CHAPTER 1

INTRODUCTION TO CLINICAL PHARMACY

Clinical pharmacy is the branch of Pharmacy where pharmacists provide patient care that optimizes the use of medication and promotes health, wellness, and disease prevention. Clinical pharmacists care for patients in all health care settings but the clinical pharmacy movement initially began inside hospitals and clinics. Fig. 1.1 indicates the role of clinical pharmacy in patient care.

Clinical Pharmacist

Clinical pharmacist is the expert in therapeutic use of medication therapy, evaluation and recommendation of drugs to the patient and other health care professionals. The term clinical pharmacy is being used to describe the new growth of pharmacists. It comprises of functions necessary to discharge a particular set of social responsibilities related to therapeutic drug use in the following major categories.

1. Prescribing drugs
2. Dispensing and administering drugs
3. Documenting professional services
4. Direct patient involvement
5. Reviewing drug use
6. Education
7. Consolation

Aim of Clinical Pharmacy

The aim of clinical pharmacy is to ensure the patient‘s maximum well being and to play a meaningful role in the safe and rational use of drugs.

The main roles of clinical pharmacy are:

1. To assist the physician in doing a better job of prescribing and monitoring drug therapy for the patient.

2. To assist medical and paramedical staff and documenting medication indications correctly.
3. To maximize the patients' compliance in drug use process.

Scope of Clinical Pharmacy

Clinical pharmacy services are of considerable importance in all the hospitals because; Clinical Pharmacy can serve as a guide to the physician for the safe and rational use of drugs. A clinical pharmacist can help to achieve economic hospital by planning safe drug policies, for suggesting means of reductions of waste, by preventing misuse of drugs and in the preparation of budget by forecasting future means of hospital based upon their drug utilization process.

The scope of clinical pharmacy is of utmost appreciation in the following areas:

1. Drug information
2. Drug utilization
3. Drug distribution
4. Drug selection
5. Drug evaluation
6. Pharmacy education and teaching.

Qualities of Clinical Pharmacist

The clinical pharmacist should have the following qualities.

1. Good communication skills
2. Clinical skills
3. Professional relationship
4. Empathy
5. Monitoring drug therapy

Role of Clinical Pharmacist in health care team

The Clinical Pharmacist has the following roles.

1. Taking medication history of the patient
2. Drug interactions
3. Selection of drug therapy

4. Drug monitoring
5. Adverse drug reactions
6. Management of drug policies
7. Research and development programme
8. Drug information

