing and detecting adverse effects from medicine is termed as Pharmacovigilance.

WHO defines an adverse drug reaction as "any noxious and unintended effects of drug which occur at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological functions".

Adverse drug effects include:

- Nausea and vomiting.
- Deafness with gentamycin.
- Death with penicillin.

4.2 TYPES OF ADVERSE DRUG REACTIONS

Adverse drug reactions are of five types; A, B, C, D and E.

1. **Type A reactions [Augmented]:** Type A reactions are common and constitute 75% of all adverse reactions. These are related to pharmacological actions and are dose-dependent. Type A reactions are predictable and can be avoided by adjusting the dosage regimen. Most of them are reversible upon stopping drug. Examples include:
   - Hypotension (antihypertensives).
   - Hypoglycaemia (insulin)

(a) **Excessive therapeutic effect:** Unwanted effects related to the main pharmacological actions of the drug that occur when the drug produces greater therapeutic effect than is necessary.

Example: Warfarin is an anticoagulant but may lead to bleeding tendency. Insulin is used for normoglycemia but may produce hypoglycaemia.

(b) **Side Effects:** Unwanted effects unrelated to the main pharmacological actions of the drug but due to other normal actions of the drug.

Example: Morphine may cause constipation during its use as analgesic.

2. **Type B reactions [Bizzare] or Idiosyncratic effect:** Type B reactions are bizarre reactions, not related to the normal pharmacological actions of the drug. They are unpredictable and not dose-related. They occur only in minority of patients. Test dose can be given for judgement.

Types:

(a) Allergic reactions (Hypersensitivity).

(b) Genetic disorders (Idiosyncrasy).

- **Hypersensitivity (allergic reactions):** Abnormal response to the drug due to antigen-antibody reactions e.g. Penicillin. These are the allergic responses to a drug. They include rashes, hypotension and bronchospasm (anaphylactic reaction).
- **Idiosyncrasy:** Idiosyncrasy is abnormal response to the drug due to genetic disorders. E.g. Succinylcholine apnea, malignant hyperthermia, Favism, Porphyria.

Secondary Effects: Unwanted effects that occur secondary to the wanted actions of the drug. Examples include overgrowth of microorganisms following use of broad spectrum antibiotics.

3. **Type C reactions (Continuous reactions):** Type C reactions are due to long term use e.g. NSAIDs causing analgesic nephropathy due to long term usage of drugs and changing doses.

4. **Type D reactions (Delayed adverse reactions):**

- **Teratogenesis** is congenital malformations occurring in the foetus due to exposure to drugs during pregnancy.
  E.g. Thalidomide may produce phocomelia (abnormal limbs).
- **Carcinogenesis** is the ability of some substances to induce cancer.
  E.g. Stilbesterol may cause adenocarcinoma of vagina in female offsprings.

Mechanisms:

- **DNA alteration:** Griesofulvin (antifungal) and alkylating cytotoxics (cancer), they are anti-mitotic, acting on spindle formation.
- **Immunosuppression:** Immunosuppressant increase incidence of cancer e.g. organ transplantation and methotrexate in rheumatoid arthritis.
- **Hormonal:** Long term use of estrogen replacement in post-menopausal therapy may induce endometrial cancer.

5. **Type E reactions (Ending of drug):** Sudden discontinuation (abrupt withdrawal) may lead to rebound adrenal insufficiency. e.g. Corticosteroids.
   Treatment should be started with smaller dose, which can be gradually increased. Patient compliance is poor if adverse reactions occur.

4.3 ADRs: PREDISPOSING FACTORS

Factors predisposing to ADRs may relate either to the properties of the drug or to the characteristics of the individual. Different factors predisposing to ADRs are discussed below:

1. **Multiple drug therapy:** The incidence of ADRs has been known to increase sharply with the number of drugs taken. E.g. occurrence of synergistic effects and additive effects.
2. **Age:** The very old and the very young are more susceptible to ADRs. In the elderly, physiologic changes due to ageing and chronic disease states often contribute to impaired drug metabolism, which can lead to increased incidence of ADRs. Neonates and children also differ from adults in the way they handle and respond to drugs, making them more susceptible to ADRs. E.g. neonates are more prone to adverse effects of chloramphenicol, Ryes syndrome due to aspirin in children and increased ADRs due to hypnotics, diuretics, etc. in elderly.
3. **Gender:** Women are generally more susceptible to ADRs then men. E.g. women are more susceptible to blood dyscrasias due to phenylbutazone and chloramphenicol than men.
4. **Intercurrent diseases:** Patients with impaired renal or hepatic function are at substantially increased risk of developing ADRs to drugs metabolized and eliminated by these organs. Other specificdisease states like human immunodeficiency virus (HIV) positive patients are also known to suffer an increased incidence of ADRs. E.g. increased occurrence of ADRs due to antitubercular drugs in human immunodeficiency virus (HIV) positive patients.
5. **Race and genetic polymorphism:** Inherited factors that affect the pharmacokinetics of drugs can also predispose to an individual's risk of ADRs. E.g. increased incidence of ADRs due to isoniazid and other cytochrome P450 metabolized drugs in poor metabolizers.

Table 4.1: Classification of Adverse Drug Reactions

Type of Reaction (Mnemonic)	Features	Examples	Management
A: Dose related (Augmented)	Common Related to the pharmacologic action of the drug – exaggerated pharmacologic response Predictable Low mortality.	Dry mouth with tricyclic antidepressants, respiratory depression with opioids, bleeding with warfarin, serotonin syndrome with SSRIs, digoxin toxicity.	Reduce dose or withhold drug Consider effects of concomitant therapy.

Type of Reaction (Mnemonic)	Features	Examples	Management
B: Non–dose related (Bizarre)	Uncommon Not related to the pharmacologic action of the drug Unpredictable High mortality.	Immunologic reactions: anaphylaxis to penicillin Idiosyncratic reactions: malignant hyperthermia with general anesthetics.	Withhold and avoid in future.
C: Dose related and time related (Chronic)	Uncommon Related to the cumulative dose.	Hypothalamic-pituitary-adrenal axis suppression by corticosteroids, osteonecrosis of the jaw with bisphosphonates.	Reduce dose or withhold; withdrawal may have to be prolonged
D: Time related (Delayed)	Uncommon Usually dose related Occurs or becomes apparent sometime after use of the drug.	Carcinogenesis Tardive dyskinesia Teratogenesis Leucopenia with lomustine.	Often intractable.
E: Withdrawal (End of use)	Uncommon Occurs soon after withdrawal of the drug	Withdrawal syndrome with opiates or benzodiazepines (e.g., insomnia, anxiety).	Reintroduce drug and withdraw slowly.
F: Unexpected failure of therapy (Failure)	Common Dose related Often caused by drug interactions.	Inadequate dosage of an oral contraceptive when used with an enzyme inducer. Resistance to antimicrobial agents	Increase dosage Consider effects of concomitant therapy.

QUESTIONS

1. What is adverse drug reaction?
2. Enlist the types of adverse drug reaction.
3. What is ADR? Discuss the types of adverse drug reaction.
4. Write the predisposing factors for ADR's?

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