Clinical Pharmacology and Drug Development

Toxicology

Module 2 Topic 5

Toxicology

- **Toxicology** - study of the adverse effects of chemical, physical, or biological agents on people, animals, and the environment.
- It is necessary to prove that a new drug is safe before its first administration to humans.
- ***In vitro toxicology*** studies provide an early indication of the potential for some kinds of toxic effects
- In vitro studies include **Cytotoxicity** studies using cells from higher organisms e.g. liver cells, blood cells etc., **Dermal** or **ocular toxicity** studies, such as Dermal Corrosion, Skin Irritation, and Eye Irritancy

Toxicology

***In vivo* toxicology** methods are used for the following purpose:

- Establish a safe starting dose for clinical studies
- Provide a drug-treatment regimen that would produce the least toxicity
- Assess target organ toxicity and its reversibility
- Provide insight into biomarkers for clinical monitoring

Toxicology

Types of Toxicity studies

- **Safety pharmacology studies** - determine the effects of the drug on specialized organ systems (e.g., cardiovascular, respiratory, neurologic)
- **Acute toxicity studies** – assess the adverse effects of a drug that may result either from a single exposure or from multiple exposures in a short period of time (usually less than 24 hours)

Toxicology

Types of Toxicity studies (contd)

- **Sub-acute toxicity** - show the ability of a toxic substance to cause effects for more than one year but less than the life time of exposed organism
- **Chronic Toxicity/Carcinogenicity** - determine the effects of long-term exposure to the drug, including the ability to produce cancer

Toxicology

Types of Toxicity studies (contd)

- **Reproductive Toxicity/Teratogenicity** studies evaluate the effects of a drug on reproductive function and ability to produce birth defects
- **Mutagenicity** tests evaluate the likelihood of induction of alterations in the information content (DNA) of an organism or cell that are not due to the normal process of recombination at the time of cell division

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

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

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