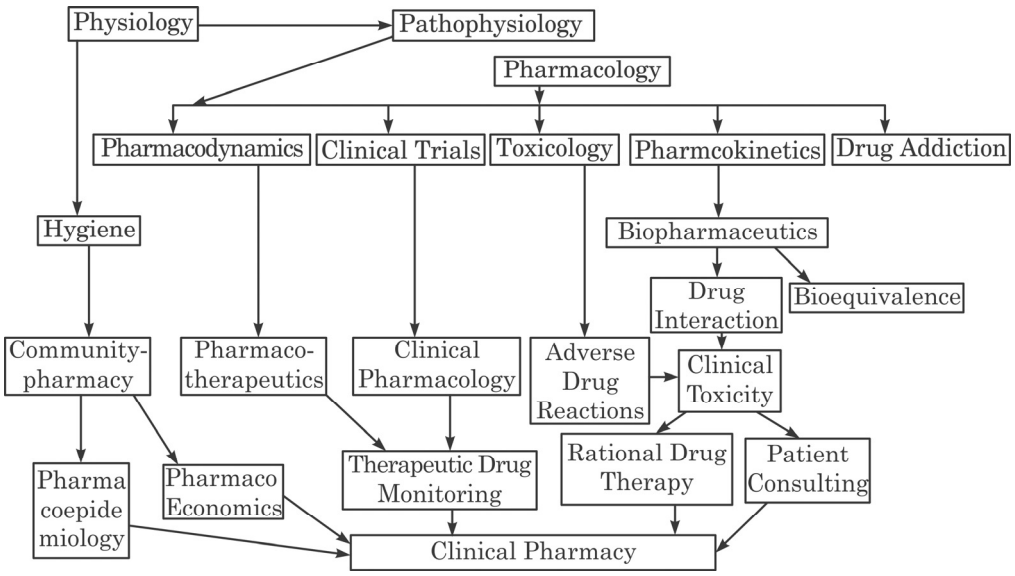

Fig. 1.1 Role of Clinical Pharmacy in Patient Care

Duties of Clinical Pharmacist

The daily routine duties of Clinical Pharmacist are,

1. Assisting pharmacokinetic consultations with necessary follow up.
2. Monitoring drug therapy schedule.
3. Taking rounds with health care team
4. Teaching pharmacy students
5. Patient counseling
6. Review of hospital forbid art
7. Preparation of drug monograph to be reviewed by pharmacy and the therapeutic community of hospital.

In this manner, clinical pharmacy is totally patient oriented and deals with rationale of drug therapy.

Clinical Pharmacokinetics

Clinical Pharmacokinetics is the science of the rate of movement of drugs within biological systems, as affected by the absorption, distribution, metabolism, and elimination of medications.

It involves

- Study of the time course of a drug's movement through the body.
- Understanding of what the body does to (or with) the drug.
- Application of Therapeutic Drug Monitoring (TDM) and individualization of drug therapy

Pharmacokinetics (PK) - What the body does to the drug

- Absorption; distribution, metabolism, excretion (ADME)

Pharmacodynamics (PD) - What the drug does to the body

- Drug concentration at the site of action or in the plasma is related to a magnitude of effect

Pharmacokinetic processes depend on two fundamental kinetic processes- zero order kinetics and first order kinetics.

Zero order kinetics: Zero order kinetics is where the plasma concentration of a drug decreases at a constant rate. A graph of this will show a linear relationship between time from peak concentration and plasma concentration (Fig. 1.2).

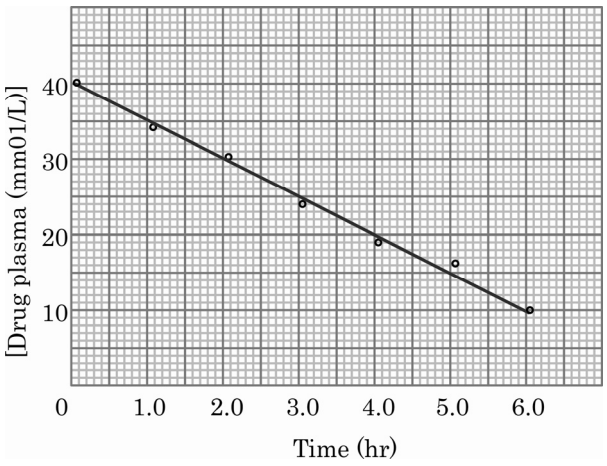

Fig. 1.2 Zero order kinetics

Examples of zero-order processes

1. The entry of drug into the circulation during intravenous infusion.
2. The absorption of many depot forms of administration e.g., Fluphenazine decanoate in oil (used in schizophrenia).

First-Order Reaction

A first-order reaction depends on the concentration of only one reactant (a unimolecular reaction). Other reactants can be present, but each will be zero-order (Fig. 1.3).

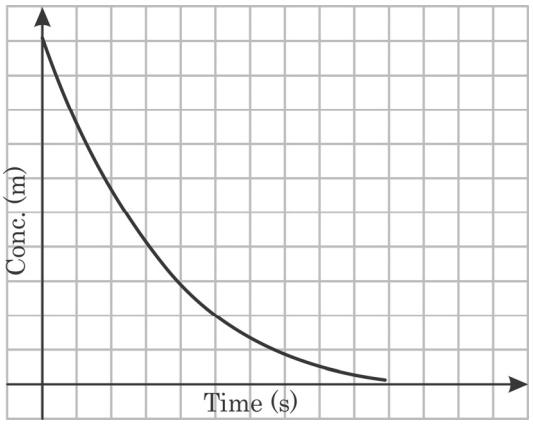

Fig. 1.3 First order kinetics

Pharmacokinetic Processes

Absorption

- Must be able to get medications into the patient's body
- Drug characteristics that affect absorption:
  - Molecular weight, ionization, solubility, and formulation
- Factors affecting drug absorption related to patients:
  - Route of administration, gastric pH, contents of GI tract

