Clinical Pharmacology and Drug Development

Drug Adverse Reactions

Module 2 Topic 6

Adverse Reactions

Sometimes a drug may have effects that -

- are undesirable
- have a potential to cause harm to the patient

- **Side Effects**
- **Adverse Reactions**
- **Toxicity**

Side Effects

- Known and frequently experienced, expected reactions to a drug seen at therapeutic doses
- Often related to the pharmacological actions of a drug
- For example, anticholinergic drugs given to relieve painful intestinal spasm may also affect the eye causing blurred vision, the mouth leading to dryness, and urinary bladder causing retention of urine
- May gradually disappear as the body gets accustomed

Adverse Reactions

- Less common, unexpected, unpredictable effects of a drug that are not related to the usual pharmacological actions of the drug given at normal therapeutic doses
- For example, rash, swelling of face, or jaundice
- Due to
  - Allergy
  - Absence of an enzyme that inactivates the drug
  - Drug interactions

Toxicity

- Harmful effects of the drug seen when the blood levels of a drug exceed the toxic level
- Due to
  - Overdose of a drug
  - Impaired metabolism
  - Impaired excretion of the drug

Adverse Reactions

Causes of Adverse Drug Reactions

- **Dose-related ADRs**
  - Decreased drug clearance in patients with impaired renal or hepatic function
  - Drug-drug interactions
    - competition for drug binding site of plasma proteins between warfarin and aspirin
    - induction or inhibition of CYP450 enzymes by many drugs resulting in altered metabolism of other drugs e.g. cimetidine & propranolol

Adverse Reactions

Causes of Adverse Drug Reactions

- **Allergic ADRs**
  - Not dose-related and require prior exposure
  - Allergies develop when a drug acts as an antigen or allergen
  - After a patient is sensitized, subsequent exposure to the drug produces allergic reaction

Allergic ADRs

Types of allergic reactions

- **Type I** - immediate, anaphylactic (IgE)
  - e.g., anaphylaxis with penicillins
- **Type II** - cytotoxic antibody (IgG, IgM)
  - e.g., methyldopa and hemolytic anemia
- **Type III** - serum sickness (IgG, IgM)
  - antigen-antibody complex
  - e.g., procainamide-induced lupus
- **Type IV** - delayed hypersensitivity (T cell)
  - e.g., contact dermatitis

Adverse Reactions

Causes of Adverse Drug Reactions

- **Idiosyncratic ADRs**
  - Unexpected, not dose-related, or allergic
  - They occur in a small percentage of patients given a drug
  - Idiosyncrasy is an imprecise term that is defined as a genetically determined abnormal response to a drug

Adverse Reactions

Classification of Adverse Drug Reactions

Severity	Description	Example
Mild	No antidote or treatment is required; hospitalization is not prolonged.	Antihistamines (some): Drowsiness Opioids: Constipation
Moderate	A change in treatment (eg, modified dosage, addition of a drug), but not necessarily discontinuation of the drug, is required; hospitalization may be prolonged, or specific treatment may be required.	Hormonal contraceptives: Venous thrombosis NSAIDs: Hypertension and edema
Severe	An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR.	ACE inhibitors: Angioedema
Lethal	An ADR directly or indirectly contributes to a patient's death.	Acetaminophen overdosage: Liver failure Anticoagulants: Hemorrhage

Adverse Reactions

Treatment

- Modification of dosage
- Discontinuation of drug, if necessary
- Switching to a different drug

Drug Treatment in Special Risk Groups

Patients at special risk are

- Infants and children
- Pregnant women
- Women who are breastfeeding their babies
- Elderly patients
- Patients with liver or kidney diseases

Special Risk Groups

Infants and children

- Infants and children need a lower dosage of a drug than adults because of their lower body weight and differences in body composition

Special Risk Groups

Pregnant women

- Greater care is needed during pregnancy to protect the unborn baby from any harm
- Drugs taken by the mother can enter the baby's blood circulation
- With certain drugs and / or at particular stages of pregnancy, there is a risk of developmental abnormalities, retarded growth or post – delivery problems affecting the child

Special Risk Groups

Women who are breastfeeding their babies

- Drugs may cross from mother to the baby through the breast milk
- This means that a breastfed baby may receive small amounts of whatever drugs the mother is taking
- For example, sedatives taken by mother may make the baby drowsy

Special Risk Groups

Elderly patients

- Older people are particularly at risk when they take medicines due to -
  - changes associated with ageing
  - need to take several drugs at the same time for a multitude of ailments
- Greater risk of accumulating drugs in the body because –
  - the liver is less efficient at metabolizing the drugs
  - the kidneys are less efficient at excreting them

Special Risk Groups

Patients with liver disease

- Liver transforms the complex drug molecules into simpler substances easily removable from the body
- Significantly altered if the liver is affected by disease/s
- Can lead to accumulation of drugs in the body
- Many drugs may have to be avoided completely

Special Risk Groups

Patients with kidney disease

- People with poor kidney function are at greater risk of adverse reactions to a drug
- Firstly, there is a drug accumulation in the body because of smaller amounts of drug are being excreted from the body in urine
- Secondly, kidney diseases can cause proteinuria, which lowers the plasma protein binding of drugs rendering a higher proportion of drug free and active in the blood circulation