Absorption in the Pediatric Patient

- Gastrointestinal pH changes
- Gastric emptying
- Gastric enzymes

- Bile acids and biliary function
- Gastrointestinal flora
- Formula/food interaction

Distribution

- Membrane permeability
  - cross membranes to site of action
- Plasma protein binding
  - bound drugs do not cross membranes
  - malnutrition = ↓albumin = ↑ free drug
- Lipophilicity of drug
  - lipophilic drugs accumulate in adipose tissue
- Volume of distribution

Pediatric Distribution

- Body Composition
  - ↑ total body water and extracellular fluid
  - ↓ adipose tissue and skeletal muscle
- Protein Binding
  - albumin, bilirubin, α_1-acid glycoprotein
- Tissue Binding
  - compositional changes

Metabolism

- Drugs and toxins are seen as foreign to patients bodies
- Drugs can undergo metabolism in the lungs, blood, and liver
- Body works to convert drugs to less active forms and increase water solubility to enhance elimination
- Liver - primary route of drug metabolism
- Liver may be used to convert pro-drugs (inactive) to an active state
- Types of reactions
- Phase I (Cytochrome P450 system)
- Phase II

Phase I reactions

- Cytochrome P450 system
- Located within the endoplasmic reticulum of hepatocytes

- Through electron transport chain, a drug bound to the CYP450 system undergoes oxidation or reduction
- Enzyme induction
- Drug interactions

Phase I reactions types

- Hydrolysis
- Oxidation
- Reduction
- Demethylation
- Methylation
- Alcohol dehydrogenase metabolism

Phase II reactions

- Polar group is conjugated to the drug
- Results in increased polarity of the drug
- Types of reactions
  - Glycine conjugation
  - Glucuronide conjugation
  - Sulphate conjugation

Elimination

- Pulmonary: expired in the air
- Bile: excreted in feces
  - enterohepatic circulation
- Renal
  - glomerular filtration
  - tubular reabsorption
  - tubular secretion

Pediatric elimination

- Glomerular filtration matures in relation to age, adult values reached by 3 years of age
- Neonate: decreased renal blood flow, glomerular filtration, and tubular function yields prolonged elimination of medications
- Aminoglycosides, Cephalosporins, penicillin's : longer dosing interval

Basic Clinical Pharmacokinetic Parameters

The three basic pharmacokinetic parameters of first order elimination are:

(i) Volume of distribution (V_d)
(ii) Clearance (Cl)
(iii) Half life ($t_{1/2}$)

Above parameters have specific well defined utility.

(i) Volume of Distribution (V_d)

Apparent volume of distribution is the volume of serum plasma or blood that is occupied by the drug in the body

V_d is a proportionality constant that equates the serum drug concentration (SDC) to the total amount of drug in the body. V_d has no physiological basis and thus it does not relate to volume of serum, blood or total body water.

$$V_d = \frac{\text{Dose}}{\text{Serum Drug Concentration}}$$

Since elimination of drug occurs from the moment of drug input the equation more commonly used is;

$$V_d = \frac{\text{Clearance}}{\text{Elimination rate constant}}$$

It helps to:

(i) Determine a loading dose of a drug.
(ii) Determine amount of drug in the body.
(iii) Make qualitative assessment of distribution of drug in the body.

(ii) Clearance (Cl)

Cl is a descriptive term used to evaluate the efficiency of drug removal from body. Drugs are cleared primarily by kidneys (Clr) and liver (Clh). Clearance can be expressed as an estimate of efficiency flow, a sum or a ratio.

Cl = Clh + Clr + Clearance of other eliminating organs.

Cl is a proportionality constant that relates the rate of drug elimination to the SDC. It is a flow rate measured in units of volume per time (i.e. milliliters per minute. Cl helps to determine the steady state concentration that will be achieved from a specific maintenance dosage.

Elimination of drug from body follows two patterns:

(i) ***First order elimination*** (Linear or concentration independent): Here the rate of elimination is directly proportional to the concentration of drug in serum i.e. as serum drug concentration rises the drug is eliminated at a faster rate.

(ii) ***Michaelis – Menten elimination*** (non-linear or concentration dependent): Here the rate of elimination does not change in proportion to changes in serum concentration i.e., as serum drug concentration rises, rate of elimination increases less than proportionately e.g. phenytoin. For such drugs careful monitoring of drug levels is essential.

If the Cl of a drug is known, then the rate of drug elimination can be calculated by multiplying the Cl by the SDC (assuming first order drug elimination).

(iii) Half – Life ($t_{½}$)

Half life is the time required for the serum drug concentration to get decreased to one half, irrespective of the starting concentration. This is illustrated in Fig.1.4. Each down stroke represents a halving of the plasma concentration and each across stroke is the time taken for that halving to occur i.e., the half – life.

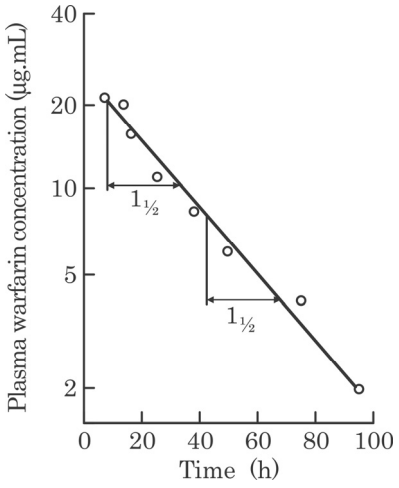

Fig. 1.4 The principle of half-life ($t_{1/2}$). When plasma concentration versus time data are linear in a semi-logarithmic plot, the time it takes for the plasma concentration to fall from any value to half that value is a constant, the half-life.

The following are the uses of half-life:

(i) ***As a guide to the time it takes for a drug to be eliminated from the body:***

For most drugs, the half-life measured in plasma or serum, is directly related to the half life of the drug in the tissues. However, some drugs have short half-lifes in the plasma but are stored in the tissue, from which they are released slowly; this is true of the vitamin A analogues.

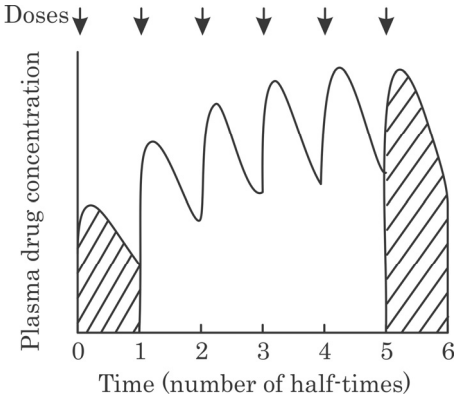

Fig. 1.5 The theoretical plasma concentrations of a drug over a period of time during its repeated oral administration.

(ii) ***As a guide to the rate of accumulation of drug in the body during multiple dosing*** (*Fig 1.5*)

It is only variable that determines the rate of which drug accumulates in the body during regular multiple dosing. For example, if we consider the regular oral administration of a drug that is rapidly absorbed. After the first dose, the concentration of drug in plasma rises sharply as the drug is absorbed, it reaches a peak and then starts to fall, as the drug is distributed around the body and eliminated. After the second dose, the rise in concentration to the next peak is the same as after the first dose, but because the new peak is higher than the first, the rate of fall is faster (first-order kinetics). After each successive dose, the increase in the plasma concentration is same but, because the peak is always higher, the size of the fall after peak becomes progressively larger with successive doses. Eventually the size of the fall in plasma concentration after the peak is as great as the size of the preceding rise and a steady state is reached. At steady state, the amount of drug eliminated from the body in a single dose interval is the same as the amount that enters it.

Strictly speaking this is not a true steady for two reasons:

(i) Because plasma concentrations are fluctuating all the time.

(ii) Even the mean of those concentrations does not reach a true steady value until infinite time.

However, for practical purpose, a steady state is said to have occurred after four to five half-lifes, when 94-97% the eventual steady state value will have been reached.

No. of half-life	B % accumulated	Total
1	50	50%
2	50 + 25	75%
3	50 + 25 + 12.5	87.5%
4	50 + 25 + 12.5 + 6.25	938.%
5	50 + 25 + 12.5 + 6.25 + 3.125	96.9%

This means that the time taken to reach steady state depends only on half-life of the drug, and neither on the size of the dose nor frequency of administration (Fig. 1.6)

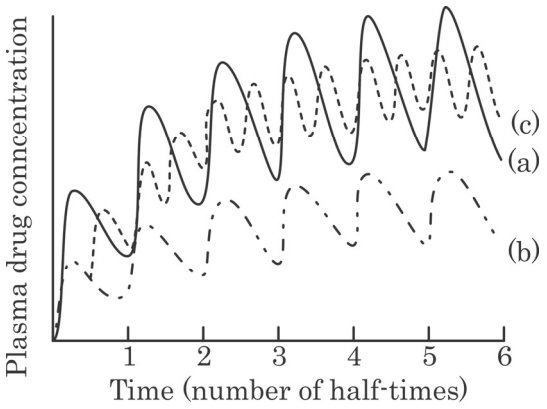

Fig. 1.6 The effects of varying the dose and frequency of administration on the time taken to reach steady state and the eventual steady-state plasma concentration.

(iv) As a guide to the relationship between the loading dose and maintenance dose:

When a drug has a longer half life than 24 hours (e.g. digoxin 40 hours; Digitoxin 7 days) it takes several days or weeks (4 – 5 half lifes) of regular administration of the same daily dose before the steady state

plasma concentration are reached. Such a delay may be unacceptable. So if a loading dose can be given followed by administration of a regular maintenance dose to maintain the steady state (Fig. 1.7).

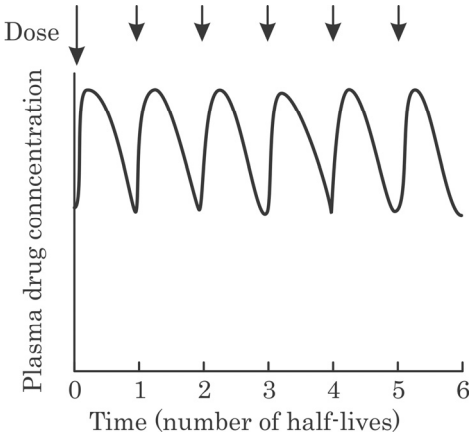

Fig. 1.7 The effect of an initial loading dose. If the correct loading dose is given, a steady state can be achieved rapidly and then maintained by giving a smaller maintenance dose.

Even when the half-life of a drug is short, it is sometimes desirable to give a loading dose if a very rapid effect is required e.g. Lidocaine in the treatment of cardiac arrhythmias.

Relationship between half-life ($t_{½}$), Clearance (Cl), volume (V) and Steady State Concentration (C_{ss})

1. Cl and V are independent pharmacokinetic parameters not influencing each other and whose values determine the elimination rate constant (or half life) of drug from the serum and the C_{ss} achieved after maintenance dosing.
2. Half life is a dependent function whose value depends on Cl (inversely proportional) and V (directly proportional).
3. Cl can be considered as representing the sum of all drug elimination process in the body and V represents the distribution of drug and is influenced by the pharmacodynamic characteristics of the clearing agent.
4. The C_{ss} achieved after constant Iv infusion (e.g. Lidocaine theophylline) or mean C_{ss} achieved after multiple oral dosage depends on Cl only, it is not influenced by V.

Methodology for Clinical Pharmacokinetic Study

1. **Scheme of Administration:** Both single dose and multiple dose studies should be performed within the recommended dose range and dose intervals.

   Multiple dose studies should be whenever possible continued long enough to establish steady state concentrations of the drug and for such steady state levels, their dose-dependence and variability should be determined. Accumulation kinetics of drug predicted from the kinetic constants obtained from single dose studies should be verified experimentally; different dosage should be included in one study to determine dose dependence and to decide whether changes from linearity to non linearity occur at dosage levels which are normally used. After discontinuation of a prolonged treatment, the possibility of very slow terminal decrease in plasma concentrations, which can reflect the existence of a deep compartment, should be investigated. This might explain the discrepancy between the long action of the substance and the apparent short elimination half life as measured after a single dose administration.

2. **Subject Selection**

   (a) ***Initial studies***: Initial studies are generally performed in a restricted number of fasting healthy adult volunteers in well defined controlled conditions. When the substance carries too serious a risk to healthy volunteers (e.g. anti-cancer drugs, they are conducted in patients suffering from diseases for which the drug is considered to be indicated.

   (b) ***Further studies:*** Further studies should be conducted in patients suffering from diseases for which the drug is claimed to be indicated. The relation between dose, plasma concentration and therapeutic effects, where this is feasible should be studied. Particularly, it should be established that the pharmacokinetic behavior of the drug in patients corresponds to that in healthy subjects. The full range of kinetic studies need only be repeated in patients if studies indicate that the pharmacokinetics in this group differ from those in healthy volunteers.

   (c) ***Influence of various pathophysiological states***: It is very useful to know the kinetics of drugs in a very large number of pathophysiological situations; however, it is clear that this

knowledge requires multiple, long and expensive studies which cannot all be performed before licensing.

Therefore, the only studies which should be reasonably submitted before marketing are those which seem to be necessary in regard to the properties, indications, contra-indications, routes of elimination, scheme of administration of the drug and those which are required to define the necessary dosage changes which cannot be calculated from the pharmacokinetic parameters available from volunteers under standardized conditions and in patients without functional disturbances of the systems of absorption, distribution or elimination.

In so far as the indications render this relevant, kinetics should be studied in patients at extreme of age9 infants, children and elderly). For drugs intended to be orally administered, it is important to study the effects of food on absorption. Other factors like body weight, time of day, environment factors, genetic differences, alcohol, smoking habits, concomitant medication, sex, may influence the results and the interpretation of later clinical studies. Then the kinetic studies should be extended accordingly.

3. **Sampling and Analysis of Drug Concentration:** The number of blood samples should be large enough and the timing appropriate to allow a adequate determination of the absorption and/or distribution and elimination phases. Plasma concentrations in the post absorption phase should possibly, be determined at above two or three half lifes to avoid confusion between distribution and elimination half lifes. If there is an evidence for a very long terminal half life, plasma concentration should be followed for a much longer time. If urinary data are obtained, the urine should be collected until there is no further detectable excretion of parent drug or metabolites within the limits of the method used. The stability of the substance during sampling and storage requires careful attention.

   The samples are then analyzed by various methods like spectro-photometry, HPLC etc.

   Specificity, accuracy (as regards recovery) and precision (sensitivity and reproducibility) of the methods should be mentioned. Both for technical reasons and safety cold analytical methods are often to be preferred to tracer radioactive techniques. If radioactive isotopes are used, the tracer dose should always be combined with a quantity of

non labeled drug within the therapeutic dose range. However, in most cases it is necessary to develop suitable cold analytical methods to separate and assay quantitatively the metabolites and / or the parent compound. The mathematical methods are then used (graphical representation, computer analysis, pharmacokinetic formulas) to get various pharmacokinetic parameters. Proper statistical analysis of the data obtained should be made and the inter and intra individual variations estimated in at least some of the studies whether the number of subjects is large enough. As an illustration a pharmacokinetic study of paracetamol has been given as under.

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